ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2001; 19 (3): 255-265
1170-7690/01/0003-0255/$22.00/0

Cost Effectiveness of Emedastine versus Levocabastine in the Treatment of Allergic Conjunctivitis in 7 European Countries

Carlos Gouveia Pinto,[1] *Antoine Lafuma*,[2] *Francis Fagnani*,[2] *Mark J.C. Nuijten*[3] and *Gilles Berdeaux*[4]

1 Universade Técnica de Lisboa, Instituto Superior de Economia e Gestao, Lisboa, Portugal
2 Cemka, Bourg-la-Reine, France
3 Medtap Netherlands, Jisp, The Netherlands
4 Alcon France, Rueil-Malmaison, France

Abstract

Objective: To assess the cost effectiveness of emedastine, a new antihistamine, versus levocabastine in the treatment of acute allergic conjunctivitis (AAC) in Belgium, France, Germany, The Netherlands, Norway, Portugal and Sweden.

Design and setting: Randomised double-blind multicountry clinical trial followed by economic modelling from the treatment provider perspective.

Patients: A total of 221 patients (109 emedastine, 112 levocabastine) with AAC were included.

Methods: The clinical trial compared the efficacy and safety of emedastine 0.05% and levocabastine 0.05%, both twice daily, for 42 days, using ocular redness, itching, days without symptoms and clinical failure as outcome measures. The cost of first-line treatment failure, including visits, drugs and laboratory examinations, was established in each country from a panel of ophthalmologists and general practitioners. Full sensitivity analyses were conducted.

Results: From day 7 to 42, patients treated with emedastine had less itching ($p < 0.001$) and less redness ($p < 0.001$). The failure rate was 10% less ($p < 0.02$) with emedastine and patients treated with emedastine had an incremental 8.5 days ($p < 0.01$) without symptoms. Emedastine and levocabastine were equally well tolerated. In all European countries, the cost of failure was lower with emedastine. Emedastine was found to be economically dominant relative to levocabastine, i.e. more effective and less expensive, in Belgium, Germany, Portugal and Sweden; in France, The Netherlands and Norway the incremental cost was low (less than 1 euro per additional symptom-free day).

Conclusion: Through a model based on a randomised clinical trial and cost estimates of treatment failure derived from practitioner interviews, emedastine is a cost-effective treatment of AAC.

Allergic conjunctivitis is one of the most common ocular allergic disorders[1,2] with a prevalence estimated from 5 to 22% of the population.[3-8] Acute allergic conjunctivitis (AAC) is the most frequent form, accounting for 50 to 90% of cases of allergic conjunctivitis.[9] The onset of AAC is typically related to the presence of specific air-borne allergens such as pollens, spores or moulds.[10]

Characteristic signs and symptoms include bilateral and periodic itching and occasionally burning, photophobia and foreign body sensation. Ocular examination reveals mild conjunctival hyperaemia and oedema, eyelid oedema and excessive lacrimation. Concurrent rhinitis is common, although in a subset of patients the ocular symptoms may occur exclusively.

Traditional therapies include drugs aimed at controlling the conjunctival secretion of histamine, the primary mediator of the allergic reaction: oral antihistamines (H_1 antagonists) as well as topical corticosteroids, mast cell stabilisers, nonsteroidal anti-inflammatory drugs and antihistamines sometimes given concurrently with a vasoconstrictor.[10] Diagnosis and treatment of AAC is performed either by general practitioners (GPs) or by ophthalmologists, with some variations between countries.

Usually the different types of allergic conjunctivitis do not threaten the patients' vision, especially when diagnosed and treated by effective therapy. Nevertheless, allergic conjunctivitis is an important health problem because of its morbidity,[11] since:

- it alters the quality of life/well-being of the patients[12,13]
- it is a cause of work or school days lost[14]
- although it is treated mainly on an outpatient basis with low medical costs, its high prevalence leads to high expenditures for sickness funds, i.e. $US1.8 billion per year (1990 values) in the US.[15]

The aim of this study was to compare the cost (from a treatment provider perspective) of the treatment of one episode of AAC by 2 antihistamines (levocabastine and emedastine) in various European Union (EU) countries: Belgium, France, Germany, The Netherlands, Norway, Portugal and Sweden. These drugs have been compared through a well-controlled randomised double-blind clinical trial.

Patients and Methods

Experimental Design

Two sources of data were used: (i) failure rates and time without symptoms were estimated from a European clinical trial; and (ii) the standard average cost of a failure was obtained from a panel of practitioners. A decision tree was constructed to aggregate cost of first-line success and cost of failure.

