EXPERT REVIEWS

Pharmacoeconomics of levocetirizine in allergic rhinitis and chronic idiopathic urticaria: considerations for the USA

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Background: Levocetirizine, a recent, second-generation oral antihistamine, was approved by the US FDA in May 2007 to treat symptoms of allergic rhinitis and chronic idiopathic urticaria. **Objective:** To review the economic literature for levocetirizine. **Methods:** Two reviewers conducted a systematic review of the literature to identify abstracts that met the inclusion criteria. Abstracts that were considered acceptable were retrieved with full text for further assessment. **Results:** A total of 82 potential studies were identified. After reviewing abstracts, 11 articles were preselected for potential inclusion. Of the 11 full-text articles, three articles met the inclusion criteria. **Conclusion:** The pharmacoeconomic literature for levocetirizine was limited. The findings were consistent across the literature, suggesting levocetirizine improved outcomes, leading to incremental cost savings and cost-effectiveness. Since many of the available levocetirizine data come from European studies, differences in practice patterns and medical resources should be considered when extrapolating data to a US clinical setting.

KEYWORDS: absenteeism • allergic rhinitis • chronic idiopathic urticaria • health-related quality of life • incremental cost savings • indirect costs • presenteeism

Allergic rhinitis (AR) is estimated to affect 10–30% of adults and up to 40% of children in the USA, making it the sixth most common chronic illness [101]. This disease commonly develops before the age of 20 years, with its prevalence increasing throughout childhood and peaking during adolescence [1]. Common symptoms include sneezing; rhinorrhea; itchy nose, palate and/or throat; itchy, watery eyes; and nasal congestion. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, developed by the American Academy of Allergy, Asthma and Immunology in collaboration with the WHO, define persistent AR (PER) as rhinitis with symptoms present for more than 4 days a week, lasting for more than 4 weeks [2].

Until recently, AR was merely considered a healthcare nuisance and was not included in the regular health surveys conducted by the US government. However, data from the National Ambulatory Medical Care Survey show that AR was responsible for more than 1 million physician office visits in 2005, putting it in the top 20 primary diagnostic groups and making AR a significant economic burden on the healthcare system [102].

In terms of overall economic burden of illness, allergic rhinitis ranks fifth among chronic conditions in the USA. This is according to a study that combined published productivity data and cost estimates drawn from a large medical/occupational database [3]. Average medical costs and the costs of absenteeism, short-term disability and presenteeism can total up to US$271 per eligible employee per year [3]. This figure does not include the costs of treating comorbid conditions associated with AR, such as sinusitis, upper respiratory infections, otitis media with effusion and nasal polyps. Moreover, AR can aggravate asthma; several studies have documented that treatment costs are significantly higher in patients with comorbid AR and asthma than in those with asthma alone [4,5].

It is also well established that AR reduces quality of life. In particular, AR can affect the quality of sleep [6,7] and contribute to secondary

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daytime somnolence, learning impairment, decreased cognitive performance and decreased productivity in both children and adults [8–10]. In a nationally representative survey of US allergists conducted in January 2006 [103], 52% of patients with AR employed full-time were reported to have missed work in the past 12 months due to AR, or had AR symptoms that interfered with their work performance [11].

In another large survey conducted from December 2001 to September 2002, 55% of 8267 US employees reported experiencing AR symptoms for an average of 52.5 days per year [12]. Employees with AR were absent from work for 3.6 days per year because of their condition and were unproductive 2.3 h per work day when experiencing symptoms. In this study, the average total cost of absenteeism and presenteeism was US$593 per employee per year.

Chronic idiopathic urticaria (CIU) affects only an estimated 0.5% of the population, although approximately 15% experience some form of urticaria during their lifetime. This condition is defined as daily or almost daily occurrence of wheals (small swelling of the skin) and pruritus (intense itching sensation) for 6 or more weeks when there is no identifiable cause, such as predominant physical urticaria or urticarial vasculitis. The pruritus can be relentless and the wheals can be cosmetically disfiguring. Angioedema occurs concurrently with CIU in 90% of cases, but systemic symptoms are rare [13]. No current epidemiologic data on CIU are available, partly because many studies are confounded by inclusion of physical urticarias. Some estimate that the average duration of CIU in adults is 3–5 years [13].

