ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Allergen immunotherapy for the treatment of allergic rhinitis, asthma, and/or insect sting allergy

FINAL PHARMACOECONOMICS REPORT

September 2015

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the allergen immunotherapies Drug Class Review

Acknowledgments

The Ontario Drug Policy Research Network (ODPRN) is funded by grants from the Ontario Ministry of Health and Long-term Care (MOHLTC) Health System Research Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations.

Study Team

Pharmacoeconomics Team: Doug Coyle, Karen Lee, Mirhad Lončar, Kylie Tingley

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Briefing

- This report assessed the current evidence regarding the comparative cost-effectiveness of allergen immunotherapies in the treatment of allergic rhinitis, asthma, and/or insect sting allergy.

- Previously published studies were generally supportive of the cost-effectiveness of allergen immunotherapy products in comparison with standard symptomatic therapy. Results, however, should be interpreted with caution as the majority of studies received industry funding and there was a lack of relevant Canadian studies.

List of abbreviations	
AAI	adrenaline auto-injector
AG	Assessment Group
CAD	Canadian Dollar
CBA	cost-benefit analysis
CCA	cost-comparison analysis
CEA	cost-effectiveness analysis
CUA	cost-utility analysis
EQ-5D	European Quality of Life-5 Dimensions
EUR	Euro
GBP	British Pound
HAD	high-dose antihistamine
HTA	health technology assessment
ICS	inhaled corticosteroids
NHS EED	National Health Service Economic Evaluation Database
NHS HTA	National Health Service Health Technology Assessment programme
NICE	National Institute for Health and Care Excellence
PhVIT	Pharmalgen venom immunotherapy
QALY	quality-adjusted life year
RCT	randomized controlled trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RSUI	Rhinitis Symptom Utility Scale
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
ST	symptomatic therapy
TBA	trial-based analysis
UK	United Kingdom

Contents

List of Exhibits

Executive Summary

Research Questions

RQ1. What is the current evidence for the comparative cost-effectiveness of allergen immunotherapy in the treatment of allergic rhinitis, asthma, and/or insect sting allergy?

RQ2. What is the budget impact of alternative policies for reimbursing allergen immunotherapy options versus placebo, other immunotherapies, or standard pharmacotherapy, in the treatment of allergic rhinitis, asthma, and/or insect sting allergy?

Systematic Review of Published Economic Evaluations

In brief, this review highlights the current published evidence on the comparative cost-effectiveness of pharmacologic treatments for the management of allergic rhinitis, asthma, and/or insect sting allergy. Since there were two recently well conducted reviews of economic evaluations which focused on the use of immunotherapy products in the treatment of relevant allergic disorders,[1,2] this review assessed published economic evaluations since 2011, when the last search was completed by the previous review authors. All economic evaluations selected for inclusion in this updated review received sponsorship from manufacturers of allergen immunotherapy products, and study findings consistently favoured the sponsor's product. The absence of well conducted independent analyses relevant to the current decision-making context precluded any inferences regarding the cost-effectiveness of immunotherapies for the treatment of allergic rhinitis, asthma, and/or insect sting allergy in Canada.

Two previous reviews of published economic evidence which examined the use of immunotherapy products in treating bee and wasp venom allergy and allergic rhinitis, respectively, were conducted by the NHS HTA programme in the UK; these reviews served as the basis for evaluating the cost-effectiveness evidence prior to this update. The first review was published in 2012 and aimed to assess the cost-effectiveness of Pharmalgen venom immunotherapy in the treatment of hymenoptera venom allergy; however, the review authors did not identify any relevant health economic studies. A second review was published in 2013 focusing on the cost-effectiveness of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) products for treating seasonal and perennial allergic rhinitis; a total of 14 relevant economic evaluations were identified. All of the identified studies were conducted within European settings and 11 of the 14 economic evaluations were funded by the pharmaceutical industry or had an author who was affiliated to a manufacturer. Overall, studies varied in their modeling methods, the assumptions made, as well as the effectiveness data used to model disease progression; variability among chosen perspectives was observed to a lesser extent as most analyses adopted a societal perspective or combination of perspectives. Findings across studies included in this review consistently favoured the use of immunotherapy, either SCIT or SLIT, over standard symptomatic treatment, with some evidence suggesting that SCIT may be more cost-effective than SLIT when the two treatments were directly compared. Nevertheless, the lack of Canadian-specific analyses and

dominance of industry-funded research limits the applicability of the results of these economic evaluations.

Since 2011, five additional published economic evaluations have been identified, all of which were conducted within European jurisdictions. The published evidence comprised three cost-utility analyses (two Markov models and one decision tree), one cost-effectiveness/cost-utility study, and one cost-comparison analyses based on trial data. None of the included studies were free from industry sponsorship, and direct comparisons between SLIT and SCIT therapies were only noted within two economic evaluations. In addition, study findings consistently supported the sponsor's product. Given these findings, coupled with the dearth of relevant Canadian literature, the generalizability of the results of this review as they relate to the current decision-making context is poor.

In the absence of well-designed independent analyses from the Canadian perspective, inferences regarding the cost-effectiveness of allergen immunotherapies in the treatment of allergic rhinitis, asthma, and/or insect sting allergy as they relate to the Canadian decision-making context should be made with caution. Given that the existing published evidence failed to adequately address the specific research question of this review, further research may be required to address this evidence gap.

For a detailed report of the review of economic literature relating to this drug class, refer to Appendix A – Systematic Review of Economic Evidence.

Budget Impact Analysis

See companion report "Allergen Immunotherapy Products: budget impact analysis" for budget impact analysis.

