FINAL CONSOLIDATED REPORT
October 2015

ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Allergen Immunotherapy

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.
Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.
Tara Gomes received grant funding from the Ministry of Health and Long-term Care.
No other 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 Immunotherapy Drug Class Review.

Acknowledgments

This review was funded by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund. The work was also supported by The Keenan Research Centre of St. Michael's Hospital (SMH), the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario MOHLTC and by the Canadian Institute for Health Information (CIHI). Datasets provided by ICES were linked using unique encoded identifiers and analyzed at ICES. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI. No endorsement by SMH, ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

Study Team

- Formulary Modernization Team: Paul Oh, Sandra Knowles
- Qualitative Team: Radha Sayal, Alekhya Mascarenhas, Sobia Khan, and Julia E. Moore from the Knowledge Translation Program at the Li Ka Shing Knowledge Institute
- Systematic Review Team: George A. Wells, Jesse Elliott, Shannon Kelly, Amy Johnston, Becky Skidmore, Joshua Kofsky
- Pharmacoepidemiology Team**:** Tara Gomes, Diana Martins, Kimberly Fernandes Samantha Singh, Mina Tadrous, Nikita Arora, David Juurlink, Mike Paterson, Muhammad Mamdani
- Pharmacoeconomics Team: Doug Coyle, Karen Lee, Kylie Tingley, Mirhad Loncar
- Research Team, Clinical Expert: Paul Keith
- Research Team, Representative from Committee to Evaluate Drugs: Henry Wu

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).

List of abbreviations	
AB	Alberta
BC	British Columbia
CI	Confidence interval
CIHI	Canadian Institute for Health Information
DIN	Drug identification number
EAP	Exceptional Access Program
ICES	Institute for Clinical Evaluative Sciences
LU	Limited Use
MB	Manitoba
MOHLTC	Ministry of Health and Long-Term Care
NB	New Brunswick
NIHB	Non-insured Health Benefits
NL	Newfoundland
NS	Nova Scotia
NU	Nunavut
NW	Northwest Territories
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
ON	Ontario
OPDP	Ontario Public Drug Programs
PEI	Prince Edward Island
PIN	Product identification number
QC	Quebec
RCT	Randomized controlled trial
RR	Risk ratio
SCIT	Subcutaneous immunotherapy
SK	Saskatchewan
SLIT	Sublingual immunotherapy
SMH	St. Michael's Hospital
YK	Yukon Territories

Executive Summary

Allergen immunotherapy is used most commonly for treatment of patients with allergic rhinitis, although it is also used for patients with allergic asthma and in patients with stinging insect (Hymenoptera) hypersensitivity. In Canada, allergen immunotherapy is available either as sublingual administration (SLIT) or subcutaneous administration (SCIT). There are three commercially available SLIT products in Canada: Oralair, Ragwitek and Grastek. SCIT products are generally formulated specifically for the allergic patient (one exception is Pollinex R, which is available as a commercially formulated product). The compounding of patient-specific serums is done by commercial laboratories, pharmacies or in physician offices. In Ontario, two SLIT products (namely Oralair and Ragwitek) are listed as Limited Use on the Ontario Drug Benefit (ODB) formulary. SCIT products (including Pollinex and patient-specific serums) are available through the "Ontario Drug Benefit Program: Allergy Products" program.

As part of the formulary modernization review, an evaluation of allergen immunotherapy was undertaken, in order to provide policy recommendations for these products in Ontario.

Key Considerations for Reimbursement Options

Efficacy and Safety

A total of 19 unique systematic reviews, published between 2010 and 2015, were included in our review. All reviews included randomized controlled trials (RCTs), while two reviews also included non-randomized studies. The duration of therapy ranged from 2 weeks to more than 5 weeks; only one systematic review compared the efficacy and safety of immunotherapy of short (<3 years) and long (>3 years duration).

In patients with allergic asthma, SCIT and SLIT were found to be more effective than placebo in reducing asthma symptom scores and/or symptom and medication scores (i.e., use of antiallergic medications). Anaphylaxis was reported for SCIT but not SLIT; no deaths were reported in the reviews that assessed mortality.

In patients with allergic rhinitis, SCIT and SLIT are more effective than placebo at reducing allergic rhinitis symptom scores, total combined medication-symptom scores and improving disease-specific quality of life. As well, SCIT is better than SLIT at improving medication scores and may be better than SLIT at improving symptom scores, although there was no significant difference in disease-specific quality of life. Anaphylaxis was reported for both SCIT and SLIT. Additionally, venom immunotherapy was shown to be effective for preventing systemic allergic reactions to an insect sting.

Accessibility

In Ontario, two SLIT products (i.e., Oralair and Ragwitek) are available on the ODB formulary as Limited Use products. SCIT is available through the "Allergy Product" program for eligible ODB patients. In 2013/14, there were 8,116 publically-funded allergen immunotherapy users

in Ontario. This data does not include any users of commercially available SLIT products, as they were introduced onto the ODB formulary in 2014.

Pharmacoeconomics

Cost effectiveness literature review: Previously published studies were generally supportive of the cost-effectiveness of allergen immunotherapy products in comparison with standard symptomatic therapy with some evidence suggesting that SCIT may be more cost-effective than SLIT when the two treatments were directly compared. Results, however, should be interpreted with caution as the majority of studies received industry funding and there was a lack of relevant Canadian studies.

Budget impact analysis: The potential budget impact of new policies addressing costs of SCITs and restrictions on unstable combinations is varied, and relies heavily on the assumptions regarding costs per claim reimbursed. For example, if costs are restricted to the minimum amount currently reimbursed by the OPDP ($106.50/claim), this could lead to savings of over $1.5M/year (or 45% decrease in cost). However, reimbursing all claims at the mean amount currently reimbursed would lead to excess costs of over $860,000 annually.

Final recommendations

Allergen immunotherapy (SCIT) is not dispensed through licensed pharmacies for most patients in Ontario and is funded through a separate Allergy Products program. In contrast, sublingual products (SLIT: namely Oralair and Ragwitek) are listed as Limited Use on the ODB formulary. In our drug class review of allergen immunotherapy, we do not propose a new distribution system for SCIT products, although this may be explored by the Ontario Public Drug Programs (OPDP).

Based on our review and input from stakeholders and the Citizen's Panel, the following recommendations are suggested for allergen immunotherapy products (SCIT and SLIT) for the OPDP:

Recommendation 1: Limit duration of therapy to 5 years for aeroallergens

- Although the optimal duration of immunotherapy is unknown, three to five years for aeroallergen (i.e., airborne particles that cause allergic reactions) SCIT has been recommended. Patients receiving venom immunotherapy may require life-long administration. For SLIT, three years of therapy (pre- and co-seasonal) is recommended by various guidelines.