In the first study to document what chronic urticaria (CU) means from a patient's quality-of-life perspective, at least half of 142 subjects diagnosed with CU reported that the condition interfered with work, sleep, home management, social interaction and sexual relationships [14]. Among 103 subjects who were employed, the mean number of days lost from work was 6.4 (range: 1–31) over a 4-week period and 74% of patients reported that their work performance had deteriorated. The researchers also found that sleep disruption in the patients with chronic urticaria was greater than that in a previously studied sample of 98 patients awaiting coronary bypass graft surgery. Scores for energy, social isolation and emotional reactions were similar for the two groups. Subsequent studies have confirmed considerable impairment of quality of life in patients with untreated CU or CIU [15–17].

Levocetirizine (XYZAL®) is the active enantiomer of cetirizine. Levocetirizine has high selectivity for the human H_1 receptor [18], suggesting minimal potential for anticholinergic side effects. It is absorbed rapidly, with a peak plasma level 0.9 h after dosing and is minimally metabolized, implying a low risk of drug–drug interactions [104]. It was first launched in Europe in 2001 and is currently registered in more than 80 countries. The US FDA approved levocetirizine in May 2007 for use in adults and in children aged 6 years and older as an oral antihistamine to treat the symptoms of seasonal and perennial AR (SAR and PAR, respectively) and as a treatment for uncomplicated skin manifestations of CIU [104].

Objective

The objective of this article is to summarize and discuss the published pharmacoeconomic data for levocetirizine, a second-generation oral antihistamine recently approved in the USA for treatment of AR and CIU.

Methods

A comprehensive search of the international health economic literature to identify all published research reports related to the pharmacoeconomics of levocetirizine from inception to October 2007 was performed by two independent reviewers using Medline and EMBASE. Search terms included 'cost', 'levocetirizine', 'rhinitis', 'allergic', 'seasonal', 'perennial' and 'urticaria'. In case of discrepancies between the two reviewers, a third independent researcher acted as adjudicator for final recommendations. A first adjudicated list of potential studies to be included in the review served as the final list of references for which full-text articles were retrieved and assessed for inclusion in this review.

To be included, articles had to be about original research, describing either costs alone (i.e., cost analysis and budget impact analysis) or pharmacoeconomic evaluations reporting both costs and consequences (i.e., cost–benefit analyses, cost–consequence analyses, cost–effectiveness analyses, cost–minimization analyses or cost–utility analyses) of using levocetirizine in patients with AR, CIU or both. Excluded were studies evaluating drugs that did not include levocetirizine, medical conditions/diseases other than those targeted in this review, or both. Additionally, studies with a study design different from those listed or covering a subject other than economics (e.g., reviews, abstracts, letters to the editor, brief communications, clinical or humanistic studies, or likewise) were also rejected during the data extraction phase but were considered for other information, such as unique analytic reporting or for discussion purposes.

Studies were evaluated in a narrative fashion, wherein descriptions of all relevant information regarding methodologies (i.e., study design, patients studied, type of analysis, outcome measures and other parameters) were summarized. Finally, the economic data from the included studies were abstracted into tables describing the characteristics and main outcomes reported by the included studies.

Results

A total of 82 potential references were identified during the literature search. After reviewing the abstracts and applying the inclusion and exclusion criteria defined *a priori*, 11 articles were preselected for further assessment for potential inclusion. A total of 71 papers were rejected immediately after review of the abstracts for the following reasons: lack of economic information, indication other than AR or CIU, drugs of interest were not reported or data were on animal studies. Of the 11 full articles assessed, five studies were excluded because they did not

describe levocetirizine [19–23] and three were excluded because they were literature reviews [24–26]. Finally, three pharmacoeconomic studies evaluating levocetirizine were reviewed, two on AR and one on CIU [27–29]. The main characteristics of the included studies are described in Table 1.

In the first study, Bachert and colleagues evaluate the economic considerations of levocetirizine based on results from the XYZAL in Persistent Rhinitis Trial (XPERT), the first long-term (6-month) trial conducted in PER. Patients in this study also met the criteria of PER [27]. The authors conducted a cost–consequence analysis of the overall impact on treatment costs and quality of life when treating PER patients with levocetirizine. Since a majority of patients in this study were French (40.7%), the costs perspective was relative to French society and was reported in 2002 euros, based on resource utilization from the XPERT study.