Appendices

Appendix A – Systematic Review of Economic Evidence

Research Question

What is the current evidence for the comparative cost-effectiveness of allergen immunotherapy in the treatment of allergic rhinitis, asthma, and/or insect sting allergy?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

In 2013, a health technology assessment (HTA) was published by the National Health Service Technology Assessment programme (NHS HTA) in the UK which explored the clinical and cost-effectiveness allergen immunotherapy options in the treatment of seasonal and perennial allergic rhinitis. Similarly, another HTA was published one year prior which examined the clinical and cost-effectiveness of venom immunotherapy in the treatment of bee and wasp venom allergy. Given that both of these HTA reports contained a systematic review of the cost-effectiveness literature relating to pharmacotherapies of direct relevance to the present review, they were used as the basis for assessing health economic evidence identified in the literature prior to January 2011, when the last searches were completed by the review authors.

A further search of the medical literature was conducted in Ovid MEDLINE (indexed, in-process and other non-indexed citations) and EMBASE Classic & EMBASE from 2011 to present (2015 May 08) in order to capture all relevant literature since the last search was completed by NICE. Key words relating to allergen immunotherapy options approved for use in Canada for the treatment of allergic rhinitis, asthma, and/or insect sting allergy (subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), multiallergen versus single allergen SCIT, and standard pharmacotherapy (e.g. intranasal steroids, antihistamines)) were coupled with a standardized search strategy for identifying economic analyses adopted by the National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

Additional citations were retrieved for screening from the Tufts CEA Registry and NHS EED databases. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE) websites. Finally, reference lists of retrieved studies were hand searched for additional relevant articles.

Search Findings

A total of 295 potential citations relating to cost-effectiveness of allergen immunotherapies for allergic rhinitis, asthma, and/or insect sting allergy since January 2011 were identified from the initial searches, all of which were found through database searching. No additional

records were identified from grey literature sources. Following the removal of duplicate records, 276 unique citations were retrieved for screening.

One reviewer (ML) assessed the titles and abstracts of studies identified by the search strategy in order to identify potential articles for critical appraisal. Namely, of the 276 unique records screened, 28 citations were selected for full-text review. A total of 248 records were therefore excluded in the first phase of screening, and an additional 23 records were excluded following assessment of full-text articles. Any uncertainties during this two-stage screening process were resolved through consultation with a second reviewer. Exhibit 1 in Appendix A2 presents the search results, including reasons for exclusion of full-text publications.

Among the 28 references that were retrieved for full-text review, a total of 5 unique studies addressed the objective of the review and were selected for inclusion. No additional potentially relevant studies were identified from hand-searching citations of included papers or manufacturer submissions. A list of excluded studies along with reasons for exclusion is presented in Exhibit 2 of Appendix A3.

Included Studies

A list of included studies post 2011 can be found in Exhibit 3 of Appendix A4.

Prior Reviews Conducted by the NHS HTA Programme (UK)

Review by NHS HTA in 2012

In 2012, Hockenhull et al.[1] conducted a systematic review of published economic evaluations focusing on Pharmalgen for the treatment of bee and wasp (hymenoptera) venom allergy. Although the authors identified three studies as part of the review process, none of the studies compared Pharmalgen with the selected comparators (i.e. adrenaline auto-injectors, high dose antihistamines or avoidance advice). Therefore, no published economic evidence relevant to the decision problem in this review was identified. The review, however, was limited to the use of Pharmalgen in the treatment of bee and wasp venom allergy and therefore did not assess the cost-effectiveness of venom immunotherapies in general.

Review by NHS HTA in 2013

More recently in 2013, Meadows et al.[2] conducted a review of the cost-effectiveness literature focusing on subcutaneous and sublingual allergen immunotherapy in adults and children with allergic rhinitis, and identified a total of 14 relevant published economic analyses. All of the included studies were conducted within European settings (Italy, Germany, France, Denmark, Czech Republic), with five analyses incorporating multiple settings. While most studies were labelled as CUAs (5 studies), there were also four cost-consequence analyses, two CEAs, and one CEA/CUA, one CEA/CBA, and one CEA/CCA. Treatment comparators comprised SCIT versus standard care (5 studies), SLIT versus standard care (6 studies), as well as SCIT and SLIT compared with standard care (2 studies); one study compared different forms of SCIT to SLIT and standard care. Nine studies modeled patients with seasonal allergic rhinitis while the remaining five included patients with both seasonal and perennial allergic rhinitis, with or without asthma. A societal perspective was adopted in six studies, as

compared with two studies which reported findings solely from the perspective of the health care payer, and another five which adopted a combination of cost perspectives; one study did not state the perspective of the analysis. Furthermore, more than 70% (11 out of 14) of the included studies received support from manufacturers of allergen immunotherapy products or had an author that was affiliated with industry; in contrast, there was only one independently-funded study and two which did not report any funding support.

When focusing on the single independently-funded CCA which examined the use of SLIT, SCIT, and symptomatic treatment from the Czech health care payer and societal perspective, base-case findings indicated that SLIT was associated with lower costs (from all perspectives) when compared with SCIT. However, these findings are based on a small (n=64) open-label trial, and limited by the study design as no combined measure of cost-effectiveness was derived.

Base-case results across industry-funded and industry-affiliated studies consistently favoured specific allergen immunotherapy, either SCIT or SLIT, over standard symptomatic therapy. Among seven studies which compared SLIT with standard care, SLIT was found to be cost saving or more cost-effective. Four of these studies further reported costs per QALY gained for the use of a specific SLIT therapy, Grazax, and all found Grazax to be cost-effective below a willingness-to-pay threshold of £20,000/QALY. Furthermore, all six studies which compared SCIT with standard treatment found that SCIT was associated with improved outcomes and/or reduced long-term costs. Two studies provided cost per QALY estimates for SCIT; one study revealed a low ICER while the other found that SCIT either dominated symptomatic therapy or was associated with a low ICER value. Nevertheless, significant uncertainty surrounded the results of the former study, and sensitivity analyses were lacking in the latter. Direct comparisons between SCIT and SLIT were only observed in one industry-affiliated study, and findings revealed that SCIT was more effective and more cost-effective over the long term, although results were limited by the study design and assumptions made.