Only costs contributing to the difference between the 2 strategies were taken into account.[16] The cost of success was estimated from the daily cost of emedastine or levocabastine multiplied by the suc-

Table I. Sources of data related to resource utilisation costing

Resource	Belgium	France	Germany	The Netherlands	Norway	Portugal	Sweden
Exchange rate (euro)	40.3399 Belgian francs	6.55957 French francs	1.95583 Deutschmarks	2.20371 Dutch guilders	8.24 Norwegian kroner	200.482 escudo	8.26 Swedish kronor
Private/public practice	Mainly public	Mainly public	12 : 88	36 : 64	Mainly public	Unknown, fixed arbitrarily at 1 : 1	Mainly public
Ratio of ophthalmologist to general practitioner in allergic conjunctivitis	47 : 53	1 : 1	60 : 40	7 : 93	15 : 85	Unknown, fixed arbitrarily at 1 : 1	Unknown, fixed arbitrarily at 1 : 1
Visits (references)	27	28, 29	30, 31	32	33	34, 35	36, 37
Drugs (references)	38	39	40	41, 42	43	44	45
Laboratory examinations, procedures (references)	27	46	30, 31	34, 47-50	51	34	52

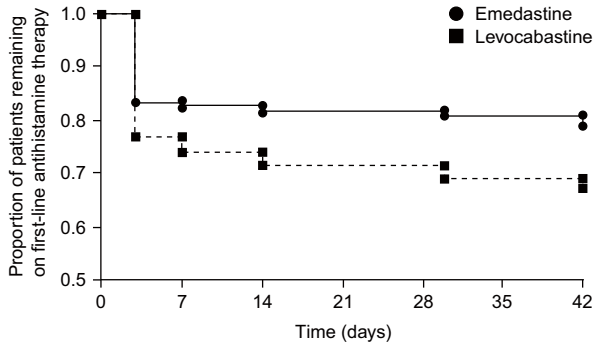

Fig. 1. Survival curves illustrating the instantaneous success rate incidence by treatment group. Failure is defined as patients whose symptoms (redness and itching) were stable or worsened since the first visit.[60] χ^2 analysis at day 42, $p < 0.045$; Wilcoxon life test, $p < 0.02$.

cess rate. Therefore, the cost of success was independent of the number of bottles required to treat for 42 days. The cost of failure was estimated from the cost of purchasing 1 bottle of emedastine/levocabastine (mean time to failure was 8 days, covered by 1 bottle of drug) plus the cost of failure, multiplied by the failure rate.

The time horizon of the model (a decision tree) was 42 days, i.e. the clinical trial duration. No discounting was performed because of the timeframe of the model.

Clinical Efficacy and Effectiveness

Effectiveness was derived from a randomised, multicentre, double-blind, parallel-group clinical trial including 221 patients from Europe (UK, Italy, France, Germany, Spain and Portugal), South Africa and Australia, recruited by 18 investigators.[17]

Patients of either gender and any race who met the following criteria could be included: scores of 4 in itching (very frequently), and conjunctiva hyperaemia scores of 2 (colour overall is more red than pink, calibre of vessels has increased so that vessels have lost their delicate web-like pattern) or more in both eyes, a history of allergic conjunctivitis for at least 1 allergy season and a positive skin test (within the past 12 months) to at least 1 common pollen indigenous to the area at the time of the study.

Levocabastine ophthalmic suspension 0.05% or emedastine ophthalmic solution 0.05% was given twice a day in the affected eyes for 42 days.

The primary clinical efficacy end-points were itching and ocular redness, and the secondary end-points were chemosis, eyelid swelling, patient diary data and physical global assessment. Itching and redness were measured at days 0, 3, 7, 14, 30 and 42. Patients were asked to complete a diary card 4 times a day. Itching and redness were self-evaluated according to a score from 0 (no symptoms) to 9. Standardisation through a photo catalogue given to the patient was performed in order to estimate the intensity of symptoms as reliably as possible.

Two effectiveness measures were used from this clinical trial: (i) failure, defined by the protocol as 'no improvement or worsening in ocular redness, combined with no improvement in itching'; and (ii) time without symptoms estimated from the diary card (at every recorded time with no redness and no itching, 0.25 days were added to time without symptoms, since the measures were performed 4 times a day).

The statistical analysis was conducted using SAS software (release 6.12; SAS Institute, Cary, NC, USA). The failure rate incidence was calculated at each scheduled visit and the comparison between emedastine and levocabastine was performed using the maximum likelihood ratio test applied to

survival curves. Missing values in diary cards were estimated through the 'last observation carried forward'[18] technique. Comparison between the 2 groups were worked out using a nonparametric test. All the tests were 2-sided, with alpha being fixed at 5%.

Resource Utilisation

The number of days of treatment available from a bottle was estimated from the following parameters: size of the bottle (ml), size of the drop (µl), expiry date, daily dosage. The size of the drops was estimated from a standardised methodology taking different sources of variations into account (the bottle, the order of the drop, the measure itself) estimated through a specific experimental design (balanced block analysis of variance).

As the clinical trial patients were not followed-up in case of failure, no primary data concerning resource utilisation were available. Therefore, resource utilisation for the second-line treatment was estimated through interviews with 10 GPs and 10 ophthalmologists (11 in Portugal), in each country, except Norway (5 GPs and 5 ophthalmologists).

The interviews were standardised by the use of a predetermined questionnaire. Interviewers were trained before conducting interviews. The list of the practitioners and the standard questionnaire are available upon request.