The XPERT study was a double-blind, placebo-controlled, multicenter, multinational trial of 551 adults diagnosed with PER in five European countries (Belgium, France, Germany, Italy and Spain). Patients received either placebo or levocetirizine (5 mg, orally, every day) for 6 months. The primary end points were the health-related quality-of-life score as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at week 4 and the Total 5 Symptom score (rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus) [30]. Secondary end points included general health status as measured by the short-form patient questionnaire (SF-36), as well as assessment of pharmacoeconomic parameters for direct and indirect costs related to AR comorbidities, such as asthma, sinusitis and otitis media [31]. Direct costs included medical costs, drug costs and cost of comorbidities, while indirect costs included the estimated costs for absenteeism and presenteeism.

Overall, the placebo group's total costs were 160.27 versus 108.18 for the active treatment group (levocetirizine 5 mg). Indirect costs accounted for the highest proportion of total costs for both the placebo group (152.24) and the treatment group (89.61) [27]. Direct incremental costs were analyzed for working patients between the levocetirizine arm and the placebo arm, yielding an incremental cost of 10.54 for total direct costs for the levocetirizine group, but cost savings of 52.09 in productivity-related indirect costs per patient.

Similarly, for health-related quality of life as measured by the disease-specific instrument, the change from baseline for the placebo group versus treatment group was significant ($p < 0.001$), -1.01 versus -1.49, respectively, with the active treatment group demonstrating a greater improvement [27].

The authors concluded that levocetirizine appeared to provide meaningful improvements in patient quality of life and to decrease overall costs of the disease over the 6-month treatment period (Table 2). A full, incremental cost–effectiveness or cost–utility analysis was not performed.

In the second publication included in this review, Bousquet *et al.* also analyzed data from the XPERT study relative to French society (all costs), French social security (reimbursed

Table 1. Description of pharmacoeconomic studies of levocetirizine in allergic rhinitis and chronic idiopathic urticaria.

Author (year)	Country (costing source)	Perspective	Type of evaluation	Disease condition	Study drug	Comparator	Cohort description	Study time horizon	Ref.
Bachert (2004)	France	Societal	Cost–consequence analysis	AR	Levocetirizine	Placebo	Persistent AR patients	6 months	[27]
Bousquet (2005)	France	Employer, societal, social security	Cost–consequence analysis	AR	Levocetirizine	Placebo	Persistent AR patients	6 months	[28]
Kapp (2006)	France	Payer, societal	Cost–effectiveness analysis	CIU	Levocetirizine	Placebo	Patients with CIU (i.e., episodes of hives of characteristic wheal and flare appearance, occurring regularly [at least three times a week for at least 6 weeks during the previous 3 months] without identifiable cause)	30 days	[29]

AR: Allergic rhinitis; CIU: Chronic idiopathic urticaria.

Table 2. Summary of outcomes, sensitivity analyses, study limitations and conclusions of levocetirizine in allergic rhinitis and chronic idiopathic urticaria.

Study	Disease condition	Pharmacoeconomic outcome	Parameters modified in sensitivity analyses	Results of sensitivity analyses
Bachert (2004)	AR	Improvements in SF-36 and RQLQ overall scores. Reduction in costs per working patient per month. Treatment cessation because of lack of effect, comorbidities and overall costs of disease and comorbidities per working patient per month (160.27 vs 108.18) were lower in the levocetirizine group.	N/A	N/A
Bousquet (2005)	AR	Incremental cost analysis per patient treated. Overall cost of PER patients without long-term therapy was 355.06 per patient per month. Levocetirizine yielded an additional cost of 2.78 per patient per month. However, levocetirizine reduced the total cost of the disease and its comorbidities by 152.93 per patient per month.	Monetary value of workdays lost	Uncertainty of the monetary value of a UDA day by assigning 25, 50 or 75% of the net salary to each UDA lost
Kapp (2006)	CIU	Incremental cost per pruritus-free day per month. The levocetirizine group experienced an additional mean 6.5 pruritus-free days per month. Treatment with levocetirizine was cost saving, with a mean gain of 91.93 per patient per month.	N/A	N/A

AR: Allergic rhinitis; CIU: Chronic idiopathic urticaria; HRQoL: Health-related quality of life; N/A: Not addressed; PER: Persistent allergic rhinitis; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; SF-36: Short-form version 36; UDA: Usual daily activities.

direct medical costs) and French employers (lost workdays), as shown in Figure 1 [28]. Days with usual daily activities (UDA) lost per month was used as the chosen outcome for the cost–consequence analysis, rather than quality-of-life measures.