In considering the body of cost-effectiveness literature, the review authors warned that caution should be taken when interpreting these results owing to the large number of country-specific analyses and differences in methodological approaches (limiting applicability), as well as due to limitations in the effectiveness data used, the assumptions made, and the fact that most studies received sponsorship from manufacturers of allergen immunotherapy products or had ties with industry.

Summary and Critical Appraisal of Included Studies Post 2011

Included Studies

Among the five economic evaluations published since 2011 that were selected for inclusion, four were conducted in Germany,[3-6] and there was one Italian study.[7] All five studies received sponsorship from pharmaceutical manufacturers. A brief overview of the study characteristics of these five economic analyses is presented in Exhibit 4 of Appendix A5.

Three of the included analyses were cost-utility analyses, two of which applied a Markov state transition model for estimating costs and outcomes,[5,6] and one which used a decision tree.[7] Moreover, one study was a Markov-based cost-effectiveness/cost-utility analysis,[4] and the

remaining analysis was a cost-comparison analysis based on a multicentre RCT which measured lung function in 65 patients suffering from mite-induced allergic asthma.[3] The time horizon considered across included studies spanned the period from 3 years[3] to 9 years.[4-6] Four analyses adopted a health care payer perspective,[3-6] while indirect costs and productivity losses were only accounted for in the study by Ruggeri et al. (2013).[7]

Treatment comparators across the included studies comprised subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) options evaluated against each other and/or in comparison with symptomatic therapy or placebo. Namely, two studies examined the comparative cost-effectiveness of SLIT and symptomatic therapy[4] or placebo,[7] while another study compared SCIT with a high-dose hypoallergenic preparation.[3] Conversely, SLIT was compared with both a mix of allergen compounds (SCIT) and symptomatic treatment in one CUA,[5] while two SLIT options (Oralair and Grazax) in comparison with a SCIT and symptomatic treatment were the focus of another economic evaluation.[6]

The target populations considered across these studies were adults with grass pollen-induced allergic rhinitis and/or conjunctivitis (3 studies),[5-7] as well as children and adolescents suffering from mite-induced allergic asthma or grass pollen-induced rhinoconjunctivitis, with or without concomitant asthma (2 studies).[3,4] All studies were based on European populations.

There were four studies which expressed their outcomes in terms of quality-adjusted life years (QALYs) gained; however, one trial-based analysis assessed the mean annual morning peak flow (lung function) in relation to the mean annual total costs associated with the treatment arms.[3] Utility estimates for modeled patient groups were largely derived from previously published literature, and two studies applied the Rhinitis Symptom Utility Scale (RSUI) as a proxy to estimate utility values.[5,6]

On the whole, findings reported in the selected review articles generally favoured either SCIT or SLIT over standard symptomatic treatment. Namely, two studies compared SLIT with symptomatic therapy or placebo, in children and adults respectively, and both found that SLIT was cost-effective at a willingness-to-pay threshold of £30,000/QALY gained.[4,7] Conversely, one study compared SCIT with standard care (high-dose hypoallergenic preparation) in children and adolescents with allergic asthma and found that SCIT was associated with better outcomes, but also with additional costs over the treatment course. In two studies where SLIT and SCIT were directly compared against each other and with symptomatic therapy, SLIT was found to be more cost-effective than SCIT and symptomatic therapy at £20,000/QALY willingness-to-pay over the 9-year time horizon.[5,6] One study assumed a disease-modifying effect of a specific SLIT therapy, Oralair, which led to fewer patients on this treatment developing chronic asthma; however, there is a lack of long-term effectiveness data to support this finding, limiting the utility of this study.[6] A detailed synthesis of the interventions and results of the included economic evaluations is presented in Exhibit 5 of Appendix A5.

Concerns and Considerations Relating to the Literature

Canadian Content

There were no published economic evaluations conducted from a Canadian perspective which addressed the research question of this review. Cost-effectiveness evidence relating to

allergen immunotherapy for the treatment of allergic rhinitis, asthma, and/or insect sting allergy is dominated by European country-specific analyses; as a result, any inferences that may follow from such analyses can be potentially misleading.

Sponsorship and Industry Affiliated Studies

In the previous reviews conducted by the UK NHS HTA programme, the majority of studies were sponsored by allergen immunotherapy manufacturers or had ties with industry. There was only independent analysis identified in the 2013 HTA report by Meadows et al.,[2] and two studies did not disclose any funding sources.

Since 2011, five additional economic evaluations were identified in the literature; however, all five studies received industry sponsorship. There studies may be susceptible to biases and limitations that have been found in manufacturer-sponsored evaluations.[8]

Canadian Studies

There were no economic evaluations identified in the published literature which examined the comparative cost-effectiveness of allergen immunotherapy options in the management of allergic rhinitis, asthma, and/or insect sting allergy from a Canadian perspective.

Non-Canadian Studies

Independent studies

There was only one independent economic evaluation identified in the published literature as part of the 2013 NHS HTA cost-effectiveness review. In addition, two independent economic analyses were conducted by the NHS HTA programme as part of the aforementioned HTA reports published in 2012 and 2013. Study findings are summarized below.

NHS HTA Economic Analyses (2012, 2013)

As part of the 2012 NHS HTA report, the Assessment Group (AG) conducted a cost-utility analysis to compare the cost-effectiveness of the concomitant use of pharmalgen venom immunotherapy (PhVIT) with high-dose antihistamine (HDA) and adrenaline auto-injector (AAI) in relation to HDA+AAI and avoidance advice only in the treatment of patients with a history of type 1 IgE-mediated systemic allergic reactions to bee and wasp venom. A 1-year cohort decision tree model was used to simulate disease progression over a course of 10 years from the perspective of the UK healthcare system. The economic model was populated using data elicited from available published literature, physician consultations and the results of a brief economics survey 44 allergy clinics in the UK which provide PhVIT.