Economic Analysis

All results were expressed in euro (EUR), taking into account the fixed parity for the countries belonging to the euro zone[19] or the exchange rate (01 January 2000) for the others. The economic perspective was that of the treatment provider and followed the guidelines of the countries participating in this economic evaluation.[20-26]

Indirect costs were not taken into account, since there were no national statistics documenting the loss of productivity in AAC in all countries and interviews were not considered as an appropriate source for this type of data. Moreover, the number of workdays lost has been found to be rather low in AAC[14] and their associated cost could be close to zero since patients return quickly to work. This was confirmed by the French expert interviews and preliminary data from an ongoing EU piggy-back clinical trial (unpublished data).

Table I describes the sources used to value resource utilisation in monetary terms. Public practice was defined as a practitioner using national tariffs: these estimates came mainly from national tariff lists. The ratio of ophthalmologists versus GPs practising in allergic conjunctivitis was taken from

Table II. Resource utilisation as prescribed/requested by ophthalmologists after failure of first-line topical antihistamine therapy (source: practitioner interviews). The sum of percentages might exceed 100%, since a patient may receive more than 1 drug and some drugs may include more than 1 entity

Resource (% of ophthalmologists prescribing/requesting)	Belgium	France	Germany	The Netherlands	Norway	Portugal	Sweden
Topical drugs	135.0	117.5	106.0	96.4	100.0	118.2	161.5
corticosteroids	71.0	30.5	36.0	44.0	60.0	95.5	55.0
mast cell stabilisers	33.0	14.9	64.0	32.4	20.0	4.5	61.5
antihistamines	13.0	35.0	6.0	10.0	0	0	35.0
antimicrobials	0	28.1	0	0	0	18.2	0
others	18.0	9.0	0	10.0	20.0	0	10.0
Systemic drugs	20.0	73.0	1.5	3.4	20.0	9.1	20.0
corticosteroids	0	0.5	0	0	0	0	0
antihistamines	20.0	72.5	1.5	3.4	20.0	9.1	20.0
Laboratory examinations, procedures	38.0	14.2	1.0	19.1	10.0	0	10.1
Visits (number)	2.32	1.31	1.49	1.80	1.81	1.13	2.26
ophthalmologists	1.78	1.26	1.41	1.66	1.80	1.13	1.82
other specialists	0.54	0.05	0.08	0.14	0.01	–	0.44

Table III. Resource utilisation as prescribed/requested by general practitioners after failure of first-line topical antihistamine therapy (source: practitioner interviews). The sum of percentages might exceed 100%, since a patient may receive more than 1 drug and some drugs may include more than 1 entity

Resource (% of ophthalmologists prescribing/requesting)	Belgium	France	Germany	The Netherlands	Norway	Portugal	Sweden
Topical drugs	80.3	97.1	10.0	57.5	20.0	0	137.3
corticosteroids	19.8	33.1	0	10.0	0	0	31.0
mast cell stabilisers	16.5	32.0	0	7.5	20.0	0	57.3
antihistamines	16.5	28.5	10.0	25.0	0	0	27.0
antimicrobials	14.3	3.5	0	5.0	0	0	0
others	13.2	0	0	10.0	0	0	22.0
Systemic drugs	50.0	71.1	102.5	62.5	80.0	100	61.5
corticosteroids	0	2.6	0	0	0	0	15.0
antihistamines	50.0	57.0	82.5	62.5	80.0	100	46.5
others	0	11.5	20.0	0	0	0	0
Laboratory examination, procedures	17.0	0	27.5	9.3	22.0	0	2.0
Visits (number)	2.32	1.34	1.61	1.58	1.06	1.03	1.87
general practitioners	1.68	1.18	1.41	1.56	1.04	1.01	1.21
ophthalmologists	0.48	0.10	0.09	0.01	0.02	0.02	0.47
other specialists	0.16	0.06	0.11	0.01	0	0	0.19

IMS data.[53-57] These data were not available in Sweden and Portugal, and they were fixed arbitrarily at 1 : 1, since access to ophthalmologists was unrestricted, like in Belgium, France and Germany. The Netherlands presented a special case since most of the ophthalmologists were hospital-based and no statistics were available for the others. Sources of resource utilisation cost data came mainly from year 2000 data; a 2% yearly rate was applied to data prior to year 2000, before converting costs to euros.

In all countries, prices of 'listed-for-reimbursement' drugs[27,34,38-52] were controlled and referenced by the national authority. The list of official tariffs was used.

Except for ophthalmologists in The Netherlands [costs regulated by COTG (Centraal Orgaan Tarieven Gezondheidszorg)] and the private sector in Portugal, the cost of visits is also regulated by the state.[27,28,30,31,34,36,37,46-50] Some statistics estimating the extra cost linked to public activities were available in France,[29] and the cost of a production unit was increased by 10% in Germany to take into account the 12% of private practice. In Portugal, the cost of private visits was estimated using the price recommended by the Portuguese Medical Association.[35] In The Netherlands, ophthalmologists were hospital-based and their activities were regulated by both the national authorities and the global budget approach. As the Dutch visit tariff was far lower than the opportunity cost, specific surveys[58] were conducted to estimate 'real cost'.