Recommendation 2: Require drug identification numbers (DIN) on all prescriptions for subcutaneous allergen immunotherapy

- Only extracts with associated DINs should be used in the manufacturing of patient-specific serums. Whenever possible, standardized extracts should be utilized.
- The requirement of DINs on the prescription will prevent the inclusion of in-house manufactured allergen extracts that may not meet minimum manufacturing standards set out by Health Canada.

Recommendation 3: Clinical criteria for use of subcutaneous allergen immunotherapy be developed

- Clinical criteria to include:
    - Diagnosis: allergic rhinitis, allergic asthma, history of Hymenoptera insect sting allergy
    - Previous therapy: documentation of previous therapy (e.g., intranasal corticosteroid, antihistamine) for patients with allergic rhinitis or allergic asthma (but not patients with history of insect sting allergy)

Recommendation 4: Coverage of sublingual immunotherapy be limited to commercially available SLIT products.

- Ontario currently provides coverage for two commercially available SLIT products (as tablets): Oralair and Ragwitek. However, some clinicians use other commercially available allergen extracts (intended for use in SCIT) to prepare patient-specific SLIT administered as drops. The use of the commercially available allergen extracts for sublingual administration is considered “off-label” use and has little evidence to support it.
- It is recommended that patient specific allergen extracts only be administered subcutaneously. Therefore, it is recommended that OPDP not provide coverage for patient specific allergen extracts for sublingual use.

Recommendation 5: Develop pricing structure for patient-specific allergen immunotherapy

- There is currently no pricing structure for compounding of patient-specific allergen immunotherapy. A large variability was found with costs for individual claims ranging from $106.50 to $709.00.
- A maximum allowable claim cost is recommended for subcutaneous allergen immunotherapy. The actual amount may vary for environmental and venom immunotherapy.
- Further studies to develop a pricing structure are needed, with expanded stakeholder engagement.

Recommendation 6: Provide guidance for safe manufacturing practices

- Cross-reactivity of allergens, the optimal therapeutic dose for each allergen and interallergen degradation must be considered when combining allergens. In our review, 13% of allergen serums were characterized as possibly unstable based on evidence-based guidelines for immunotherapy mixtures. In general, extracts with high proteolytic enzyme activity (e.g., mold/fungi, cockroach) should not be combined with allergens with low enzyme activity (such as pollen, dander, dust mite), as studies have demonstrated a significant loss of potency. In addition, it is not recommended to mix venom extracts together or venom extracts with other allergen extracts.
- It is recommended that all manufacturing facilities (including pharmacies and physician’s offices) follow guidelines as set out by the AAAAI or USP 797. Both guidelines emphasize aseptic technique, handwashing, appropriate refrigerated

storage, use of personal protective equipment, beyond-use dating and patient identification on labels.

- Engagement with the Allergy Asthma & Immunology Society of Ontario, College of Physicians and Surgeons of Ontario, Ontario Pharmacists Association and manufacturing facilities is suggested to aid in implementation of this recommendation.

Table of Contents

List of Exhibits

Rationale for Review

In Canada, allergen immunotherapy is available either for sublingual administration (SLIT) or for subcutaneous administration (SCIT). There are three commercially available SLIT products in Canada: Oralair, Ragwitek and Grastek. SCIT products are generally formulated specifically for the allergic patient (one exception is Pollinex R, which is available as a commercially formulated product).The compounding of patient-specific serums is done by commercial laboratories, pharmacies or in physician offices. The cost of these compounded products is not standardized. In Ontario, two SLIT products (namely Oralair and Ragwitek) are listed as Limited Use on the Ontario Drug Benefit (ODB) formulary. SCIT products (including Pollinex and patient-specific serums) are available through the “Ontario Drug Benefit Program: Allergy Products” program.

As part of the formulary modernization review, an evaluation of allergen immunotherapy was undertaken, in order to provide policy recommendations for these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: http://www.odprn.ca

Background Information

Allergen immunotherapy involves the administration of gradually increasing doses of a specific allergen to a patient with a history of allergy; the goal of allergen immunotherapy is to reduce sensitivity and minimize future symptomatic reaction on natural exposure to the causative agent.[1] Traditionally, allergen immunotherapy has been administered subcutaneously (SCIT: subcutaneous immunotherapy), although more recently the sublingual route has also been used (SLIT: sublingual immunotherapy).

Allergen immunotherapy is used for a number of different conditions, although it is used most commonly for treatment of patients with allergic rhinitis. Other indications for allergen immunotherapy include patients with allergic asthma and patients with stinging insect (Hymenoptera) hypersensitivity.[2]

Allergic rhinitis, characterized by rhinorrhea, nasal obstruction, nasal itching and sneezing, is associated with decreased quality of life, work and educational performance.[3;4] It is a global health problem, and affects approximately 10-20% of the Canadian population.[5] Allergic rhinitis and asthma frequently co-exist.[6] Longitudinal data indicate that children with allergic rhinitis have a two- to sevenfold increased risk of asthma later in life.[7] As well, allergic rhinitis is associated with significantly worse asthma control in adults and children.[8]

The treatment goal for allergic rhinitis is relief of symptoms. Options include avoidance measures of triggers (e.g., dust mites, grass pollen), pharmacotherapy and allergen immunotherapy. Pharmacotherapeutic options include intranasal corticosteroids, oral antihistamines, and leukotriene receptor antagonists.[3] Allergen immunotherapy is used in

patients with allergic rhinitis who have poor relief with standard pharmacotherapy or in those who experience adverse effects. Allergen immunotherapy may have persistent benefits after immunotherapy is discontinued, may decrease the development of new sensitizations, and may reduce the development of asthma in patients with allergic rhinitis.[9;10]

Conventional SCIT treatment schedules involve a gradual increase in the allergen content of injections, usually involving one or two injections per week over a 3- to 6-month period.[11] Due to the risk of severe allergic reactions, SCIT must be administered in a clinical setting with full resuscitation facilities available. In contrast, SLIT has a large safety record and can be self-administered by the patient in a non-clinical setting, for example in their home. For the SLIT products, the administration needs to start 2-4 months prior to the pollen season, and continues throughout the pollen season. The grass pollen season in Ontario is typically June and July, and ragweed season is from August until October.

Public plan reimbursement of allergen immunotherapy in Canada

In Ontario, Ragwitek and Oralair are listed as Limited use (LU) drugs on the Ontario Drug Benefit formulary. LU drugs have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Oralair was reviewed and listed on the ODB formulary as a Limited Use product in March 2014. Ragwitek was listed on the ODB formulary as a Limited Use product in May 2015. Grastek was reviewed in January 2015, and a decision to not consider funding was made.