Results of the base case analysis showed that in comparison with AAI+HDA, PhVIT+AAI+HDA was associated with an incremental gain of 0.00011 QALYs per patient at an additional cost of £2029 per patient (1.00 GBP = 1.59 CAD). Conversely, PhVIT+AAI+HDA was associated with an increase in 0.00029 QALYs and an additional cost of £2185 per patient compared with avoidance advice only. The ICER of PhVIT+AAI+HDA compared with AAI+HDA was therefore £18,065,527 per QALY gained, and an ICER of £7,627,835 per QALY gained was generated in comparison with avoidance advice. Two subgroups were also

considered in the economic evaluation: patients at high risk of future stings (five stings per year) and patients whose quality of life improves from reduced anxiety due to PhVIT. Base case findings indicated that PhVIT+AAI+HDA was dominant over both AAI+HDA and avoidance advice among the 'high risk of sting' patient subgroup, and that ICERs of £23,868/QALY and £25,661/QALY were generated in comparison with AAI+HDA and avoidance advice, respectively, among the patients experiencing a quality of life improvement from reduced anxiety; therefore, the AG drew the conclusion that the use of PhVIT+AAI+HDA may be cost-effective in both patient subgroups. Furthermore, sensitivity and scenario analyses demonstrated that base case findings were robust to changes in model assumptions. Nevertheless, a number of concerns were raised with respect to the data used to inform the economic model and assumptions made, limiting the applicability of the results.

Within the more recent 2013 NHS HTA, Meadows et al. conducted a cost-effectiveness/cost-utility analysis comparing SCIT, SLIT, and symptomatic therapy in the treatment of patients with seasonal allergic rhinitis. Two preferred Markov models were developed for adults and children, but a lack of suitable data on transition probabilities prevented the authors to populate the economic models. Instead, a simpler model was constructed which used data on quality of life improvement based on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) from direct and indirect comparison meta-analyses. Deterioration in disease was modeled over a course of 6 years from the perspective of the UK health care system. Utility values were assigned to each of the model's health states based on mapping changes in RQLQ to changes in European Quality of Life-5 Dimensions (EQ-5D) using several assumptions, and costs were obtained from published UK sources. Results were expressed as both costs per unit improvement in RQLQ and costs per QALY gained.

Base case findings revealed that immunotherapy (SCIT or SLIT), as compared with symptomatic treatment, became a cost-effective strategy after around 6 years of treatment at a willingness to pay threshold of £20,000-£30,000 per QALY. Based on the same threshold, SCIT was found to be cost-effective compared with SLIT after around 5 years. As a result of considerable uncertainty which surrounds these findings, especially uncertainty associated with the effectiveness estimate, the authors warn that results should be interpreted as purely suggestive and point out that they are based on a very simple analysis. Moreover, it was not possible to conduct a CEA for children due to a lack of available data, and potential cost-savings stemming from disease-modifying effects of allergen immunotherapy were not considered.

Industry-sponsored and industry-affiliated studies

All five economic evaluations identified since 2011 received sponsorship from manufacturers of allergen immunotherapy products, and the sponsor's product was favoured in all cases. This finding is consistent with the cost-effectiveness literature identified in the previous NHS HTA review, and it is not surprising given that skew in industry-funded pharmacoeconomic studies is well documented.[8] A detailed overview of these studies is presented in Exhibit 5 of Appendix A5.

Overall Conclusions

In brief, all studies identified in this updated review (post 2011) were of limited applicability to the current Canadian setting, owing mainly to the dominance of industry-sponsored, European country-specific analyses. There were no Canadian studies identified in previous reviews conducted by the NHS HTA programme; similarly, no Canadian economic evaluations were identified in the published literature since 2011.

Cost-effectiveness evidence suggests that well-designed independent analyses from the Canadian perspective are lacking, and further research may be required to address this evidence gap. In the absence of relevant Canadian evidence, caution should be taken when making inferences regarding the cost-effectiveness of allergen immunotherapies for the treatment of allergic rhinitis, asthma, and insect sting allergy in Canada.

Appendix A1: Search Strategy

The following is the search strategy used in Ovid interfaces MEDLINE and EMBASE for allergen immunotherapy in the treatment of allergic rhinitis and/or asthma:

Embase Classic+Embase (1980 to 2015 May 19), **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** (1946 to 2015 May 19)

1. Rhinitis, Allergic, Seasonal/
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab.
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab.
4. or/1-3
5. Rhinitis/
6. rhinitis.ti,ab.
7. or/5-6
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab.
9. Trees/ or Poaceae/
10. 8 or 9
11. 7 and 10
12. Desensitization, Immunologic/
13. allergens/
14. (desensiti* or hyposensiti*).ti,ab.
15. immunotherapy/
16. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab.
17. (grazax or pollinex or alutard).ti,ab.
18. or/12-17
19. 4 or 11
20. 18 and 19
21. exp animals/ not humans/
22. 20 not 21
23. 22 use pmrz
24. economics/
25. exp "costs and cost analysis"/
26. cost of illness/
27. exp health care costs/
28. economic value of life/
29. exp economics medical/
30. exp economics hospital/
31. economics pharmaceutical/
32. exp "fees and charges"/
33. (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
34. (expenditure$ not energy).tw.
35. (value adj1 money).tw.
36. budget$.tw.
37. or/24-36
38. 23 and 37
39. exp allergic rhinitis/
40. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab.
41. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season*

allergic).ti,ab.
42. or/39-41
43. rhinitis/
44. rhinitis.ti,ab.
45. 43 or 44
46. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab.
47. tree/ or grass pollen/
48. 46 or 47
49. 45 and 48
50. desensitization immunologic/
51. allergen/
52. (desensiti* or hyposensiti*).ti,ab.
53. immunotherapy/
54. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab.
55. (grazax or pollinex or alutard).ti,ab.
56. or/50-55
57. 42 or 49
58. 56 and 57
59. exp animal/ not human/
60. 58 not 59
61. 60 use emez
62. cost benefit analysis/
63. cost effectiveness analysis/
64. cost minimization analysis/
65. cost utility analysis/
66. economic evaluation/
67. (cost or costs or costed or costly or costing).tw.
68. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
69. (technology adj assessment$).tw.
70. or/62-69
71. 61 and 70
72. 38 or 71
73. remove duplicates from 72
74. limit 73 to yr="2011 -Current"