Lastly, levocabastine was not available on the Portuguese market. The cost of isospaglumic acid (NAAGA) was taken as a proxy of the cost of levocabastine, since it was the most often prescribed drug in AAC.[59] From a medical point of view, this was a conservative approach since isospaglumic acid has never established superiority over levocabastine.

Results

Clinical Efficacy and Effectiveness

From day 7 to day 42, patients treated with emedastine had a lower itching score ($p < 0.0001$) and a lower redness score ($p < 0.0001$) than patients treated with levocabastine.

Figure 1 describes time to failure by treatment group. The mean time to failure was 8 days across all groups of patients pooled together. Fewer patients treated with emedastine ($p < 0.02$) had treatment failure (21.10%) compared with those treated

with levocabastine (33.04%). The median time without symptoms (redness and itching) was 1.75 days with levocabastine and 10.25 days with emedastine: this difference was statistically significant ($p < 0.01$) [patients treated with emedastine had 8.5 days more without symptoms].

The safety of the 2 drugs was found to be similar, and both compounds were well tolerated.

Economic Analysis

The size of 1 bottle of levocabastine is 4ml (except in France, 3ml), the size of 1 drop is 39.6µl (internal data) and the mean number of drops per bottle is 101 (75 in France). With 2 drops a day in each eye (the dosage used in the clinical study), the number of days of treatment available from a bottle of levocabastine was 25 (18 days in France). Because the emedastine bottle is bigger (5ml) and the drop size is smaller (34µl), the number of days of treatment per bottle of emedastine at the same daily dosage was limited by the expiry date to 28. To summarise, because the drop size of emedastine was smaller and because its bottle size was bigger, 3 additional days were available per bottle.

As well as this daily cost, tables II and III describe the resource utilisation of ophthalmologists and GPs, respectively, when facing failure of the first-line antihistamine therapy. Some differences were found between countries and between GPs and ophthalmologists. Prescriptions in France and Sweden were usually for 2 products (true for both GPs and ophthalmologists), whereas practitioners in Germany, The Netherlands and Norway prescribed 1 product on average. Practitioners in Belgium and Sweden asked their patients to re-visit more often than those in France and Portugal. Belgian ophthalmologists and German GPs requested the most laboratory examinations.

Topical corticosteroids were mostly prescribed by ophthalmologists, whereas systemic antihistamines were mostly used by GPs. The exception was France, where ophthalmologists coprescribed an oral antihistamine with a topical compound in 72.5% of patients. No major differences between GPs and ophthalmologists were found either in the average number of visits or in the requests for laboratory examination.

Table IV describes the standard cost of failure of the first-line antihistamine in each country for GPs and for ophthalmologists. Outside GP visits in Sweden, visit costs represented 1.5 to 3 times the cost of drugs, except in Portugal where this ratio was closer to 18 for ophthalmologists. The cost of an ophthalmologist visit is about 50% or more higher than that of a GP visit, except in Germany where it was 50% lower. An especially large difference was observed for Portuguese ophthalmologists (EUR96.85) and Portuguese GPs (EUR37.97).

Table V describes the difference in costs of the 2 strategies according to the treatment provider perspective. The cost of successful emedastine treatment was higher than that of levocabastine: the extra cost of 1 emedastine bottle is not fully balanced by the 3 (10 in France) additional therapy days avail-

Table IV. Cost per patient (in euro; 2000 values) of failure of first-line topical antihistamine treatment of allergic conjunctivitis

Resource	Belgium	France	Germany	The Netherlands	Norway	Portugal[a]	Sweden
Ophthalmologist							
drugs	18.59	21.13	14.21	20.54	25.88	5.25	30.66
visit	37.70	47.96	40.43	64.60	36.90	91.60	49.98
procedure	6.37	9.01	0.17	4.98	5.00	0.00	4.81
Total	**62.66**	**78.10**	**54.81**	**90.12**	**67.78**	**96.85**	**85.45**
General practitioner							
drugs	12.89	16.35	32.58	16.70	27.97	9.88	36.50
visit	35.85	28.00	53.56	27.56	14.21	28.09	20.50
procedure	1.28	16.39	4.81	1.60	2.51	0.00	0.96
Total	**50.02**	**60.74**	**90.95**	**45.86**	**44.69**	**37.97**	**57.96**

a Cost of isospaglumic acid (NAAGA) taken as a proxy of the cost of levocabastine, since the latter is not available on the market.

Table V. Cost per patient (in euro; 2000 values) of 42 days of treatment started either with levocabastine or with emedastine. The economic perspective is that of the treatment provider

Cost	Belgium	France	Germany	The Netherlands	Norway	Portugal[a]	Sweden
Levocabastine							
cost of success	14.48	8.59	17.82	17.00	16.58	12.87	17.94
cost of failure	22.05	24.48	27.28	20.45	20.00	25.45	28.12
Total	**36.53**	**33.07**	**45.10**	**37.45**	**36.58**	**38.32**	**46.06**
Emedastine							
cost of success	21.79	23.18	24.12	24.57	23.55	16.57	25.01
cost of failure	14.72	16.95	17.85	13.67	13.31	16.44	18.48
Total	**36.51**	**40.13**	**41.97**	**38.24**	**36.86**	**33.01**	**43.49**
Incremental cost (emedastine – levocabastine)	–0.02	0.83/DFS	–3.13	0.09/DFS	0.03/DFS	–5.31	–2.57
Conclusion	Emedastine dominant	Emedastine cost effective	Emedastine dominant	Emedastine cost effective	Emedastine cost effective	Emedastine dominant	Emedastine dominant

a Cost of isospaglumic acid (NAAGA) taken as a proxy of the one of levocabastine since the latter is not available on the market.