The Limited Use criteria are as follows:

Code 457 (Ragwitek):
For the seasonal treatment of short ragweed pollen induced allergic rhinitis in patients that have not adequately responded to, or tolerated, conventional pharmacotherapy.

Notes:

- Treatment with short ragweed pollen allergen extract must be initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.
- Treatment should be initiated at least twelve (12) weeks before the onset of ragweed pollen season and should only be continued until the end of the season.

LU Authorization Period: 1 year.

Code 451 (Oralair):
For the seasonal treatment of grass pollen allergic rhinitis in patients that have not adequately responded to, or tolerated, conventional pharmacotherapy.

Notes:

- Treatment with grass pollen allergen extract must be initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.
- Treatment should be initiated four (4) months before the onset of pollen season and should only be continued until the end of the season.
- Treatment should not be taken for more than three (3) consecutive years.

LU Authorization Period: 1 year.

The program entitled “Ontario Drug Benefit Program: Allergy Products” covers the cost of allergen immunotherapy administered in a doctor’s office to treat severe allergy symptoms for patients who qualify for coverage under the ODB program (e.g., 65 years of age and older, living in a long-term care home or home for special care, registered in the Trillium Drug Program or receiving social assistance). There are no criteria (e.g., previous therapy, severity of disease) that need to be met prior for reimbursement approval of SCIT.

In Canada, most public drug programs (with the exception of Yukon Territories) provide coverage for allergen immunotherapy. SLIT products (Oralair, Ragwitek and/or Grastek) are listed on five public drug plans. Allergen extracts for SCIT administration are available in 11 (of 12) jurisdictions. In two provinces (New Brunswick and PEI), these products are covered under the Social Assistance program. Most allergen extracts are listed as a full benefit, except for Nova Scotia which lists these under their special authorization program.

Exhibit 1: Public plan listings in Canada for allergen immunotherapy

Drug	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
Sublingual allergen immunotherapy (SLIT)												
Oralair	No	No	No	Res	Pas	Pas	No	Res	No	No	No	No
Ragwitek	No	No	No	No	Pas	No	No	No	No	No	No	No
Grastek	No	No	No	No	No	Pas	No	No	No	No	No	No
Subcutaneous allergen immunotherapy (SCIT)												
Pollinex R	No	No	No	No	FB	No	No	Res	No	No	No	FB
Allergen extracts	FB	FB	Res	No*	FB	FB	SA	Res	SA	FB	No	FB

No=not listed
Pas=restricted listing – passive (e.g., Limited Use in Ontario, Exceptional Medications in Quebec)
Res=restricted listing – enforced
FB=full benefit
SA=covered under Social Assistance program
*Only cover stinging insect (Hymenoptera) immunotherapy
Current as of July 6, 2015

Objective

The objective of the drug class review for allergen immunotherapy is to provide evidence-informed policy recommendations for these treatments in Ontario.

Components of the Drug Class Review

The allergen immunotherapy drug class review is comprised of:

- qualitative analyses of perspectives of patients and prescribers
    - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for allergen immunotherapies
- environmental scans of:
    - national and international drug policies
    - considerations relating to health equity
- analysis of real-world drug utilization using:
    - administrative claims data from Ontario and across Canada (where available)
    - summaries of relevant observational literature
- systematic review of the literature
- reimbursement-based economic analyses

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Patients and Physicians

Findings of the qualitative study represented common experiences and perceptions described across patient and physician groups.

Allergen immunotherapy prescription

Clinician participants described the various factors they consider before prescribing allergen immunotherapy such as type of allergy, response to traditional pharmacotherapy and non-pharmacological strategies, skin test results, and other patient related factors.

- Physician participants considered venom therapy to be first line treatment.
- Physicians preferred and found the subcutaneous immunotherapy (SCIT) formulation to be more efficacious, however, if patient compliance was an issue they would prescribe (sublingual immunotherapy) SLIT.
- Primary care physician participants said they screen and refer severe allergy patients to allergists. Allergists will conduct skin testing, make the diagnosis, and prescribe allergen immunotherapy;
- Preparations may be made either on site or through a manufacturer. Participants

stated that some physicians may prepare these medications on site; some had concerns about the safety and efficacy of these preparations if proper equipment was not used.

- Majority of allergists agree that treatment duration should be 3-5 years; however, some clinician participants will prescribe life-long for high-risk groups (e.g., beekeepers).
- Participants speculated that allergen immunotherapy prescriptions may rise with the introduction of commercialized SLIT and pre-mixed SCIT products; however they felt that prescription trends are also linked to where and when an allergist has received medical training. As well, prescription may be linked to perception of roles: pharmacotherapy is perceived to be the family doctor's responsibility and immunotherapy is the allergist's responsibility.

> *"For venom allergy it's incredibly effective at preventing a potentially life threatening condition… the same risks apply, but you are giving them the immunotherapy in a controlled setting, so it's a completely different risk benefit ratio than it is for the you know respiratory disease where you are treating hay fever, maybe you are treating asthma, but we have other treatments for that… that you know work better, faster, safer and cheaper, but with a venom allergy it's a whole different ball game and that's when I use immunotherapy." - Allergist*

> *"The first major con was that I had to do this on a weekly basis – so I had to make myself available, at the beginning, on a weekly basis; and I had to go to the clinic, and I live kind of a busy life, so it was con but at the same time the proof it was that I was going to get better, and you just have to do what you have to do in order to, 'cause like I said my symptoms were making me suffer; so after thinking about it for all of about 2-minutes, I thought 'yes, this is something that needs to get done 'cause I need to get better – 'cause my quality of life needs to improve'." – Patient*

Access to allergen immunotherapy:

Patient on patient and physician accounts, most individuals access these medications through third party insurance. Physician and patient participants described that there were no barriers for patients who need to access allergen immunotherapy or barriers to coverage through the Ontario Drug Benefit (ODB) Allergy Product program.

- Clinician participants suggested that the Limited Use criteria for allergen immunotherapy should revolve around symptom severity and an adequate trial of traditional pharmacotherapy allergy medication.
- Participants believed there is a lack of standardization of how allergen immunotherapy is dispensed (i.e. on-site, manufacturer, or pharmacy), which has resulted in a variety of prices for the same products across the various dispensing outlets.