The following is the search strategy used in Ovid interfaces MEDLINE and EMBASE for venom immunotherapy in the treatment of insect sting allergy:

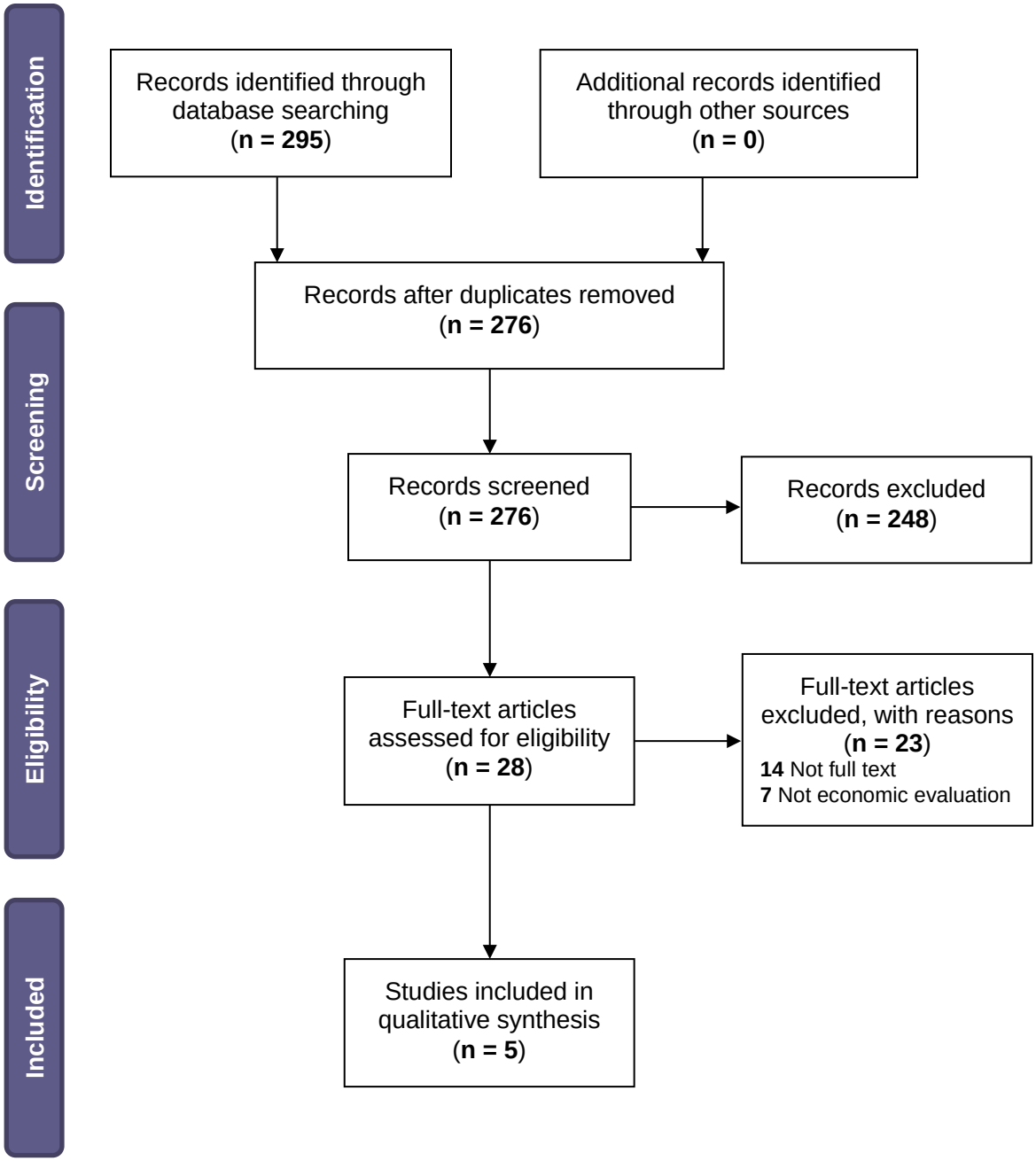
Embase Classic+Embase (1980 to 2015 June 9), **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** (1946 to 2015 June 9)

1. exp wasp/or exp bee/or exp hymenoptera/or exp bumblebee/or exp honeybee/or exp orchid bee/or exp stingless bee/
2. (wasp$ or bees or honeybee$ or bumblebee$ or orchid bee$ or yellow hornet$ or yellow jacket$ or white hornet$ or poliste$).tw.
3. exp hymenoptera venom/or exp bee sting/or exp bee venom/or exp wasp venom/
4. ((wasp$ or bees) adj (venom$ or sting$ or hypersensitivit$ or allerg$ or anaphyla$ or systemic reaction$)).tw.
5. (pharmalgen or venom immunotherapy).af.
6. exp pharmalgen/
7. or/1–4