DFS = day free of symptoms.

able in a bottle of emedastine. Because emedastine was more effective than levocabastine, the costs of failure of the former were lower. Consequently, 42 days of treatment started with emedastine costs that were less than those with levocabastine, except for in France, The Netherlands and Norway where less than EUR1 had to be paid per additional symptom-free day. Since emedastine provided more days without symptoms, this model suggests that emedastine economically dominates levocabastine in the treatment of AAC in Belgium, Germany, Portugal and Sweden, and reaches a low cost-effectiveness ratio in France, The Netherlands and Norway, although no official thresholds have been published in AAC.

Sensitivity Analysis

Sensitivity analyses were performed on the parameters associated with a high level of uncertainty: the ratio of private/public paying patients, the ratio of ophthalmologists/GPs in the treatment of AAC and extreme values of the first-line failure cost.

The results of the main sensitivity analyses are presented in table VI and figure 2. In Germany and Portugal, emedastine was always less expensive than levocabastine. In the other countries, the additional cost was always lower than EUR1.5 per symptom-free day.

Discussion

Levocabastine was chosen as the comparator since this was one of the most potent and well documented topical compounds in the treatment of AAC. One study[61] has demonstrated the equivalence of levocabastine and lodoxamide in the treatment of AAC, whereas a comparison between lodoxamide and isospaglumic acid showed the superiority of lodoxamide on ocular symptoms,[62,63] indirectly suggesting a better efficacy for levocabastine over isospaglumic acid. Individual studies have demonstrated the equivalence (a trend in favour of levocabastine without statistical significance)[64,65] or the superiority[66-68] of levocabastine over cromoglycates. This was confirmed by a review of the clinical trials performed by Janssens[69] and Noble and McTavish,[70] supporting the better efficacy of levocabastine, although the efficacy of sodium cromoglycate 2% is still debatable since this low concentration is associated with a mediocre level of efficacy,[62,66] even against placebo. Lastly, azelastine did not show any superiority over levocabastine.[71]

Our results were based on modelling since no economic parameters were collected during the clinical trial. However, it has to be emphasised that the primary objective of the clinical trial was to

evaluate redness and itching, and, therefore, several compulsory visits were scheduled in the protocol to determine the onset of action. As most of the cost would have been protocol driven in this trial,[72] no resource utilisation data were collected.

The cost of failure after first-line treatment was estimated from a small sample of ophthalmologists and GPs since we did not expect large variability. This was confirmed by our findings.

No costs related to adverse effects were included in this model, since the tolerability of the 2 drugs was found to be similar, and, therefore, they would not have contributed to the cost difference between the 2 strategies.

Indirect costs were not taken into account. This was due to the lack of national statistics. Nevertheless, the number of days of work missed is expected to be low for a nonsevere and acute disease; consequently, indirect costs should have very few consequences for the results of our study. Indeed, since the full activity of antihistamines is reached after 3 or 5 days of treatment, patients could make up for this lost time when returning to work. Even in case of failure, patients could go back to the practitioner within 3 days and obtain topical corticosteroids, which are efficacious very quickly. Lastly, not including indirect costs leads to an underestimation of the true benefits of emedastine.

We took efficacy measures from our clinical trial as a proxy of effectiveness since, at that time, no national data were available. This is in accordance with most of the international health economics guidelines. In fact, if withdrawals were accounted for in clinical trials, and if these were integrated when calculating the costs of failure, efficacy would have been close to effectiveness. However, the dosages of the 2 drugs were fixed by the protocol and might, therefore, have been far from usual practice. Lastly, concomitant medications were fixed by the protocol and their use might differ in usual practice.

Therefore, despite the methodological difficulties, the sensitivity analyses we performed showed the robustness of our findings, including the extreme sensitivity analysis based on the minimal and maximal costs reported during the practitioner interviews. Emedastine dominated levocabastine except in France, The Netherlands and Norway, where the incremental cost was lower than EUR1 per symptom-free day.

France had the highest incremental cost-effectiveness ratio, because the price of levocabastine in France is very low, 50% less than in the other countries. Overall, drug prices in France are lower than in other EU countries, a fact that is even more pronounced with ophthalmological drugs.[73] Therefore, for a new drug to be more cost effective, its incremental efficacy must be very high, and it is possible for ceiling effects to jeopardise the valuation of innovation. Nevertheless, the incremental cost to be paid per day without symptoms is rather low. On a French budget approach, knowing that about 300 000 episodes of AAC are treated with levocabastine per year,[53] an additional EUR2.1 million would have to be allocated for the treatment of AAC if all patients were switched to emedastine, which represents less than 2.5% of the drug costs for this disease.

