November 21, 2003

Sent to all the Staff Contributors and Medical Advisory Board members

Dear Dr. ,

As a BCBSA TEC Assessment Staff Contributor or Medical Advisory Board member, we are writing to you in regards to your June 2003 publication, Volume 18, No. 4, entitled Sublingual Immunotherapy (SLIT) for Adults. Healthcare insurers regard your assessment documents as a benchmark for determining coverage. As a provider of allergy care, we felt it necessary to share with you additional, updated evidence pertinent to your assessment. Our concern is that coverage decisions made based upon the information presented in your review document will have a costly impact on insurers and negatively affect the quality of life of many patients who benefit from SLIT. Allergy leaders agree on the fact that immunotherapy has a significant positive impact. We ask you to consider amending your assessment based on the information presented.

We've known of the value of SLIT for many years as we have successfully treated thousands of patients, many who are members of BCBS plans (WI, MN, IL, MI and IA/Wellmark…). These members/patients come to us because they have run out of, or have no viable, alternatives to address their allergic disease. They continually share with us their growing frustration with the rejection of SLIT treatment when they are seeing significant results. Many take the matter into the appeal process with your plans. They see/learn through the media, on-line resources, friends and family members that SLIT has helped thousands of people all over world. They see an impressive body of research accumulated over many years and ask…why isn't SLIT advancing in the U.S.?

We commend you and your colleagues' effort in producing the most extensive TEC assessment of SLIT to date. Your assessment focused on the question…does SLIT work as well as injection (ASIT)? As you document, there are few head-to-head comparative studies of these therapies, and we would agree that SLIT being judged superior to injections is difficult to determine with few studies. Should there be more head-to-head research? Certainly that could answer this question. We are aware of an additional, major, head-to-head study that was recently accepted for publication. But, your consideration is needed of the 50+ non-comparative DBPC SLIT studies that show SLIT is safe and effective. Thus, the question better addressed is …where does SLIT fit as a therapeutic tool for allergists as a route of administration for currently untreated populations of chronic allergy sufferers? This is a logical question given the international allergy community has crossed this bridge and have hundreds of thousands of properly indicated allergy sufferers benefiting from SLIT. Is there a difference in SLIT in the U.S. and elsewhere? These questions are addressed in the supporting materials.

At the heart of an Evidence Based Medicine (EBM) evaluation of SLIT we present to you the April 2003 report released by the Cochrane Collaboration. U.S. allergy leaders acknowledge Cochrane as one of the most trusted, thorough and independent sources for health technology assessment available. Their SLIT review included 22 sublingual studies that met international criteria for their "methodological quality", and were carefully selected by experienced allergy researchers. A total of fifteen (15) studies are common between your assessments and the Cochrane Review. Dr. Steven Durham led the triumvirate of reviewers for Cochrane. He is one of the most active and well-published international researchers in immunotherapy, studying all routes of administration. Dr.

Durham and his colleagues are well respected in the U.S. We expect the allergy experts you worked with for your review as TEC Staff Contributors, or BCBSA Medical Advisory Panel members, would know Dr. Durham's work well.

The Cochrane Review concludes of SLIT results "…demonstrates the efficacy of SLIT compared to placebo in terms of reduction in rhinitis symptoms scores and anti-allergic medication requirements". Regarding the question…Does SLIT work better than injection immunotherapy? Their review, like yours, concludes that this is not possible to determine from the limited head-to-head studies addressing this question. But, Cochrane reviewers do go on to state, "the results are convincing and consistent findings across a large number of studies including 979 patients." They also go on to address the question…is SLIT safe? The reviewers say, "Of particular note is the apparent safety of SLIT confirming its potential for outpatient based treatment with home administration of allergen, which is increasingly employed in continental Europe." The Cochrane Review presents sound evidence to shift the discussion of injections **rather than** sublingual. It redirects the decision to where different forms of immunotherapy can positively impact patient outcomes using two clearly viable routes of administration.

The balance of this document is presented in the spirit of collaboration in raising awareness on SLIT treatment and addressing areas where ambiguous information may be interpreted in your report. When taken in its totality, you will see that SLIT is not only effective, but also extremely safe, thus attributing to improved patient compliance. We also have extensive experience and evidence showing the net cost effectiveness of SLIT over a course of treatment (3-5 years). Most importantly, SLIT is a treatment available to patients who benefit the most from immunotherapy, those with severe allergies and chronic conditions (asthma, sinusitis, urticaria...). It impacts their healthcare utilization to yield insurers a high return on investing in the coverage of this technology.

