

Allergen Immunotherapy

Stakeholder Review #1: Information Session

September 2015

GENERAL

Comment: Allergen immunotherapy is a medical therapy that is fairly specialized. We feel your recommendations should specify that the government should provide re-imbusement for allergen immunotherapy that is prescribed by specialists with an expertise in allergy and clinical immunology.

Response: *Currently, the majority of Pollinex-R beneficiaries received their first prescription from a general practitioner, whereas the majority of non-pollen allergen extract beneficiaries (76%) received their first prescription from an immunologist (36%) or pediatrician (34%). 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. A statement has been added to Recommendation 1: “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.”*

Comment: In the Draft consolidated Report on page 16, it is noted that some immunotherapy claims were for “mixed (environmental and food)(3%)”. Food immunotherapy is not yet the standard of care in Canada. This type of immunotherapy is generally completed with oral desensitization or via patch therapy in clinical studies. Food immunotherapy should never be given subcutaneously and this practice should not be reimbursed by provincial coverage. This approach is dangerous as it has a very high risk of anaphylaxis.

Response: *Although allergen immunotherapy (SCIT or SLIT administration) for food was not part of this drug class review, a rapid review (see Environmental Report) was conducted. A section has been added regarding 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. 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. Allergen-specific immunotherapy (administered subcutaneously or sublingually) has been used for the treatment of food allergies, as standardized vaccines are not available. 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.

Comment: In the Draft Budget Impact Analysis on page 5, you estimate the costs for SCIT aeroallergen immunotherapy at \$130 and SCIT venom at \$410. We would suggest using reasonable reimbursement based on the prices provided by the major allergy laboratories such as Omega or ALK. If you wish, estimate the cost based on the lowest price provided by the laboratory to the patient.

Response: *In our budget impact analysis, we used a large range from \$106 to \$224/claim to calculate the budget impact. Estimates for standardized pricing have been developed from analysis of past claim data (using minimum cost and mean costs). In addition, a separate cost analysis was derived from calculations based on compounding fee structures for pharmacies for other injectable products. We have recommended that further studies are needed to develop a pricing structure; stakeholders involved in this discussion should include individual manufacturing facilities (such as ALK-Abello). No changes have been made to the report.*

Comment: **In the Consolidated Report under recommendation 6 on page 7, insect venom is listed as an immunotherapy with high proteolytic activity and therefore, should not be mixed with other allergens. Insect venom immunotherapy should never be mixed with aeroallergen immunotherapy. A separate sentence should be used regarding the proteolytic activity of venom immunotherapy. Including insect venom immunotherapy with mold and cockroach might be confusing for some readers.**

Response:

Thank you for your comment. We have clarified this information to read: Cross-reactivity of allergens, the optimal therapeutic dose for each allergen and interallergen degradation must be considered when combining allergens. 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. It is not recommended to mix venom extracts together or venom extracts with other allergen extracts.

Comment: **We agree that discussing aspects around cost of immunotherapy, the provincial groups are good references and contacts. But the Canadian Society of Allergy and Clinical Immunology has been the leading group regarding the proper prescribing of immunotherapy in Canada. The Canadian Society of Allergy and Clinical Immunology would be happy to be included in any future discussions around the medical and prescribing issues regarding allergen immunotherapy.**

Response: *We have added in the Canadian Society of Allergy and Clinical Immunology as a possible additional stakeholder to include in discussions regarding costs of immunotherapy.*

Comment: **We agree to having some clinical treatment requirements before coverage of immunotherapy is provided. As mentioned throughout the document, immunotherapy is the first line treatment for insect sting allergy. For aeroallergen immunotherapy, oral antihistamines and intranasal corticosteroids should be tried before allergen immunotherapy is prescribed.**

Response: *Thank you for your comment. No change has been made to the report.*

Comment: As mentioned in the recommendation 1 of the report: “Although the optimal duration of immunotherapy is unknown, three to five years for SCIT has been recommended. Patients receiving venom immunotherapy may require life-long administration. For SLIT-T, three years of therapy (pre- and co-seasonal) is recommended.” Hence, we question the value of the LU Authorization Period for only 1 year. It might be more cost-effective for the province of Ontario to avoid repeated visits to physicians. Furthermore, it would help patients and save them the hassles of having to take an appointment with often hard to see physicians, having to miss work and sometime travel long distances.

Response: *Although the optimal duration of therapy is three years for SLIT allergen immunotherapy, a patient assessment is appropriate on an annual basis to delineate whether continued therapy with SLIT is indicated. Therefore, no changes have been made to the report.*

Comment: SLIT-T is safe and leads to long term benefits. In addition, its initiation is controlled by physicians with adequate training and experience in the treatment of respiratory allergic. To help patients that may benefit to receiving treatment at a different time or for a different duration than what is indicated by the criteria, it might be appropriate to accept year-long initiation with SLIT-T. New SLIT-T products are coming (House dust mite, pets,...) and year-long initiation will be important to help patients.