Table VI. Sensitivity analyses of incremental cost (a negative figure represents savings with emedastine) in euros (2000 values) of 42 days of treatment started either with levocabastine or with emedastine according to different scenarios. The economic perspective is that of the treatment provider

Scenario	Belgium	France	Germany	The Netherlands	Norway	Portugal[a]	Sweden
Patients treated by general practitioner	0.09/DFS	0.96/DFS	–5.72	0.14/DFS	0.08/DFS	–1.79	–0.93
Patients treated by ophthalmologist	–0.82	0.70/DFS	–1.41	–4.09	–2.05	–8.82	–4.21
Minimal cost of failure	0.30/DFS	1.47/DFS	–0.24	0.37/DFS	0.34/DFS	–4.43	0.21/DFS
Maximal cost of failure	–2.54	0.02/DFS	–10.36	–3.56	–0.65	–9.85	–8.01

a Cost of isospaglumic acid (NAAGA) taken as a proxy of the cost of levocabastine since the latter is not available on the market.

DFS = day free of symptoms.

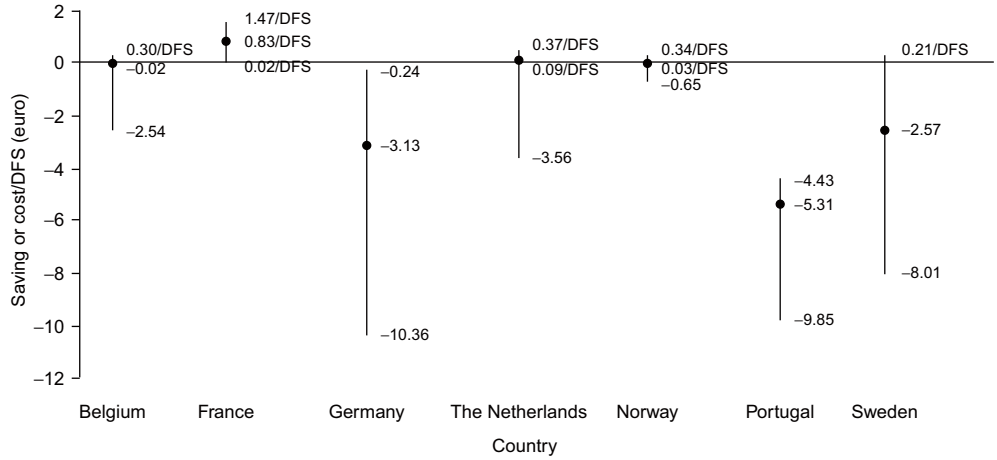

Fig. 2. Incremental costs and cost-effectiveness ratios of emedastine versus levocabastine. Confidence limits were calculated according to the extreme scenario. Negative values reflect savings from emedastine. Positive values reflect the incremental cost to be paid per incremental day free of symptoms (DFS).

From a macroeconomic point of view, the cost-shifting generating the savings observed in several countries is likely to occur since it is directly linked to the incremental efficacy of emedastine and, therefore, does not require any adaptations of the organisation of the healthcare system: emedastine avoids some visits only because of its better efficacy (cost-shifting within and only within the outpatient envelope).

Finally, besides the economic consequences, efficacious treatment is the way to avoid the short and long term complications of allergic conjunctivitis, which were not taken into account in our short term modelling approach. Moreover, symptoms of AAC are linked with deterioration of quality of life.[12,13] The isotropic hypothesis suggests that increasing the number of symptom-free days will have positive consequences for quality of life.

Conclusion

On the basis of the results of a randomised clinical trial, and resources and costs associated with treatment failure estimated through clinician interviews, our economic model found that emedastine is a cost-effective treatment of AAC in Belgium, France, Germany, The Netherlands, Norway, Portugal and Sweden.

Acknowledgements

The clinical trial was supported by an unrestricted grant from Alcon Laboratories Inc., Fort Worth, Texas, USA, and was conducted according to the local laws of each participating country. The economic analysis was supported by an unrestricted grant from Alcon France SA, Rueil-Malmaison, France.

References

1. Allansmith MR. Immunology of the external ocular tissues. J Am Optom Assoc 1990; 61: S16-S22
2. Friedlaender MH. Allergic and multisystem disease. In: Friedlander MH, editor. Allergy and immunology of the eye. 2nd ed. New York (NY): Raven Press, 1993: 259-60
3. Weeke ER. Epidemiology of hay fever and perennial allergic rhinitis. Monogr Allergy 1987; 21: 1-20
4. Smith JL. Epidemiology and natural history of asthma, allergic rhinitis and atopic dermatitis. In: Middleton Jr E, Reed CE, Elli E, et al. editors. Allergy: principle and practice. Vol. 2. St Louis (MO): CV Mosby, 1988: 891-929
5. Croner S, Kjellman MH. Development of atopic disease in relation to family history and cord blood IgE levels. Pediatr Allergy Immunol 1990; 1: 14-20
6. Naclerio R. Allergic conjunctivitis. N Engl J Med 1991; 325: 860-9
7. Dodge R, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. Am Rev Respir Dis 1980; 122: 567-75
8. Dart JKG, Buckley RJ, Monnickendan M, et al. Perennial allergic conjunctivitis: definition, clinical characteristics and