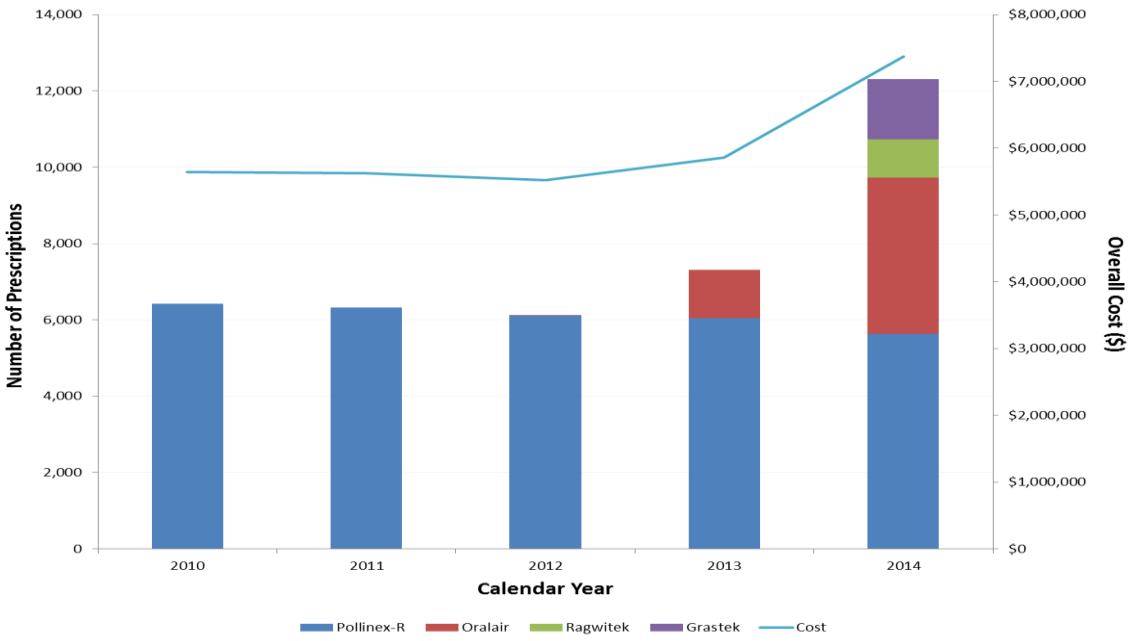
Pharmacoepidemiology Team

Current Utilization across Canada

NOTE: Due to the various means by which allergens are distributed and administered, data obtained from IMS only captured single allergen products with associated DIN numbers dispensed from pharmacies and not patient-specific allergen extracts.

Annual dispensing of prescriptions for allergen immunotherapies in pharmacies across Canada has nearly doubled (92%) over the past 5 years, from 6,423 prescriptions dispensed in 2010 (18.8 prescriptions per 100,000 population) to 12,311 prescriptions dispensed in 2014 (34.6 prescriptions per 100,000 population) (see Exhibit 2). This increase is attributable to the introduction of novel sublingual immunotherapies (SLIT) in 2013 and 2014. The introduction of these drugs to the Canadian market caused a 32% increase in costs from $5.6 million in 2013 to $7.4 million in 2014. Ontario was found to have the highest rate of prescriptions dispensed for allergen immunotherapies in Canada, which increased almost 33% from 45 prescriptions per 100,000 population in 2010 to 60 prescriptions per 100,000 population in 2014.

Exhibit 2: Total utilization and cost of immunotherapy dispensed in Canada, by drug and quarter

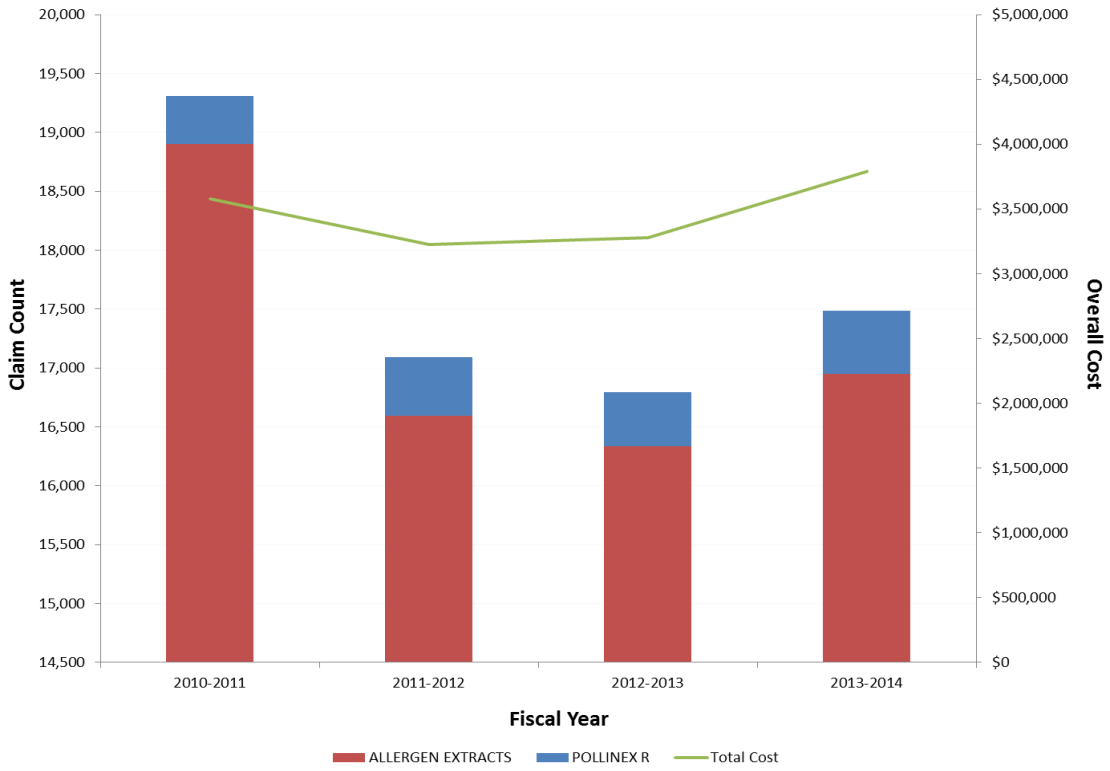


Regional variations in non-publicly funded allergen immunotherapy prescribing were observed across Canada, which is likely related to the variation of environmental allergens present and prescribing habits. Oralair was the most commonly prescribed non-publicly funded allergen immunotherapy product in the western provinces (Alberta, British Colombia, and Manitoba) in 2014. In the same year, Pollinex-R had the highest rate of prescriptions in Ontario and Quebec, Grastek use was highest in the Maritime Provinces (Newfoundland and Nova Scotia), with exception of New Brunswick where Oralair was most common.

Trends in Provincially-funded Allergen Immunotherapy in Ontario

Claims to the Ontario Public Drug Program (OPDP) allergen program for immunotherapies (allergen extracts and Pollinex-R) ranged from 19,308 prescriptions dispensed in fiscal year (FY) 2010/11 to 12,025 prescriptions dispensed in fiscal year FY2014/15. The majority of publicly-funded immunotherapy claims were for allergen extracts (98% in FY2010/11 and 96% in FY2014/15). The cost of publicly-funded immunotherapy claims ranged from $3,222,863 in FY2011/12 to $3,789,385 in FY2013/14 (see Exhibit 3). The governmental cost per claim increased between FY2010/11 to FY2014/15 for both the non-pollen allergen extracts ($181 to $235 per claim; 30% increase) and Pollinex-R ($372 to $392 per claim; 5.4% increase). The number of publicly-funded users of immunotherapy in Ontario decreased slightly over time, ranging from 8,660 users in FY2010/11 to 8,116 users in FY2013/14.