8. or/5–6
9. 7 and 8
10. health economics/
11. exp economic evaluation/
12. exp "health care cost"/
13. exp pharmacoeconomics/
14. or/10-13
15. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
16. (expenditure$ not energy).ti,ab.
17. (value adj2 money).ti,ab.
18. budget$.ti,ab.
19. or/15-18
20. 14 and 19
21. 30 and 41
22. exp Wasps/or exp Bees/or exp Hymenoptera
23. (wasp$ or bees or honeybee$ or bumblebee$ or orchid bee$ or yellow hornet$ or yellow jacket$ or white hornet$ or poliste$).tw.
24. exp Wasp Venoms/or exp Bee Venoms/
25. ((wasp$ or bees) adj (venom$ or sting$ or hypersensitivit$ or allerg$ or anaphyla$ or systemic reaction$)).tw.
26. exp “Insect Bites and Stings”/
27. or/22-26
28. (pharmalgen or immunotherapy).af.
29. exp Desensitization, Immunologic/or *Immunotherapy/or Anaphylaxis/th
30. 28 or 29
31. 27 and 31
32. Economics/
33. exp "Costs and Cost Analysis"/
34. Value of Life/
35. exp Economics, Hospital/
36. Economics, Medical/
37. Economics, Nursing/
38. Economics, Pharmaceutical/
39. or/32-38
40. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
41. (expenditure$ not energy).ti,ab.
42. (value adj1 money).ti,ab.
43. budget$.ti,ab.
44. or/40-43
45. 39 or 44
46. 31 and 45
47. 21 or 46
48. remove duplicates from 47
49. limit 48 to yr="2011 -Current"

Appendix A2: Results of Search

Exhibit 1: Flow diagram of the selection process for potentially relevant studies.



Appendix A3: List of Excluded Studies

Exhibit 2: List of excluded studies and reasons for exclusion

Study Reference	Reason for exclusion
Apter AJ. Allergen immunotherapy: Much more than a shot in the dark. Journal of Allergy and Clinical Immunology. 2013;131(4):1092-3.	Not economic evaluation
Canonica GW, Passalacqua G. Disease-modifying effect and economic implications of sublingual immunotherapy. Journal of Allergy and Clinical Immunology. 2011;127(1):44-5.	Not economic evaluation
Cicchetti A, Ruggeri M, Fiocchi A, Bonini S, Puccinelli P, Passalacqua G, et al. Economic evaluation of grass tablets for immunotherapy (oralair) compared to placebo in adults and children in Italy [abstract]. World Allergy Organization Journal Conference: 22nd World Allergy Congress Cancun Mexico Conference Start: 20111204 Conference End: 20111208. 2012;5:S68-S69.	Not full text
Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: Examining efficacy, safety and cost-effectiveness of current and novel formulations. Immunotherapy. 2012;4(6):601-16.	Not economic evaluation
Currie CJ, Bannister CA, Andreasen JN, Andersen JS. Estimation of health-related utility (EQ-5D index) in subjects with seasonal allergic rhinoconjunctivitis to evaluate health gain associated with sublingual grass allergen immunotherapy. Health and quality of life outcomes. 2014;12(1):99.	Not economic evaluation
Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: An indirect analysis of efficacy, safety and cost. Journal of Evaluation in Clinical Practice. 2014;20(3):225-38.	Not economic evaluation
Garani V, Davila I, Dordal MT, Sampayo M. Pharmacoeconomic assessment of the use of a depigmented polymerised allergen extract in comparison to symptomatic treatment in patients with allergic rhinitis [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: 33rd Congress of the European Academy of Allergy and Clinical Immunology Copenhagen Denmark Conference Start: 20140607 Conference End: 20140611. 2014;69:187.	Not full text
Kennedy J, Borish L, Robinson D, Christophel J, Payne S. Decision making analysis for immunotherapy versus nasal steroids in the treatment of allergic rhinitis [abstract]. Annals of Allergy, Asthma and Immunology Conference: 2011 Annual Meeting of the American College of Allergy, Asthma and Immunology Boston, MA United States Conference Start: 20111103 Conference End: 20111108. 2011;107(5 SUPPL. 1):A12.	Not full text
Kennedy JL, Borish L, Christophel J, Payne SC. Letters to the editor: Assessing the cost-effectiveness of allergen immunotherapy in allergic rhinitis. American Journal of Rhinology and Allergy. 2014;28(4):353-4.	Not economic evaluation
Kennedy JL, Robinson D, Christophel J, Borish L, Payne S. Decision-making analysis for allergen immunotherapy versus nasal steroids in the treatment of nasal steroid-responsive allergic rhinitis. American Journal of Rhinology and Allergy. 2014;28(1):59-64.	Not economic evaluation
Kiel MA, Roder E, Gerth Van WR, Rutten-Van Molken MPMH. Cost-effectiveness of subcutaneous immunotherapy in allergic rhinitis using one or more allergens-an analysis long overdue [abstract]. Value in	Not full text