From the societal perspective, which included all direct costs (levocetirizine, other medications and physician visits) and indirect costs (absenteeism, presenteeism, inability to perform or restricted UDA), the mean cost per patient per month for placebo versus levocetirizine was 355.06 versus 202.12 ($p < 0.001$), respectively [28]. From the social security perspective, an incremental cost of 2.78 per patient per month ($p < 0.001$) was seen in the levocetirizine group compared with the placebo group. From the employers' perspective, the net gain was 64.70 ($p < 0.001$) per patient per month in favor of levocetirizine versus no treatment. The treatment group had fewer mean lost days of work per patient per month versus patients in the placebo group (0.88 vs 1.49, respectively; $p < 0.01$) and utilized less medication (9.52, 23.38 mean days per patient; $p < 0.01$) compared with placebo. All cost data were based on 2002 euros. Overall, the authors concluded that treatment costs for AR and its comorbidities were reduced with long-term use of levocetirizine compared with placebo. Although some uncertainties were present regarding the true value assigned to UDA days lost, levocetirizine appeared to remain superior to placebo following one-way sensitivity analyses (Table 2), including a sensitivity analysis limited to data from the subgroup of French patients alone [28].

The third pharmacoeconomic evaluation of levocetirizine, published by Kapp and colleagues [29], was a cost–effectiveness analysis based on pooled data from two randomized, double-blind, placebo-controlled trials of CIU patients. The effectiveness outcome measure was pruritus-free days (PFD) experienced by patients within a 30-day period (PFD_{30}). Components of cost included medications used, medical procedures and hospitalizations for CIU or treatment of adverse events and productivity (i.e., work days lost). Productivity costs were estimated based on full days off work (absenteeism) and productivity loss while at work (presenteeism). Data for both absenteeism and presenteeism were based on fielding of the pharmacoeconomic indirect cost questionnaire. All costs were reported in 2002 euros from the French societal perspective.

Mean PFD_{30} was higher in the levocetirizine group at baseline and during the treatment period with the pooled data, with only the between-group differences during the treatment period differing significantly. Means over the treatment period for PFD_{30} for placebo versus treatment (levocetirizine 5 mg) were 5.5 versus 12 ($p < 0.001$), respectively. Incremental 6.5 PFD_{30} was observed for the treatment group compared with placebo [29].

When cost data (2002 French costs and monthly salaries) were applied to clinical outcomes for both direct and indirect components of total costs, the mean cost per patient per month for placebo versus treatment is 177.36 versus 85.43, respectively. The net difference, or incremental savings for the treatment group (Figure 2), was 91.93 ($p < 0.05$), primarily due to incremental productivity savings associated with levocetirizine [29].

The authors concluded that treating CIU with levocetirizine is dominant over placebo and that levocetirizine increases the number of PFDs from a societal perspective (Table 2) when compared with placebo.

Table 2. Summary of outcomes, sensitivity analyses, study limitations and conclusions of levocetirizine in allergic rhinitis and chronic idiopathic urticaria (cont.).

Study limitations	Primary conclusion(s)	Ref.
Use of French costs for all patients (trial included patients from Belgium, France, Germany, Italy, Spain)	Levocetirizine appears to be a rapid and effective antihistamine for the treatment of PER and provides a statistically significant and clinically meaningful improvement of symptom scores, overall HRQoL and pharmacoeconomic criteria, which are some of the key criteria for the successful treatment of the disease	[27]
Costs may underestimate burden in real practice; rescue medications monitored, limiting type and number of medications taken; some nonmedical costs not monitored, which may result in higher costs; uncertainty over true monetary value that can be assigned to workdays and UDA; use of French costs for all patients (trial included patients from Belgium, France, Germany, Italy, Spain)	The costs of nontreated PER and its comorbidities are substantial for society. These costs can be reduced through long-term treatment with levocetirizine	[28]
Data collected from two clinical trials; use of French costing for all patients; time horizon of the investigation limited to 30 days; levocetirizine treatment compared with placebo instead of existing therapies; productivity changes measured by the human capital method, which although pragmatic, may not be the most appropriate	Treating CIU with levocetirizine is dominant over placebo (i.e., it increases the number of pruritus-free days and leads to cost savings for society)	[29]

AR: Allergic rhinitis; CIU: Chronic idiopathic urticaria; HRQoL: Health-related quality of life; N/A: Not addressed; PER: Persistent allergic rhinitis; RQLQ: Rhinoconjunctivitis quality of life questionnaire; SF-36: Short-form version 36; UDA: Usual daily activities.