Exhibit 3: Total utilization and cost of publicly-funded allergen immunotherapy in Ontario, by drug and fiscal year



Characteristics of Publically-funded Allergen Immunotherapy Users in Ontario

NOTE: The reimbursement of allergen immunotherapy products is atypical, with a large proportion of prescriptions for immunotherapy dispensed directly from physician offices or manufacturing facilities and thus information is often unavailable through pharmacy claims data. Moreover, a large proportion of claims for the allergen program are submitted in hand-written forms, rather than electronically, as is most common with traditional drug claims captured in the ODB database.

In 2013, we were able to explore the characteristics of a sample (n=4,818) of publicly-funded allergen immunotherapy users in Ontario. The majority of users were treated with non-pollen allergen extracts (88%; N=4,239). Users of allergen immunotherapy in Ontario were found to be on average 65 years of age, approximately two-thirds were female (60%; N=2,880), they used an average of 9 medications in the last year, and nearly half (46%; N=2,204) had a diagnosis of asthma. We found that 10% of prescribers (N=74) accounted for 88% of allergen extract claims (N=16,221) submitted for public reimbursement and less than 6 prescribers accounted for over half (53%) of all prescriptions in this sample.

Allergen Extract Claims Analysis

From a sample (n=100) of submitted allergen extract claims to the OPDP in 2015, the majority of claims were for environmental allergens (87%), compared to venom allergens (10%) and mixed (environmental and food) (3%). Venom serums claims were more likely to be made with a single allergen (90%) while environmental serum claims were more likely to have more than one allergen [2-5 allergens (52%) and 6+ allergens (10%)]. Moreover, 13% of allergen serums were characterized as possibly unstable based on evidence-based guidelines for immunotherapy mixtures.

Systematic Review Team

A focused rapid systematic review of existing systematic reviews (including health technology assessments, network meta-analyses and meta-analyses) was done to summarize clinical and safety evidence of allergen immunotherapy for the treatment of allergic rhinitis or allergic asthma. The population of interest included adult or pediatric patients with seasonal or perennial allergic rhinitis or allergic asthma. A rapid review for venom immunotherapy was conducted separately as part of the Environmental Scan team.

Efficacy and safety

In total, 19 unique systematic reviews, published between 2010 and 2015, were included in our review. All included randomized controlled trials (RCTs), while two reviews also included non-randomized studies. The number of included studies in each review ranged from 8 to 268, and varied by the indication for allergen immunotherapy. The duration of therapy ranged from 2 weeks to more than 5 weeks; only one systematic review compared the efficacy and safety of immunotherapy of short (<3 years) and long (>3 years duration).[12] Most of the included systematic reviews compared either SCIT or SLIT (administered via drop or tablet) to placebo. One systematic review included a comparison to pharmacotherapy; however, the comparison groups were not well described and data are not included in this review[13].

Allergic asthma (Exhibit 4)

A total of 3 meta-analyses were included in our review. Of these, two involved comparison between SCIT and placebo and one involved comparison between SLIT and placebo. Outcomes that were assessed symptom score and medication score. For safety outcomes, reports of anaphylaxis and death were compiled.

- SCIT is more effective than placebo for reducing asthma symptom scores, and symptom and medication scores.
- SLIT is more effective than placebo for reducing symptom and medication scores.
- One systematic review reported on SCIT compared with inhaled corticosteroid (budesonide). Only one trial was included in the comparison and showed that budesonide had a faster onset than SCIT, but a more rapid decline in efficacy on discontinuation compared to SCIT.
- Anaphylaxis was reported for SCIT but not SLIT. No deaths were reported in the reviews that assessed this outcome.

Allergic rhinitis (Exhibit 4)

Our review included 4 systematic reviews for the comparison of SLIT and placebo, and 2 systematic reviews comparing SCIT and placebo. Two systematic reviews provided a comparison between SCIT and SLIT. An additional 5 reviews narratively assessed the efficacy of SLIT or SCIT in this population. Outcomes that were assessed were total combined symptom-medication score, symptom score, medication score, disease-specific quality of life, and adherence/discontinuation rates. For safety outcomes, reports of anaphylaxis and death were compiled.

- SCIT is more effective than placebo at reducing allergic rhinitis symptom scores, total combined medication-symptom score, symptom scores, medications scores and at improving disease specific quality of life.
- SLIT is more effective than placebo at reducing total combined medication–symptom score, symptom scores, medication scores and improving disease-specific quality of life.
- SCIT is better than SLIT at improving medication scores and may be better than SLIT at improving symptom scores. There was no significant difference in disease-specific quality of life.
- Anaphylaxis was reported for SCIT by five systematic reviews; no deaths were reported. Anaphylaxis was reported in 3 of 7 reviews that assessed SLIT.
- In one report, three deaths occurred (all non-anaphylaxis related) in three trials, all in the SLIT group; none were considered by the manufacturer to be treatment related.

Venom immunotherapy

A total of four systematic reviews and meta-analyses were identified that evaluated the efficacy and/or safety of Hymenoptera venom immunotherapy.

- Venom immunotherapy was shown to be effective for preventing systemic allergic reactions to an insect sting. In one review, a total of 3/113 (2.7%) of participants treated with venom immunotherapy experienced a subsequent systemic allergic reaction to a sting compared with 37/93 (39.8%) untreated participants (risk ratio [RR] 0.10, 95% confidence interval [CI] 0.03 to 0.28). As well, venom immunotherapy was shown to be effective in preventing large local reactions to a sting (RR 0.41, 95% CI 0.24 to 0.69) and for improving quality of life (mean difference in favour of venom immunotherapy, 1.21 points on a 7-point scale, 95% CI 0.75 to 1.67). [14]

- However, venom immunotherapy is not without risk, and patients may develop local reactions or more rarely systemic reactions during therapy.