Study Reference	Reason for exclusion
Health Conference: ISPOR 17th Annual European Congress Amsterdam Netherlands Conference Start: 20141108 Conference End: 20141112. 2014;17(7):A597.	
Langkilde LK, Andreasen JN. Disease-modifying properties of SQ-standardised grass SLIT-tablets and long-term cost-effectiveness [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: 33rd Congress of the European Academy of Allergy and Clinical Immunology Copenhagen Denmark Conference Start: 20140607 Conference End: 20140611. 2014;69:505-6.	Not full text
Lockey RF, Hankin CS. Health economics of allergen-specific immunotherapy in the United States. Journal of Allergy and Clinical Immunology. 2011;127(1):39-43.	Not economic evaluation
Najib M, Westerhout KY, Verheggen B, Schreder CH. Impact of allergen immunotherapy on quality of life and health care costs in adults and children with grass pollen-induced allergic rhinitis in Germany [abstract]. Value in Health Conference: ISPOR 17th Annual European Congress Amsterdam Netherlands Conference Start: 20141108 Conference End: 20141112. 2014;17(7):A597.	Not full text
Najib M, Westerhout KY, Verheggen B, Schreder CH. Impact of allergen immunotherapy on symptom-free days and health care costs in patients with grass pollen-induced allergic rhinitis in Germany [abstract]. Value in Health Conference: ISPOR 17th Annual European Congress Amsterdam Netherlands Conference Start: 20141108 Conference End: 20141112. 2014;17(7):A597.	Not full text
Rohmer J-P, Jutel M, Spertini F, Della CG, Bousquet J, Levy P. Economic evaluation of allergen immunotherapy for seasonal allergic rhinitis [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: 33rd Congress of the European Academy of Allergy and Clinical Immunology Copenhagen Denmark Conference Start: 20140607 Conference End: 20140611. 2014;69:507.	Not full text
Ronborg S, Svendsen U, Micheelsen J, Ytte L, Riss TJ, Andreasen J, et al. A comparative health economic evaluation of the SQ-standardised grass allergy immunotherapy tablet and subcutaneous immunotherapy in the treatment of grass pollen induced allergic rhinoconjunctivitis [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: 30th Congress of the European Academy of Allergy and Clinical Immunology Istanbul Turkey Conference Start: 20110611 Conference End: 20110615. 2011;66:629.	Not full text
Ronborg SM, Svendsen UG, Micheelsen JS, Ytte L, Andreasen JN, Ehlers L. A comparative health economic evaluation of two treatments for grass pollen induced allergic rhinoconjunctivitis [abstract]. Value in Health Conference: ISPOR 14th Annual European Congress Madrid Spain Conference Start: 20111105 Conference End: 20111108. 2011;14(7):A488-A489.	Not full text
Ruggeri M, Oradei M, Frati F, Puccinelli P, Romao C, Cicchetti A. Economic evaluation of five-grass pollen tablets for the treatment of allergic rhinitis [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: 31st Congress of the European Academy of Allergy and Clinical Immunology Geneva Switzerland Conference Start: 20120616 Conference End: 20120620. 2012;67:419.	Not full text
Slovick A, Durham SR, Till SJ. Grass pollen immunotherapy for treatment	Not economic

Study Reference	Reason for exclusion
of allergic rhinitis. BMJ. 2014;349:g6586.	evaluation
Valero A, Westerhout KY, Van De WG, Perez-Alcantara F, Azpeitia A, Najib M. Cost-effectiveness analysis of allergen immunotherapy in patients with grass pollen-induced allergic rhinitis in Spain [abstract]. Value in Health Conference: ISPOR 17th Annual European Congress Amsterdam Netherlands Conference Start: 20141108 Conference End: 20141112. 2014;17(7):A598.	Not full text
Vestergaard AS, Andreasen JN. Grass allergen immunotherapy tablets vs symptomatic treatment for allergic rhinoconjunctivitis-a health economic evaluation [abstract]. Allergy: European Journal of Allergy and Clinical Immunology Conference: European Academy of Allergy and Clinical Immunology and World Allergy Organization World Allergy and Asthma Congress 2013 Milan Italy. 2013;68:550.	Not full text
Westerhout KY, Verheggen BG, Schreder CH, Sieber J, Augustin M. Cost-effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinitis [abstract]. Value in Health Conference: ISPOR 14th Annual European Congress Madrid Spain Conference Start: 20111105 Conference End: 20111108. 2011;14(7):A494-A495.	Not full text

Appendix A4: List of Included Studies

Exhibit 3: List of included studies within the review.

Reference #	Study Reference
3	Reinhold T, Ostermann J, Thum-Oltmer S, Bruggenjurgen B. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. Clinical and Translational Allergy. 2013;3(10):1-8.
4	Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. ClinicoEconomics and Outcomes Research. 2014;6(1):187-96.
7	Ruggeri M, Oradei M, Frati F, Puccinelli P, Romao C, Dell'Albani I, et al. Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. Clinical Drug Investigation. 2013;33(5):343-9.
5	Verheggen BG, Westerhout KY, Schreder CH, Augustin M. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. Clin Transl Allergy. 2015;5(1):1-10.
6	Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. Journal of Medical Economics. 2012;15(5):906-17.

Appendix A5: Characteristics of Reviewed Studies

Exhibit 4: Brief overview of included studies.

First author, Year	Country	Sponsorship	Study type	Model type	Time horizon	Included interventions
Hockenhull, 2012	UK	HTA	CUA	Decision tree	10 years	PhVIT+AAI+HDA vs. AAI+HDA vs. AA
Meadows, 2013	UK	HTA	CEA/CUA	Markov	6 years	SCIT vs. SLIT vs. ST
Pokladnikova, 2008	Czech Republic	Independent	CCA	TBA	3 years	SCIT vs. SLIT vs. ST
Reinhold, 2013	Germany	Allergopharma GmbH & Co.	CCA	TBA	3 years	SCIT+ICS vs. ICS
Ronaldson, 2014	Germany	ALK-Abelló	CEA/CUA	Markov	9 years	SLIT+ST vs. ST
Ruggeri, 2013	Italy	Stallergenes Italy	CUA	Decision tree	4 years	SLIT vs. placebo
Verheggen, 2015	Germany	Stallergenes GmbH	CUA	Markov	9 years	SLIT+ST vs. SCIT+ST vs. ST
Westerhout, 2012	Germany	Stallergenes GmbH	CUA	Markov	9 years	SLIT (OA, GRZ) vs. SCIT (ALD) vs. ST

Note: AA=avoidance advice; AAI=adrenaline auto-injector; CCA=cost-comparison analysis; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; HDA=high-dose antihistamine ICS=inhaled corticosteroids; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; ST=symptomatic therapy; TBA=trial-based analysis.

Exhibit 5: Detailed characteristics of included studies.