At a time in this country where all facets of healthcare are under intense pressure to find ways to better manage costs and improve outcomes, you have the opportunity to bring a valuable tool in SLIT to simultaneously address both these challenges. As you so eloquently point out in your website " Evidence-based medicine is needed to find the balance in physicians delivering care to patients". We trust this exchange of ideas can help move your organizations towards acceptance of this technology. Judged on the same standards as other treatments, SLIT can be added as a valuable tool for allergist in the U.S. Thank you for allowing us to present this information and placing it in the public record. We look forward to hearing from you and your colleagues.

Jeffrey J. Kessler

President, Allergychoices, Inc.
Practice Executive, Allergy Associates of La Crosse, Ltd. *
*on behalf of Drs. David Morris, George Kroker, Vijay Sabnis Mary Morris

DETAIL RESPONSE AND SUPPORT INFORMATION

We have found several statements or areas in your report where further elucidation is needed. Each area is addressed in a direct discussion of the criteria used by BCBSA to identify "investigational" treatments. References are made to the main body of your report.

Extracts – on page 2, first paragraph, of your report it states "preparations used in the published placebo-controlled studies are unavailable in the U.S. This statement is accurate in terms of the "preparations" meaning that some European studies have been performed with preparations that use differing diluents. However, the underlying allergens are the same. In researching this question with several antigen manufacturers involved in both the European and U.S. markets, the resounding conclusion is that there is no meaningful difference in the allergens. An issue that is being resolved is the standardization in units of measure (AU, BAU, mcg…). The fact that a broader selection of the diluents can be used in the sublingual preparations does not negate the research outcomes. For instance, the typical sublingual vial prepared for a patient is diluted with a 50% glycerinated solution to enhance the stability of the vial while the patient is administering a treatment set of the drops (30-45 days). There is no identifiable issue with the suitability of standardized allergen extracts for SLIT administration.

Dose concentrations - on page 2 paragraph 2 of your report it states " …allergen doses for SLIT usually are 50 to more than 300 fold greater than doses for subcutaneous injection." The research studies that you included in your report, along with those of the Cochrane, and 6 additional studies subsequent to your review, indicate a quite different dosing range conclusion. In an extensive review of the literature performed and published this May by Kargers in the text *Local Immunotherapy in Allergy*, Chemical Immunology and Allergy Vol. 82. An analysis of nearly twenty studies showed that efficacy and safety for SLIT occurred over a broad range of dosing regimens. In fact, from equivalent (1X) average subcutaneous dosing, to 200 times it. An effective dosing range is not unusual for immunotherapy in that it may vary considerably based upon many factors concerning the patient and allergen type. Injection dosing for example has been demonstrated as effective over a broad range (20X), albeit not as broad as sublingual. There are many potential reasons for the wider range in dosing with sublingual. A primary reason is its safety profile, being well tolerated. The mucosa is quite tolerant of higher doses of antigens, but evidence shows extremely high doses (200X or more) are not providing efficacy advantage. Additionally, the flexibility with how SLIT can be administered (multiple times daily, daily, multiple times weekly…) contributes to the cumulative doses. What is becoming clear from research is the importance of keeping the allergen constantly resident in the mucosa. The dosing regimens employed at the Allergy Associates of La Crosse, and taught to other allergists through the Allergychoices education programs, are typically 3-20X injection doses, matching very closely with the average found in looking across all SLIT studies.

Criteria for a good study – on page 2, under statement 2 your report discusses the scientific evidence in terms it "…must permit conclusions concerning the effect of the technology on health outcomes". The studies included in your report were considered "unsatisfactory" for a variety of reasons, only two studies were considered "good". Respectfully, we submit that the World Health Organization (rated the majority of these studies "A") and Cochrane reviewers found the majority of the same studies to be "methodically sound". Additionally, there have been six (6) SLIT treatment studies and one safety study published subsequent to date of the studies included in your report and potentially meritorious to be included in your review. (see following list)

1. Andre, et al "A Double-Blind Placebo-Controlled Evaluation of Sublingual Immunotherapy with a Standardized Ragweed Extract in Patients with Seasonal Rhinitis, Intl Arch Allergy Immunol, 131: pgs. 111-118, 2003.

2. Ippoliti, F, et al "Immunomodulation during sublingual therapy in allergic children", Pediatric Allergy and Immunology, Vol. 14, pgs. 216-221, 2003

3. Mortemousque, B, et al "House-dust mite sublingual –swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study", Clinical and Experimental Allergy, Vol. 33, pgs. 464-469, 2003.

4. Cirla, A.M. et al "A pre-seasonal birch/hazel sublingual immunotherapy can improve the outcome of grass pollen injective treatment in bisensitized individuals. A case-referent, two year controlled study", Allergol et Immunopath Vol. 31(1) 31-43, 2003.