Review of observational literature on adherence of allergen immunotherapy

Studies investigating the adherence of SCIT and SLIT therapies varied widely in their reported adherence rates and the study results are generally inconclusive. Adherence across studies for both SLIT and SCIT was quite variable, ranging from 7-99.3% for SLIT and 3.9-96.3% for SCIT. Results are heavily limited by the largely heterogeneity and confounding across studies. Although clinical consensus is that patients must adhere to immunotherapy for 3 years in order for disease modification to occur, studies demonstrated that the maximum adherence to allergen immunotherapy at 3 years may be half of the patients who initiated the therapy, if not lower. This is concerning considering that adherence is essential to treatment success. Numerous reasons for discontinuation were explored including lack of efficacy, financial concerns, inability to follow treatment schedule, regimen schedule (rush or conventional), inconvenience and other unrelated medical conditions (e.g., pregnancy), with adverse events found to be only a small factor contributing to discontinuation. Future research should further explore reasons for discontinuation for both SCIT and SLIT utilizing standardized 3-year study designs that longitudinally assess or control for the various factors influencing adherence in the real-world.

Exhibit 4: Summary of efficacy and safety data from systematic reviews

Comparison	Efficacy	Anaphylaxis reported?
Allergic asthma		
SCIT v. placebo		Not assessed
		Yes
SLIT v. placebo		No
Allergic rhinitis		
SCIT v. placebo		Not assessed
		Yes
		Yes
SLIT v. placebo		Not assessed
		Not assessed
		Yes
		No
SLIT v. SLIT*		Not assessed
SCIT v. SLIT		Yes
		Not assessed

*Oralair v. Grazax

From **LEFT** to **RIGHT**, circles represent: **total combined symptom–medication score, symptom score, medication score, disease-specific quality of life, adherence/discontinuation**

- A green circle indicates that immunotherapy is significantly better than placebo
- A red circle indicates that immunotherapy is significantly worse than placebo
- A grey circle indicates that there is no significant difference between immunotherapy and placebo
- A white circle indicates that the outcome was not available for analysis

In cases of immunotherapy v. immunotherapy, significance is reported relative to the first agent listed in the heading.

Food Allergies

IgE-associated food allergies affect approximately 3% of the population. Milk, eggs, wheat, peanuts, nuts, sesame, fish, fruits and vegetables are common inducers of IgE-associated food allergy.[15] Management of food allergy relies primarily on allergen avoidance. In the case of food allergies, allergen-specific immunotherapy is most frequently conducted orally, by administration of the offending food instead of a vaccine.[16] Allergen-specific immunotherapy (administered subcutaneously or sublingually) has been used for the treatment of food allergies, as standardized vaccines are not available.[15] Use of subcutaneous allergen immunotherapy for food allergies is not recommended due to safety concerns. Although sublingual allergen immunotherapy has been studied for some food allergies, the evidence for its efficacy and safety is still limited and cannot be recommended for routine use at this time.

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

The current evidence regarding the comparative cost-effectiveness of allergen immunotherapies in the treatment of allergic rhinitis, asthma and/or insect sting allergy was assessed. 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,[17;18] our review assessed published economic evaluations since 2011, when the last search was completed by the previous review authors. Previously published studies were generally supportive of the cost-effectiveness of allergen immunotherapy products in comparison with standard symptomatic therapy, with some evidence suggesting that SCIT may be more cost-effective than SLIT when the two treatments were directly compared. Results, however, should be interpreted with caution as the majority of studies received industry funding and there was a lack of relevant Canadian studies. 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.

Budget Impact Analyses

The potential budget impact of new policies addressing costs of SCITs and restrictions on unstable combinations is varied, and relies heavily on the assumptions regarding costs per claim reimbursed. For example, if costs are restricted to the minimum amount currently reimbursed by the OPDP ($106.50/claim), this could lead to savings of over $1.5M/year (or 44% decrease in cost). However, reimbursing all claims at the mean amount currently reimbursed would lead to excess costs of over $860,000 (increase of 24%) annually.

Exhibit 5: Budget impact of introduction of standardized pricing

Baseline costs: $3,578,359[a]			
Cost Assumption	Total Cost[c]	Net budget impact	% change
Minimum Costs ($106.50/claim)	$2,021,438	↓$1,556,921	↓43.5%
Mean Costs ($223.75-379.60/claim)[b]	$4,438,589	↑$860,229	↑24.0%
Research Team Estimates ($130 for environmental, $410 for venom immunotherapy)	$2,941,999	↓$636,360	↓17.8%

[a]*Based on data from Ontario in fiscal year 2013/14*
[b]*Claim costs differed for environmental allergen and venom allergen claims.*
[c]*Based on duplication of unstable components of claims.*

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of Allergen Immunotherapy

No accessibility issues were identified in Ontario in our review for allergen immunotherapy in patients eligible for coverage through ODB, including those 65 years and older.

Recommendations for Consideration

Allergen immunotherapy is administered sublingually or subcutaneously. Currently there are two commercially available SLIT products available as Limited Use on the ODB formulary, namely Oralair and Ragwitek. The Allergy Products program in Ontario covers the cost of SCIT products administered in a doctor's office to treat severe allergy symptoms for patients who qualify for coverage under the ODB program. Currently, a special form is completed by the prescriber or dispenser and authorization is granted once the form has been approved.

Key Considerations

Efficacy and safety

For patients with allergic asthma:

- SCIT is more effective than placebo for reducing asthma symptom scores, and SLIT is more effective than placebo in reducing symptom and medication scores (i.e., use of antiallergic medications).
- Anaphylaxis was reported for SCIT but not SLIT. No deaths were reported in the reviews that assessed this outcome.

For patients with allergic rhinitis:

- SCIT is more effective than placebo at reducing allergic rhinitis symptom scores, total combined medication-symptom score, and at improving disease specific quality of life.
- SLIT is more effective than placebo at reducing total combined medication-symptom score, symptom scores, medication scores and improving disease-specific quality of life.
- SCIT is better than SLIT at improving medication scores and may be better than SLIT at improving symptom scores. There was no significant difference in disease-specific quality of life.
  Anaphylaxis was reported for SCIT by five systematic reviews; no deaths were reported. Anaphylaxis was reported in 3 of 7 reviews that assessed SLIT.

For patients with systematic reactions to Hymenoptera insect stings:

- Venom immunotherapy is an effective therapy for prevention of future allergic reactions as well as improving quality of life.
- However, some patients may develop local reactions or more rarely, systemic reactions during therapy.

Accessibility

- In Ontario, two SLIT products (i.e., Oralair and Ragwitek) are available on the ODB formulary as Limited Use products. SCIT is available through the “Allergy Product” program for eligible ODB patients.
- In 2013/14, there were 8,116 publically-funded allergen immunotherapy users in Ontario. This data does not include any commercially available SLIT products, as they were introduced onto the ODB formulary in 2014.