prevalence. A comparison with seasonal allergic conjunctivitis. Trans Ophthalmol Soc U K 1986; 105 (5): 513-20
9. Friedlander MH, Okumuto M, Kelley L. Diagnosis of allergic conjunctivitis. Arch Ophthalmol 1984; 102: 1198-9
10. Abelson MB, Weintraub D. Levocabastine eye drops: a new approach for the treatment of allergic conjunctivitis. Eur J Ophthalmol 1994; 4 (2) : 91-101
11. Knight A. The role of levocabastine in the treatment of allergic rhinoconjunctivitis. Br J Clin Pract 1994; 48 (3): 139-43
12. Juniper EF, Thompson AK, Ferrie PJ, et al. Validation of the standardized version of the Rhino-conjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol 1999; 104: 364-9
13. De Graaf-in't Veld T, Koenders S, Garrelds IM, et al. Relationship between nasal hyperreactivity, quality of life, and nasal symptoms in perennial rhinitis. J Allergy Clin Immunol 1996; 98 (3): 508-13
14. US Department of Health and Human Services (DHHS). Asthma and allergies: an optimistic future. Bethesda (MD): DHHS, 1980. DHHS publication no. NIH80-388.
15. McMenamin P. Cots of hay fever in the United States in 1990. Ann Allergy 1994; 73: 35-9
16. Drummond M, Stoddard G, Torrance G. Methods for economic evaluation of health care programmes. Oxford: Oxford University Press, 1989
17. Verin Ph, Easty LD, Secchi A, et al. Clinical evaluation of twice daily emedastine 0.05% eye drops (Emadine® eye drops) versus levocabastine 0.05% eye drops in patients with allergic conjunctivitis. Am J Ophthalmol. In press
18. Pocock SJ. Clinical trials: a pragmatic approach. New York (NY): John Wiley and Sons, 1983
19. Council Regulation (EC) No. 2866/98 of 31 December 1998 on the conversion rates between the euro and the currencies of the Member States adopting the euro. Official Journal of the European Communities 1999 Dec 31: L359/1-L359/2
20. Alves Da Silva E, Gouveia PC, Sampaio C, et al. Methodological guidelines for economic evaluation studies of medicines. Lisbon: Ministry of Health, National Institute of Pharmacy and Medicines (Infarmed), 1998
21. Collège des économistes de la santé. Rapport d'une commission d'experts présidée par le Pr Emile Lévy, sous l'égide du collège des économistes de la santé. Recommandations de bonnes pratiques des méthodes d'évaluation économique des stratégies thérapeutiques. Paris: Société Française d'Evaluation des Soins et des Technologies, 1997
22. German recommendations for health care economic evaluation studies. Revised version of the Hannover consensus. Hannover consensus group. Med Klin 2000; 95 (1): 52-5
23. Belgium Society for Pharmacoepidemiology. A proposal for methodological guidelines for economic evaluation of pharmaceuticals. Antwerpen: Belgian Society of Pharmacoepidemiology – Pharmaco-Economic Committee (ESPE-PEC), 1995
24. Belgium Society for Pharmacoepidemiology. Perspectives for pharmaco-economic evaluation in Belgium. Antwerpen: Belgian Society of Pharmacoepidemiology – Pharmaco-Economic Committee (ESPE-PEC), 1998
25. Health Insurance Council. Dutch guidelines for pharmacoeconomics research. Amstelveen: Zickenfondstaad, 1999. Publication no. CURE/cuo.228/2
26. Norwegian guidelines for pharmaco-economic analysis in connection with application for reimbursement. Oslo: The Norwegian Medicines Control Authority Department of Pharmacoeconomics, 1999 Nov
27. Data on file, Institut National d'Assurance Maladie-Invalidité (Bruxelles), 2000
28. Nomenclature générale des actes professionnels. Nomenclature des actes professionnels. Paris: Union des caisses nationales de Sécurité Sociale, 2000
29. Dumesnil S, Grandfils N, Le Fur P, et al. Santé, soins et protection sociale en 1997, Enquête sur la santé et la protection sociale 1997, N°1255. Paris: CREDES éditeur, 1999 Feb
30. Broglie MG, Pranschke-Schade S, Schade H-J, et al. Gebühren – Handbuch 2000. Kommentar für Ärzte. EBM. GOÄ. Wiesbaden: Inter Medical Kommunikations GmbH, 2000
31. Grunddaten zur Vertragsärzlichen Versorgung in der Bundesrepublik Deutschland. Köln: Kassenärztlichen Vereinigungen, 2000
32. LINH (Landelijk Informatie Netwerk Huisatsenzorg) jaarrapport Kompas. Utrecht: Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Nivel), 1998
33. Data on file, NMA, Norwegian Medical Association (Oslo), 2000
34. Portaria no. 348-B/98, Diário da República, Número 138/98, 2.° Suplemento, I-Série B, de 18 de Junho 1988, Lisboa
35. Codigo de nomenclatura e valor relativo de actos medicos. Lisboa: Ordem dos medicos, 1998
36. Landstingförbundets årliga sammanställning av patientavgifter i öppen hälso-och sjukvård ån 2000. Stockholm: The Federation of Swedish County Council, 2000
37. Socialstyrelsen. Socialstyrelsons meddelandeblad nr 16/99: om högkostnadsskydd vid köp av läkemedel m.m. från och med den 1 juni 1999. Stockholm: The National Insurance Board Statistics, 1999
38. Associations Pharmaceutiques Belges. Tarif des spécialités pharmaceutiquesn n°2. Bruxelles: La Société Royale, 2000 Apr
39. Edition du Vidal. Paris: Vidal, 2000
40. Lauer taxe. Fürth: Pharma Daig & Lauer GmbH, Fischer Software GmbH, 2000 May
41. Z-Index, May 2000. Den Haag: Uitgave van Z-Index, 2000
42. Van der Kuy A, editor. Farmacotherapeutisch Kompas. Amstelveen: College voor Zorgverzekeringen, 1999
43. Felleskatalogen. 42nd ed. Oslo: Elanders Publishing, 2000
44. Simposium terapêutico. Enciclopedia de especialidades farmacêuticas Portuguesas. Lisbon: Ed Simposium, 1999
45. LINFO. Farmaceutiska Specialiteter i Sverige (FASS) 2000. Stockholm: Läkemedelsinformation AB, 2000
46. Nomenclature générale des actes professionnels. Nomenclature des actes de biologie médicale. Paris: Union des caisses nationales de Sécurité Sociale, 2000
47. Tarieflijst Instellingen. Utrecht: CTG (Centraal Tarieven Gezondheidszorg), 1999
48. Utrecht: CTG (Centraal Tarieven Gezondheidszorg), 2000. TB-Number 5600-1000-00-1
49. Utrecht: CTG (Centraal Tarieven Gezondheidszorg), 2000. TB-Number 5600-1500-00-1
50. Utrecht: CTG (Centraal Tarieven Gezondheidszorg), 2000. TB-Number 5600-1900-00-1
51. Data on file, Rikstrygdeverket (Oslo), 2000
52. Hälso-och sjukvårdens ansvarsnämnd (HSAN). Stockholm: Avgiftshandboken, 2000
53. Data on file, IMS Data (Paris), 2000
54. Data on file, IMS Data (Bruxelles), 2000
55. Data on file, IMS Data (Frankfurt), 2000
56. Data on file, IMS Data (Amsterdam), 2000
57. Data on file, IMS Data (Oslo), 2000
58. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek: methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor Zorgverzekeringen, 2000
59. Data on file, IMS Data (Lisboa), 1999