Discussion

The present literature review identified few articles reporting the economic impact of levocetirizine use in AR and CIU. Three publications were identified; two of them were cost–consequence analyses based on data from one randomized, controlled trial in PER, while the third was based on a pooled analysis of two randomized trials in CIU.

In each of the three pharmacoeconomic articles reviewed, improved outcomes were observed with levocetirizine when compared with placebo. Similarly, a greater reduction in costs was computed for levocetirizine treatment compared with no treatment. AR cost savings for levocetirizine ranged from 52.09 [27] to 152.93 [28] compared with placebo from the French societal perspective, while for CIU, the net benefit from the French societal perspective was 91.93 for levocetirizine compared with placebo (Table 3) [29].

The primary driver for incremental cost savings for both AR and CIU was indirect costs associated with the ability to perform daily activities, including fewer lost work days. As a proportion of the overall cost per patient per month, the contribution of indirect cost of treatment of AR was high, ranging from 91 [28] to 83% [27] for levocetirizine and 98 [28] to 95% [27] for the placebo group. Similarly, for CIU, the contribution of indirect costs as a proportion of overall costs was high for levocetirizine versus placebo, 84 and 92%, respectively [29]. Clearly, the contribution of indirect costs (absenteeism, presenteeism and restrictions of daily activities) as a proportion of the overall total cost (total cost equals direct and indirect costs) are important and significant considerations for AR and CIU and cannot be ignored when evaluating the costs and consequences of an intervention.

Important differences should be taken into consideration when adapting findings to the US clinical setting. Practice patterns and medical resources were not clearly stated or itemized and were captured in a controlled setting, making direct comparisons and projections difficult. Furthermore, unit costs for physician contacts and medical resources were not reported, further complicating the ability to adapt findings to a US setting.

Assuming, however, that these aspects are potentially similar when applied to a US setting, results might be equally significant to payers, employers and the US healthcare system overall. The reason for this assertion is twofold. First, the incremental cost savings of levocetirizine compared with placebo are greater in both indirect and overall costs. Second, with an estimated 10–30% of Americans affected by AR, the overall costs to the healthcare delivery system can be a significant burden; the greatest impact will thus likely be to employers, since most of the indirect costs are attributable to absenteeism and presenteeism.

From the payer's perspective, findings are also likely to be important, even though the contribution of direct costs (medical resources consumed) represents less than 10% of the overall cost. When applied to the general population with AR and CIU, the payer's initial cost of coverage for levocetirizine is likely to be more than offset by the reduction in direct costs associated with reduced frequency of physician visits and medical resources consumed versus placebo during the provision of care.