Response: *The currently approved products (Oralair, Ragwitek, Grastek) are administered pre- and co-seasonal (starting between 8-16 weeks before allergy season and maintained throughout the season). There are no commercially available SLIT-tablet products for other allergens such as house dust mite, cats, dogs etc. Once these products are available, recommendations for their administration can be reviewed. No changes have been made to the report.*

Comment: This review provided the opportunity to review the evidence behind all SLIT-T products. GRASTEK™ was accepted by RAMQ (INESSS) with the same clinical evidence that was submitted to CDR/Ontario/PCPA. We are convinced that GRASTEK™ could help many allergic patients in Ontario as it does in Quebec. If the result of this review allows for it, it might be appropriate for the ODPN to highlight the fact that GRASTEK™ owns evidence that is similar or better than other SLIT-T products and underling the incongruity of GRASTEK™ not being available for Ontarians.

Response: *Grastek has already been reviewed by the OPDP (January 22, 2015) and the funding decision was not to provide coverage. In our drug class review, we did not consider individual commercially available products but rather looked at the category (e.g., SLIT-tablets). No changes have been made to the report.*

Comment: Contrarily to SCIT, for which all doses need to be administered under medical supervision, only the first SLIT tablet needs to be supervised and all other doses are self-administered by the patients without having to go to a clinic. SLIT-T can be done at home, hence could be more convenient for patients, in addition to be less costly to the health care system (fewer visits to physicians). However, the requirement to have having access to an allergist or a trained physician to prescribe can be a challenge for patients. They also often forget to plan in advance of the allergy season and take appointments late in the season. Widening the right to prescribe SLIT-T to General Practitioners would save significant time and money to patients, as demonstrated by literature (i.e. Time and Motion Study submitted with RAGWITEK™).

Response: *It is recommended that the patient should be under the care of a clinician with expertise in allergy and clinical immunology due to the specialized nature of allergen immunotherapy (e.g., diagnosis, choice of immunotherapy, safety). A statement has been added to Recommendation 1: 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.*

Comment: An important angle not much discussed in the report is the importance of diagnosis (allergy testing). We simply want to bring to your attention the importance to have broad access to diagnosis/testing for patients to get accurate and frequent testing before they can have access to immunotherapy products through public reimbursement. Allergies evolve overtime hence that would help ensure the right treatment goes to the right patient.

Response: *Thank you for your comment. Our drug class review only focused on treatment with allergen immunotherapy; diagnosis of allergies was outside the scope of our review. No changes have been made to the report.*

Comment: Recently, many trials have been published mixing the results of SLIT-T (tablet) and SLIT-D (drops). Even though they have a similar mode of absorption their pharmacodynamics is different and the evidence of one formulation cannot be applied to the other. Therefore it is pivotal to differentiate between SLIT-T (which have received NoC, and are standardized tablets) and SLIT-D (drops, which are non-standardized). This is as important as differentiating SCIT to SLIT and should be emphasized in the report.

Response: *One of the recommendations is that coverage of sublingual immunotherapy be limited to commercially available SLIT products. A more detailed review of SLIT (via drop and tablet administration) was done for the Environmental Scan report. In the summary it states: In meta-analyses that have compared SLIT tablets and drops, SLIT tablets are more effective than drops in terms of symptom improvement. No changes have been made to the consolidated report.*

Comment: Based on understanding, no head to head studies have been realized between SLIT-T and SCIT (only between SLIT-D and SCIT), hence it might be appropriate to double check and possibly correct the report to make sure it is accurate. In the same spirit, the report would probably be more balanced if the number of death associated to SCIT was also reported, not only the number for SLIT-T.

Response: *In the review of systematic reviews, our rapid review team included SCIT and SLIT products; all SLIT products (including tablet and drops) were evaluated as one group. A more detailed discussion of SLIT administered via drop or tablet was done for the Environmental Scan report. A statement has been added to the consolidated report to clarify the statement: Most of the included systematic reviews compared either SCIT or SLIT (administered via drop or tablet) to placebo.*

A more detailed explanation of the deaths associated with SLIT is provided in the report (see comment below).

Systematic Review Unit

Comment: In a few of your documents, there is reference to 3 deaths that occurred in patients receiving SLIT. In the table on page 22 of the Draft Systematic Review Report it is noted “There were no deaths reported in studies GT-07, GT-02, GT-14, GT-12 and P05239. In studies GT-08, P05238, and P08067 one death was reported in each study, as described below, but none were considered by the manufacturer to be treatment related.” Allergists believe that there have not been any deaths with the use of SLIT. If these deaths were not treatment related, then comments regarding death and SLIT should be removed or greatly downplayed. If these deaths are felt to be remotely related to SLIT, then this should be highlighted and all allergists should be made aware of this risk.

Response: *Thank you for your comment. We agree that this information could appear potentially conflicting. In our review of systematic reviews, we have summarized the findings of previously published systematic reviews. Our outcome of interest was all-cause death, defined as any death reported in a systematic review. In this way, we did not make a distinction between deaths related or unrelated to the study medication.*

In the 2014 review by the Canadian Agency of Drugs and Technologies in Health, the authors state that “In studies GT-08, P05238, and P08067, one death was reported in each study, as described below, but none were considered by the manufacturer to be treatment related.”

The additional text provided by the authors states that “In study GT-08 (first year), a 31-year-old male participant in the PPAE treatment group was diagnosed with subarachnoid haematoma/ subarachnoid haemorrhage and later died. In study P05238, a 28-year-old male patient in the PPAE group suffered a multiple drug overdose. In study P08067, a 42-year-old male patient who had been treated with PPAE completed the study and had reported no adverse events during the study. He later died. He had been off the study drug for a month. The cause of death was reported as unknown.”

This information has been added to the Systematic Review team's report, as well as to the consolidated report.