60. Study C-95-54. Internal report. Fort Worth (TX): Alcon Laboratories, 1997. (Data on file)
61. Richard C, Trinquand C, Bloch-Michel E. Comparison of topical 0.05% levocabastine and 0.1% lodoxamide in patients with allergic conjunctivitis. Study Group. Eur J Ophthalmol 1998; 8 (4): 207-16
62. Denis D, Bloch-Michel E, Verin P, et al. Treatment of common ocular allergic disorders; a comparison of lodoxamide and NAAGA. Br J Ophthalmol 1998; 82 (10): 1135-8
63. Gunduz K, Ucakhan O, Budak K, et al. Efficacy of lodoxamide 0.1% versus N-acetyl aspartyl glutamic acid 6% ophthalmic solutions in patients with vernal keratoconjunctivitis. Ophthalmic Res 1996; 28 (2): 80-7
64. Ciprandi G, Cerqueti PM, Sacca S, et al. Levocabastine versus cromolyn sodium in the treatment of pollen-induced conjunctivitis. Ann Allergy 1990; 65 (2): 156-8
65. Frostad AB, Olsen AK. A comparison of topical levocabastine and sodium cromoglycate in the treatment of pollen-provoked allergic conjunctivitis. Clin Exp Allergy 1993; 23 (5): 406-9
66. Azevedo M, Castel-Branco MG, Oliveira JF, 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; 21 (6): 689-94
67. Odelram H, Bjorksten B, Klercker T af, et al. Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis. Allergy 1989; 44 (6): 432-6
68. Davies BH, Mullins J. Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis. Allergy 1993; 48 (7): 519-24
69. Janssens MM. Levocabastine: a new topical approach for the treatment of paediatric allergic rhinoconjunctivitis. Rhinol Suppl 1992; 13: 39-49
70. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. Drugs 1995; 50 (6): 1032-49
71. 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): 161-70
72. Drummond MF, Davies L. Economic analysis alongside clinical trials: revisiting the methodological issues. Int J Technol Assess Health Care 1991; 7: 567-73
73. Le secteur de l'ophthalmologie pharmaceutique. Revue de l'ophtalmologie Française 1999; 117: 52-5

Correspondence and offprints: Dr *Gilles Berdeaux*, Alcon France, Rue Henri Sainte-Claire Deville 4, F-92563 Rueil-Malmaison Cedex, France.
E-mail: gilles.berdeaux@alconlabs.com