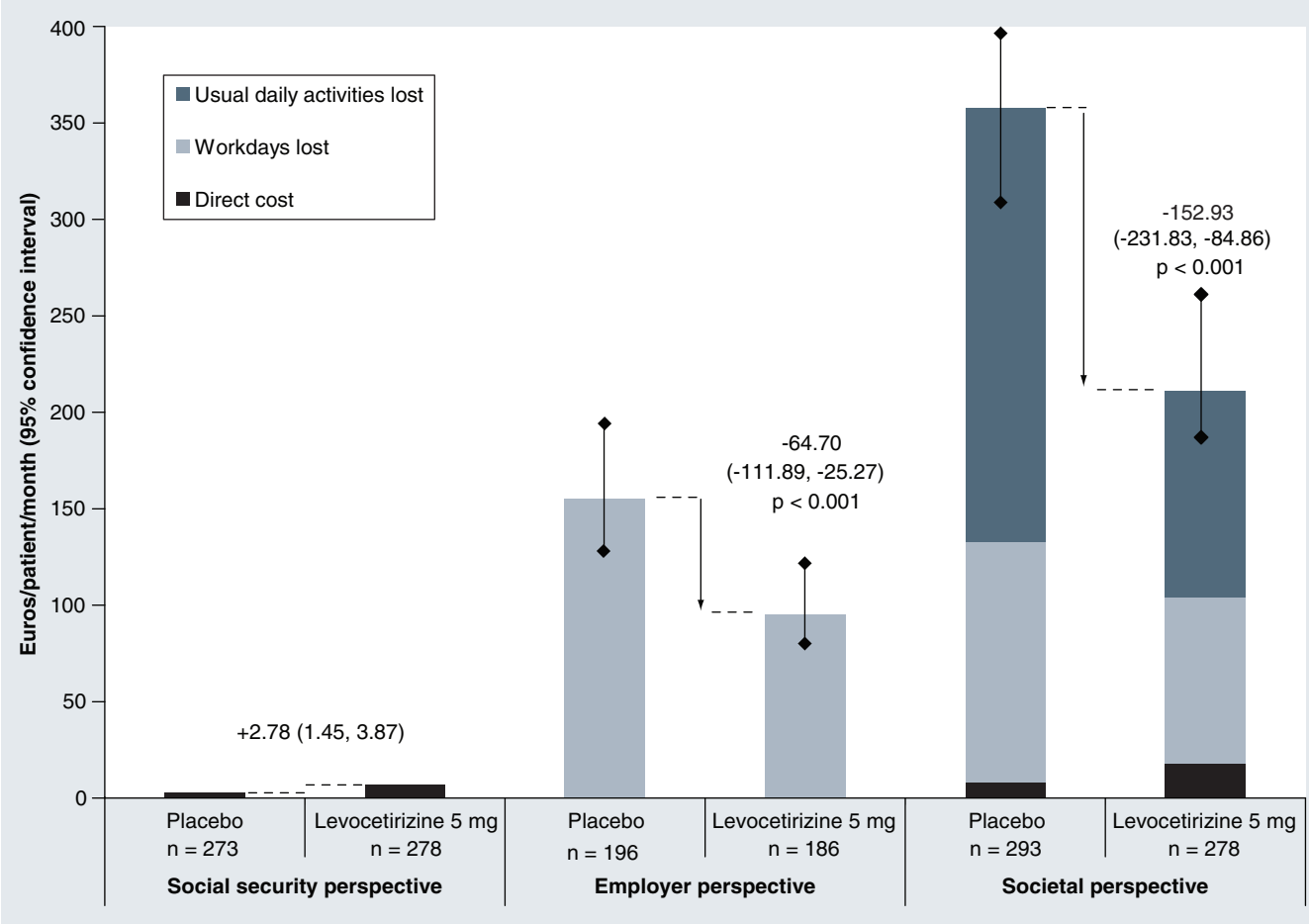

Figure 1. Cost in euros (95% confidence interval) per treatment group for persistent allergic rhinitis from the social security employer and societal perspective.
Adapted with permission from [28] © Blackwell Publishing, Oxford, UK.

Evidence from available clinical trials supports the use of levocetirizine for both AR and CIU. Levocetirizine has generally demonstrated superior suppression of histamine-induced wheal and flare compared with other second-generation antihistamines [32–35]. Clinical comparisons using environmental exposure units have generally shown levocetirizine to be efficacious when compared with fexofenadine and desloratadine in the overall relief of symptoms of SAR and PAR [36–38]. There is evidence that levocetirizine may also benefit nasal congestion, based on short-term environmental unit exposure studies [36–38] and longer term trials [39–41]. Levocetirizine has demonstrated efficacy over a 6-month clinical course in subjects with PER (as defined in the XPERT trial), with improvement of both ocular and nasal symptoms including congestion [27]. Finally, levocetirizine has been shown to be effective in relieving symptoms associated with CIU [29,42].

In summary, the results of all three studies clearly indicate a definitive impact on clinical outcomes leading to overall cost savings with levocetirizine treatment over placebo and no intervention, conservatively considering placebo as a proxy for the no-active-intervention option. However, head-to-head comparisons of levocetirizine against other active interventions (drug based or other) have not been identified through this literature review. Future cost–effectiveness studies are warranted for such direct comparisons and should clearly report all medical resources consumed and their corresponding unit costs. Furthermore, indirect costs relating to productivity will be critical for the US setting and an important consideration for both payers and employers.

Conclusion

Levocetirizine economic studies based on European cost information indicate that the use of levocetirizine results in cost savings compared with no treatment. Cost savings could also be expected in the USA. However, for USA-based cost–effectiveness studies with levocetirizine, head-to-head research with an active comparator is warranted.