Pharmacoeconomics

- *Cost effectiveness literature review:* Previously published studies were generally supportive of the cost-effectiveness of allergen immunotherapy products in comparison with standard symptomatic therapy with some evidence suggesting that SCIT may be more cost-effective than SLIT when the two treatments were directly compared. Results, however, should be interpreted with caution as the majority of studies received industry funding and there was a lack of relevant Canadian studies.
- *Budget impact analysis:* The potential budget impact of new policies addressing costs of SCITs and restrictions on unstable combinations is varied, and relies heavily on the assumptions regarding costs per claim reimbursed. For example, if costs are restricted to the minimum amount currently reimbursed by the OPDP ($106.50/claim), this could lead to savings of over $1.5M/year (or 44% decrease in cost). However, reimbursing all claims at the mean amount currently reimbursed would lead to excess costs of over $860,000 annually (18% increase).

Stakeholder Review

The ODPRN Citizen's Panel rated each of the recommendations for allergen immunotherapy on factors related to acceptability, accessibility and affordability (see Exhibit 6). Overall, panel members were in favour of all six recommendations, and voted unanimously in favor of recommendation 3.

> *"Excellent suggestion as it ensures patient safety and the patient's needs and treatment are appropriately aligned. There is also a paper trail of need for escalation of treatment should it be required."* –panel member

Exhibit 6: Budget impact of introduction of standardized pricing

	Mean score (Standard Deviation) 1 = Strongly Disagree and 7 = Strongly Agree					
	1	2	3	4	5	6
The policy is a good option to limit the burden of cost on the healthcare system.	6.4 (0.8)	6 (1.3)	7	4.8 (2.1)	6 (0.9)	6 (1.3)
I think this policy will benefit those who require the drugs.	6.4 (0.8)	6.6 (0.8)	7	6.6 (0.5)	6.2 (1.0)	6.6 (0.8)
I think this is an acceptable recommendation.	6.4 (0.8)	6.6 (0.8)	7	6 (1.5)	6.4 (0.8)	6.8 (0.4)

For recommendation 5, panel members agreed with the strategy to reduce variation in pricing structure to ensure that the cost is fair and does not become a barrier for patients to access necessary treatment. They thought more data is needed, so that a more accurate and standardized pricing structure can be developed. As well, they suggested that a consumer group should be included as a stakeholder when this pricing structure is developed.

Final Policy Recommendations

Allergen immunotherapy (SCIT) is not dispensed through licensed pharmacies for most patients in Ontario resulting in these products are funded through a unique Allergy Products program. In contrast, sublingual products (SLIT: namely Oralair and Ragwitek) are listed as Limited Use on the ODB formulary. In our drug class review of allergen immunotherapy, we

did not propose a new distribution system for SCIT products, although this may be explored by the OPDP. The following recommendations are proposed for allergen immunotherapy products (SCIT and SLIT) for the Ontario Public Drug Programs:

Recommendation 1: Limit duration of therapy to 5 years for aeroallergens

- Although the optimal duration of immunotherapy is unknown, three to five years for aeroallergen (i.e., airborne particles that cause allergic reactions) SCIT has been recommended. Patients receiving venom immunotherapy may require life-long administration. For SLIT, three years of therapy (pre- and co-seasonal) is recommended by various guidelines.
- If after discontinuation of immunotherapy of at least one year, it is deemed appropriate to restart immunotherapy for the patient (for example, due to increase in symptoms), consideration can be given to funding of a new course of immunotherapy.
- Due to the specialized nature of allergen immunotherapy, the patient should be under the care of a clinician with expertise in allergy and clinical immunology.

Recommendation 2: Require drug identification numbers (DIN) on all prescriptions for subcutaneous allergen immunotherapy (see Appendix B)

- There are many allergen extracts commercially available with associated DINs (i.e., Health Canada approved) that are used for the compounding of patient-specific serums. Once formulated for a specific patient, the patient-specific serum receives a product identification number (PIN).
- Only extracts with associated DINs should be used in the manufacturing of patient-specific serums. Whenever possible, standardized extracts should be utilized.
- The requirement of DINs on the prescription will prevent the inclusion of in-house manufactured allergen extracts that may not meet minimum manufacturing standards set out by Health Canada.

Recommendation 3: Clinical criteria for use of subcutaneous allergen immunotherapy be developed (see Appendix B)

- There are currently no criteria (e.g., previous therapy, severity of disease) that need to be met prior to approval of SCIT for a patient eligible for ODB funding in Ontario.
- Clinical practice guidelines recommend that patients with allergic rhinitis who have an inadequate response to pharmacologic interventions be referred for immunotherapy.
- Clinical criteria to include:
    - Diagnosis: allergic rhinitis, allergic asthma, history of Hymenoptera insect sting allergy
    - Previous therapy: documentation of previous therapy for patients with allergic rhinitis or allergic asthma (but not patients with history of insect sting allergy)

Recommendation 4: Coverage of sublingual immunotherapy be limited to commercially available SLIT products.

- Ontario currently provides coverage for two commercially available SLIT products (as tablets): Oralair and Ragwitek. In addition, some clinicians use other commercially

available allergen extracts (intended for use in SCIT) to prepare patient-specific SLIT administered as drops. The use of the commercially available allergen extracts for sublingual administration is considered "off-label" use and has little evidence to support it.

- In meta-analyses that have compared SLIT tablets and drops, SLIT tablets are more effective than drops in terms of symptom improvement. The use of multiallergen SLIT administration (via drops) has not been well studied and may not be as effective as single-allergen SLIT.
- It is recommended that patient specific allergen extracts only be administered subcutaneously. Therefore, it is recommended that OPDP not provide coverage for patient specific allergen extracts for sublingual use.

Recommendation 5: Develop pricing structure for patient-specific allergen immunotherapy

- There is currently no pricing structure for compounding of patient-specific allergen immunotherapy. Based on our sample of 100 requests, the average price per claim for venom immunotherapy was $336.85, for environmental/food $379.60, and for environmental allergies $223.75. Prices for individual claims ranged from $106.50 to $709.00.
- Currently, for allergen immunotherapy claims that originate from a pharmacy, information is required for reimbursement including the DIN/PIN #, drug cost/product value and cost upcharge (to a maximum of 10%). The drug cost/product value is calculated based on the actual acquisition cost.[19]
- The basic formula for billing extemporaneous preparations in a pharmacy is: [cost of ingredients] + [compounding charge (= compounding time in minutes x $0.55/minute)] + [upcharge (8%) on ingredients + compounding charge] + [ODB dispensing fee] = total. Using this formula and assuming 3 allergens per patient-specific allergen serum, the total billable costs range from $40.00-$130.00, depending on whether the total cost of the allergen extract (multidose vial) is billed to the patient. Note that most patient-specific allergen serums are not compounded in a pharmacy, but rather in a physician's office or in a manufacturing facility.
- A maximum allowable claim cost is recommended for subcutaneous allergen immunotherapy. The actual amount may vary for environmental and venom immunotherapy, the latter which is significantly more expensive.
- Further studies to develop a pricing structure are needed. It is suggested that members of the OPDP, the Allergy Asthma & Immunology Society of Ontario, College of Physicians and Surgeons of Ontario, Ontario Pharmacists' Association and other interested stakeholders (e.g., individual manufacturing facilities, Canadian Society of Allergy and Clinical Immunology, consumer groups) be invited to participate in these discussions.