First Author, Year	Hockenhull, 2012	Meadows, 2013	Pokladnikova, 2008
Sponsorship	HTA	HTA	Independent
Country	UK	UK	Czech Republic
Perspective	HCP	HCP	HCP & Societal
Study type	CUA	CEA/CUA	CCA
Comparators	PhVIT+AAI+HDA vs. AAI+HDA vs. avoidance advice	SLIT vs. SCIT vs. ST	SLIT vs. SCIT vs. ST
Target population	Patients with a history of type 1 IgE-mediated systemic allergic reactions to bee and wasp venom	Adult patients with seasonal allergic rhinitis	Adult patients with seasonal allergic rhinoconjunctivitis
Time horizon	10 years	6 years	3 years
Type of model	Decision tree	Markov	TBA
Results	PhVIT+AAI+HDA vs. AAI+HDA ICER = £18,065,527/QALY gained PhVIT+AAI+HDA vs. avoidance advice only ICER = £7,627,835/QALY gained (1.00 GBP = 1.59 CAD)	SCIT or SLIT, as compared with ST, became a cost-effective strategy after around 6 years of treatment at a willingness to pay threshold of £20,000-£30,000 per QALY (based on direct comparisons). Based on the same threshold, SCIT was found to be cost-effective compared with SLIT after around 5 years (based on indirect comparison (1.00 GBP = 1.59 CAD)	Third party payer/HCP perspective: SLIT = €416 per patient SCIT = €482 per patient Societal perspective: SLIT = €684 per patient SCIT = €1,004 per patient (1.00 EUR = 1.41 CAD)

Note: AAI=adrenaline auto-injector; CCA=cost-comparison analysis; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; HDA=high-dose antihistamine ICS=inhaled corticosteroids; SCIT=subcutaneous immunotherapy; SLIT=sublingual immunotherapy; ST=symptomatic therapy; TBA=trial-based analysis.

First Author, Year	Reinhold, 2013	Ronaldson, 2014	Ruggeri, 2013
Sponsorship	Allergopharma GmbH & Co.	ALK-Abelló	Stallergenes Italy
Country	Germany	Germany	Italy
Perspective	HCP	HCP	HCP & Societal
Study type	CCA	CEA/CUA	CUA

First Author, Year	Reinhold, 2013	Ronaldson, 2014	Ruggeri, 2013
Comparators	SCIT (Acaroid)+ICS vs. ICS (high-dose hypoallergenic preparation)	SLIT+ST vs. ST	SLIT (SQ-standardized grass AIT) vs. placebo
Target population	Children and adolescents suffering from mite-induced allergic asthma	Children with grass pollen-induced rhinoconjunctivitis, with or without concomitant asthma (who have previously received symptomatic treatment)	Adult patients with grass pollen-induced allergic rhinitis
Time horizon	3 years	9 years	4 years
Type of model	TBA	Markov	Decision tree
Results	SCIT is associated with additional costs over the 3-year treatment course, but also with better effectiveness. Adjusted total mean costs per patient were €770 for SCIT and €383 for controls, and the mean annual morning peak flow per patient was 369 l/min for patients receiving SCIT, and 334 l/min for controls. (1.00 EUR = 1.31 CAD)	ICER = £12,168/QALY gained Cost per additional well day = £12.42 Additional benefits of grass AIT therapy for children with grass pollen-induced rhinoconjunctivitis can be acquired at a cost of £1202/0.10 QALY (1.00 GBP = 1.56 CAD)	Patients with medium Average Adjusted Symptom Score (AAdSS) ICER = €1024/QALY gained Patients with high AAdSS ICER = €1035/QALY gained Patients with low AAdSS no gained in QALYs so is dominated by placebo (1.00 EUR = 1.34 CAD)

First Author, Year	Verheggen, 2015	Westerhout, 2012
Sponsorship	Stallergenes GmbH	Stallergenes GmbH
Country	Germany	Germany
Perspective	HCP	HCP
Study type	CUA	CUA
Comparators	SLIT (Oralair)+ST vs. SCIT (Allergoid mix)+ST vs. ST	SLIT-1 (Oralair) vs. SLIT-2 (Grazax) vs. SCIT (Alk Depot SQ) vs. ST
Target population	Adult patients with seasonal grass-allergic rhinoconjunctivitis	Adult patients with grass pollen-induced allergic rhinoconjunctivitis
Time horizon	9 years	9 years
Type of model	Markov	Markov
Results	<u>SLIT+ST vs. ST</u> ICER=€17,007/QALY gained <u>SLIT+ST vs. SCIT+ST</u> ICER=€12,593/QALY gained (1.00 GBP = 1.34 CAD)	<u>SLIT (OA) vs. ST</u> ICER = €14,728/QALY gained Oralair (OA) is the dominant strategy in comparison to Grazax and Alk Depot SQ Cost per symptom-free day (OA vs. ST) = €28 OA results in fewer patients developing chronic asthma. After a time horizon of 9 years, the number needed to treat to prevent one case of chronic asthma is 98 patients (1.00 GBP = 1.31 CAD)

References

1. Hockenhull J, Elremeli M, Cherry MG, Mahon J, Lai M, Darroch J, et al. A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy. Health Technol Assess. 2012;16(12):i-109.

2. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess. 2013 Jul;17(27):i-322.

3. Reinhold T, Ostermann J, Thum-Oltmer S, Bruggenjurgen B. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. Clinical and Translational Allergy. 2013;3(10):1-8.

4. Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. ClinicoEconomics and Outcomes Research. 2014;6(1):187-96.

5. Verheggen BG, Westerhout KY, Schreder CH, Augustin M. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. Clin Transl Allergy. 2015;5(1):1-10.

6. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. Journal of Medical Economics. 2012;15(5):906-17.

7. Ruggeri M, Oradei M, Frati F, Puccinelli P, Romao C, Dell'Albani I, et al. Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults. Clinical Drug Investigation. 2013;33(5):343-9.

8. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: funding sources and outcomes. Int J Technol Assess Health Care. 2010 Jul;26(3):330-3.