Five-year view

The determination of which antihistamines will be used over the next 5 years will be driven both by efficacy and by the reduction of the economic burden associated with AR and CIU. Clinical studies of levocetirizine have already demonstrated unsurpassed efficacy and the potential to reduce the economic burden of both AR and CIU. With the recent approval of levocetirizine in the USA, more patients, employers and payers should benefit from the combination of efficacy and reduction of comorbid economic impact, positioning levocetirizine well over the next 5 years.

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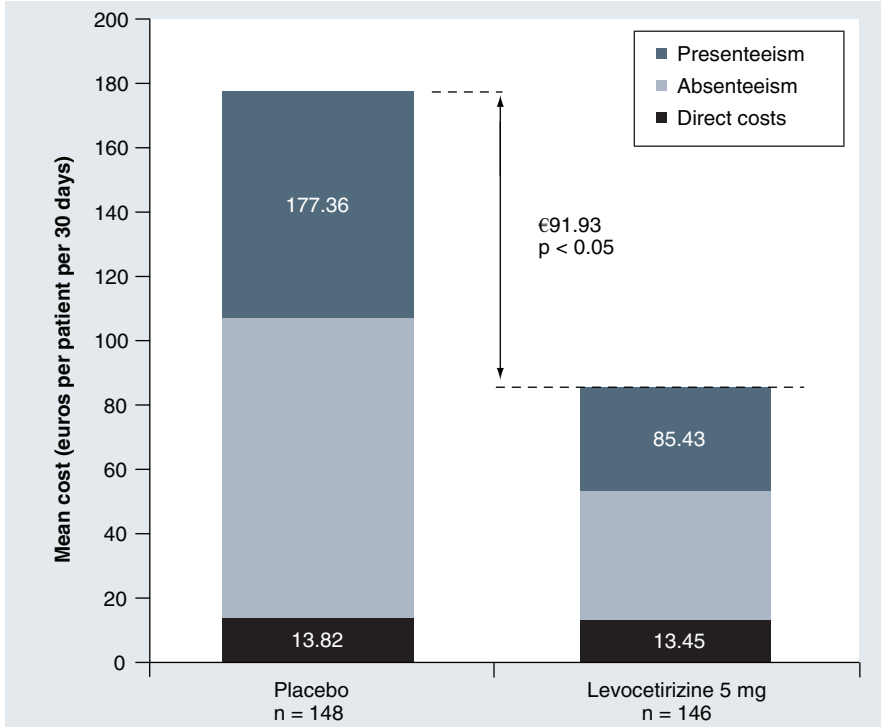

Figure 2. Mean costs for treating chronic idiopathic urticaria in the intent-to-treat population in the placebo and levocetirizine groups for the treatment period.
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Table 3. Summary of cost findings for levocetirizine versus placebo (euros).

Author (year)	Cost component	Placebo	Levocetirizine	Difference*	Ref.
Bachert *et al.* (2004)	Total direct costs	8.04	18.58	10.54	[27]
	Total indirect cost	152.24	89.61	-62.63	
Total difference (95% confidence interval): -52.09 (-98.18, -13.26)					
Bousquet *et al.* (2005)	Total direct costs	8.37	18.18	9.81	[28]
	Total indirect cost	346.7	183.93	-162.77	
Total difference (95% confidence interval): -152.93 (-231.83, -84.86)					
Kapp, Demarteau (2006)	Total direct costs	13.82	13.45	-0.37	[29]
	Total indirect costs	163.54	71.99	-91.55	
Total difference (95% confidence interval): -91.93 (-188.48, -0.68)					

*Difference = Levocetirizine minus placebo. Negative value indicates incremental cost savings with levocetirizine. Positive value indicates incremental savings with placebo.

Key issues

- The economic burden of allergic rhinitis and chronic idiopathic urticaria is high.
- Indirect costs represent a higher proportion of overall costs of these diseases compared with direct costs.
- Comparative clinical and economic data will help to clarify the relative cost–effectiveness of levocetirizine versus other currently available second-generation antihistamines.
- Levocetirizine appears to be a good first-line option for allergic rhinitis and chronic idiopathic urticaria and offers the potential to provide incremental savings to payers, employers and society.

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