Recommendation 6: Provide guidance for safe manufacturing practices for patient-specific allergen immunotherapy

- Cross-reactivity of allergens, the optimal therapeutic dose for each allergen and interallergen degradation must be considered when combining allergens.[20] . In our

review, 13% of allergen serums were characterized as possibly unstable based on evidence-based guidelines for immunotherapy mixtures. In general, extracts with high proteolytic enzyme activity (e.g., mold/fungi, cockroach) should not be combined with allergens with low enzyme activity (such as pollen, dander, dust mite), as studies have demonstrated a significant loss of potency.[21] It is not recommended to mix venom extracts together or venom extracts with other allergen extracts.

- In our review of 100 patient prescriptions for allergen immunotherapy, 13% of allergen serums were characterized as possibly unstable based on evidence-based guidelines for immunotherapy mixtures. This indicates that compounding practices in some facilities may not meet minimum standards, according to the Canadian Society of Allergy and Clinical Immunology (CSACI) and the American Academy Allergy Asthma and Immunology (AAAAI). Note we did not review these prescriptions for cross-reactivity of allergens nor appropriate dosing.
- Other safety considerations include the use of a preservative. Since the patient-specific allergen extracts are multi-dose with a one-year expiry date, a preservative must be included. Although glycerin 50% is the most effective, it also causes pain at the injection site. Human serum albumin with phenol is another diluent that is often used.
- It is recommended that all manufacturing facilities (including pharmacies and physician's offices) follow guidelines as set out by the AAAAI or USP 797. Both guidelines emphasize aseptic technique, handwashing, appropriate refrigerated storage, use of personal protective equipment, beyond-use dating and patient identification on labels.
- Engagement with the Allergy Asthma & Immunology Society of Ontario, Ontario Pharmacists Association and manufacturing facilities is suggested.

Reference List

(1) Focke M, Swoboda I, Marth K, Valenta R. Developments in allergen-specific immunotherapy: from allergen extracts to allergy vaccines bypassing allergen-specific immunologulin E and T cell reactivity. *Clin Exp Allergy* 2010; 40:385-397.

(2) Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127(1):S1-S55.

(3) Wheatley L, Togias A. Allergic rhinitis. *N ENgl J Med* 2015; 372:456-463.

(4) Keith P, Desrosiers M, Laister T, et al. The burden of allergic rhinitis in Canada: perspectives of physicians and patients. *Allergy Asthma Clin Immunol* 2012; 8(7).

(5) Canuel M, Lebel G. Epidemiology of allergic rhinitis in Quebec: from a 2008 population-based survey. *Chronic Dis Inj Canada* 2014; 34(2-3).

(6) Fiocchi A, Fox AT. Preventing progression of allergic rhinitis: the role of specific immunotherapy. *Arch Dis Child Educ Pract Ed* 2011; 96(3):91-100.

(7) Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007; 120(4):863-869.

(8) Price D. Asthma and allergic rhinitis: linked in treatment and outcomes. *Ann Thorac Med* 2010; 5:63-64.

(9) Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127(1):S1-S55.

(10) Schmitt J, Schwarz K, Stadler E, Wustenberg E. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015; Published ahead of print: doi.org/10.1016/j.jaci.2015.07.038.

(11) Cox L. Advantages and disadvantages of accelerated immunotherapy schedules. *J Allergy Clin Immunol* 2008; 122:432-434.

(12) Purkey M, Smith T, Ferguson B, et al. Subcutaneous immunotherapy for allergic rhinitis: an evidence based review of the recent literature with recommendations. *Int Forum Allergy Rhinol* 2013; 3:519.

(13) Lin S, Erekosima N, Kim J, et al. Allergen-specific immunotherapy for the treatment of allergic rhinoconjunctivitis and/or asthma: comparative effectiveness review. *Agency for Healthcare Research and Quality* 2013; 13-EHC061-EF.

(14) Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012; 10:CD008838.

(15) Valenta R, Hochwallner H, Linhart B. Food allergies: the basics. *Gastroenterology* 2015; 148:1120-1131.

(16) O'Keefe AW, De SS, Mill J, Mill C, Dery A, Ben-Shoshan M. Diagnosis and management of food allergies: new and emerging options: a systematic review. *J Asthma Allergy* 2014; 7:141-164.

(17) 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.

(18) 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; 17(27):i-322.

(19) Ontario Ministry of Health and Long-term Care. Ontario Drug Programs Reference Manual. 2005.

(20) Leith E, Bowen T, Butchey J, et al. Consensus guidelines on practical issues of immunotherapy: Canadian Society of Allergy and Clinical Immunology (CSACI). *Allergy, Asthma Clin Immunology* 2006; 2:47-61.

(21) Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127(1):S1-S55.

Appendix A: Health Equity Considerations for Allergen Immunotherapy

Populations **Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.**	**Proposed Allergen Immunotherapy recommendations**
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including allergen immunotherapy, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for allergen immunotherapy were identified.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issued identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.).	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to allergen immunotherapy through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-serviced areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.
Sexual orientation, (e.g., lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment http://www.health.gov.on.ca/en/pro/programs/heia/

Appendix B: Amended Allergy Product form (proposed)

Ontario Ministry of Health and Long-Term Care
Special Authorization (Allergen)

Patient Information (required)		Prescriber Information (required)	
Patient Name:		Prescriber Name:	
Health/Eligibility number:		CPSO #:	Specialty code:
Date of Birth:		Office Address:	
Address:		City:	Postal code:
City:	Postal code:	Office Phone:	

Clinical Information (required)

Diagnosis
□ Allergic rhinitis
□ Allergic asthma
□ History of severe venom sting allergy
NOTE: Other diagnoses, including food allergies, are not eligible for coverage.

Previous pharmacotherapy
Indicate whether patient has a history of failure or intolerance to:
□ Oral antihistamine
□ Intranasal antihistamine
□ Intranasal corticosteroid
□ Leukotriene inhibitor
□ Inhaled corticosteroid
□ Other (specify):

Prescription

Route of administration:
□ Subcutaneous
NOTE: Use of allergen extracts for sublingual administration is not eligible for coverage.

Allergen extract	Concentration	DIN (to be completed by supplier)

Total volume:		
Prescriber's signature:	Date:	
Supplier Information (required)		
Name of Supplier:	Supplier Number:	
Phone number:		
Product information (to be completed by supplier)		
DIN/PIN for final product:		
Drug extract/cost:		
Mark-up:		
Fee:		
TOTAL:		