5. Patriarca, G. et al. "Oral desensitizing treatment in food allergy: clinical and immunologic results", Ailment Pharmacol Ther, Vol 17, pgs. 459-465,

6. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy, Letter to the editor, JACI, June 2003, page 1406-09

1. 2003Grosclaude, M, et al "Safety of Various Dosage Regimens during Induction of Sublingual Immunotherapy", International Archives Allergy and Applied Immunology, Vol. 129 (3), pgs 248-253, March 2003

We ask you to reconsider the evaluation of the studies. There may be heterogeneity in the studies as a whole, but also a resounding conclusion of efficacy and safety in the results.

Inconclusive improvement in net health outcomes, medication use – on page 3, section three of your report the statement is made "…it could not be determined if whether the reduction was sufficient to result in a clinically meaningful benefit to patients". To address this statement we again turn to the Cochrane review, where using their refined meta-analysis techniques conclude that medication scores reporting "…the 17 remaining studies data from 405 immunotherapy patients and 398 placebo recipients were included. The combined SMD for medication scores following SLIT was –0.43 (95% confidence interval (–0.63to –0.23) indicating a significant reduction in medication use p=0.00003). This appears conclusive.

The technology must be as beneficial as any established alternative – on page 3, section 4 your report states, " The established alternative to SLIT is injection ASIT. Whether SLIT improves health outcomes when compared with injection ASIT cannot be determined from the available evidence." Then the balance of this section lists the many "methodological problems" that preclude the ability to a valid comparison. There are only two published head to head studies, however a third more comprehensive study, double/dummy, double blind comparing both SLIT and injection versus placebo has recently been accepted for publication in the peer reviewed journal *Allergy*. The lead researcher is Dr. Hans-Jorgen Malling, a world-renowned researcher. The study, currently available as an abstract, concludes "High dose sublingual immunotherapy is comparable in efficacy with subcutaneous immunotherapy in the treatment of birch allergic rhinoconjunctivitis, and the severe side effects are substantially reduced with sublingual immunotherapy".

Also in section 4, on page 3, the second paragraph, of your report it states "…trials of SLIT did not test the persistence of clinical benefits after effective immunotherapy was terminated." This issue has been addressed in several longitudinal studies; most recently it is addressed by a 2003 study tracking 60 children over a 10-year period, concluding "…sublingual immunotherapy is effective in children and that it maintains the clinical efficacy for 4 to 5 years after discontinuation." (See citation below).

> Di Rienzo, V., Canonica, GW, and Passalacqua G. "Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10 year prospective study", Clinical and Experimental Allergy, Vol. 33, pgs. 206-210, 2003

For many patients they have no alternative. Injection ASIT is not a viable alternative for several large classes of patients: Children 6 years and younger are not offered immunotherapy as a protocol in the U.S. Severely asthmatic, severely mold allergic, chronic urticaria and chronic sinusitis suffers are not ASIT candidates either. Additionally, a percentage of allergic patients are non-compliant due to an inability to tolerate injections with out debilitating reactions. Patients in rural geographies or those lacking transportation may not comply with an injection schedule due to the travel requirement to an allergists/physicians office.

The improvement must be attainable outside the investigational setting – on page 4, section 5, your report states, "Whether SLIT improves health outcomes when compared with injection ASIT has not yet been demonstrated in the investigational setting. It is uncertain whether FDA-licensed allergen preparations manufactured for allergy testing and injection are suitable for sublingual administration".

As presented earlier, if studies only taken in head-to-head comparison with ASIT the results of such studies are mixed. Health outcomes do improve in one study, but are equivocal in another. Newly published data (Malling) will show clear health outcomes with SLIT. Regarding the use of antigens for SLIT, again this was addressed earlier in this document. No meaningful differences in standardized antigens are found with SLIT.

The primary question of this section is…has health outcome improvement been attainable outside of the investigational setting? The evidence to answer this question is best found in the thousands of BCBS plan members around the U.S. whom have attained improvement. Many of these patients have tried to communicate this in their appeal and grievance activities with many of your health plans. An independent study earlier this year of 750 SLIT patients showed significant increases in quality of life measures, at the same time healthcare utilization (illnesses, hospitalizations, medication use…) was reduced significantly. To review a summary of the results visit www.allergy-solutions.com/images/files/b2256_file1_25705.pdf. In closing, there have been tens of thousands of patients treated successfully with SLIT in the U.S. over the past few decades. We hope you will agree that the time has come to add SLIT as another valuable tool for allergists to fight allergic disease.