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Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers sublingual immunotherapy (SLIT) as a technique of allergy immunotherapy to be **investigational.***

Background/Overview

Sublingual immunotherapy is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. It is proposed as a more convenient alternative delivery route for treating a variety of allergic disorders.

Allergen-specific immunotherapy involves administering well-characterized allergen extracts, the potencies of which are measured and compared with a reference standard. An initial induction or build-up phase progressively increases the allergen dose; this is followed by multiple years of maintenance injections at the highest dose. Allergen-specific immunotherapy has been used to treat a variety of conditions including insect allergy, allergic rhinitis, and asthma. Subcutaneous injection of allergen-specific immunotherapy is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, SLIT is the most prominent. Sublingual immunotherapy targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue for one to several minutes and then swallowed or spit out.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
No allergy extracts for SLIT are currently cleared or approved by the U.S. FDA.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Sublingual immunotherapy compared to placebo
At the time of the 2003 TEC Assessment, there were 21 published placebo-controlled trials suggesting that SLIT decreased one or more symptoms for patients with pollen or dust mite allergies. Systemic adverse effects occurred in only one study, and these were not life-threatening. However, whether SLIT improved health outcomes when compared with injection allergen-specific immunotherapy (SCIT), the gold standard comparison, could not be determined from the available evidence. There were only 2 trials that directly compared SLIT with SCIT, and these had small sample sizes and were of small duration. Due to the paucity

of studies comparing SCIT to SLIT and the lack of FDA-approved agents for use in SLIT, the use of SLIT for allergen immunotherapy was considered investigational.

Since the TEC Assessment, numerous placebo-controlled randomized, controlled trials (RCTs) and meta-analyses of RCTs have been published. In 2013, Lin and colleagues conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on allergen-specific therapy for treating allergic rhinoconjunctivitis and/or asthma. The authors identified 60 studies comparing SLIT to placebo or another intervention. (Studies using SCIT as the comparison intervention were evaluated separately; see section below on SLIT compared to SCIT). Over two-thirds of the studies (71%) compared SLIT to placebo, 14% compared SLIT to pharmacotherapy or rescue medication, and 15% compared SLIT to another intervention. Most of the studies (66%) evaluated seasonal allergens, 31% evaluated perennial allergens and the remainder addressed both types of allergens. About half of the studies used only one allergen and the other half used multiple allergens. Only 22% of the studies were rated as having a low risk of bias. Most (68%) were considered to have a moderate risk of bias and 14% to have a high risk of bias. The authors did not pool study findings because of heterogeneity among studies, i.e., in types of allergen extracts, sources of allergen extracts, doses, treatment duration, and outcome scoring systems. The review concluded that there is high-grade evidence that SLIT improves asthma symptoms compared to placebo or another intervention (13 RCTs) and moderate-grade evidence that SLIT improves rhinitis/rhinoconjunctivitis symptoms compared to placebo or another intervention (35 RCTs). There was moderate-grade evidence that SLIT improves other outcomes in this population, e.g., decreased medication use and increased quality of life. Lin and colleagues also published the findings of the systematic review in a peer-reviewed journal in 2013. The review focused on studies comparing SLIT to placebo, pharmacotherapy or another SLIT regimen and did not address SCIT. Like the AHRQ review, study findings were not pooled. The authors noted that high-quality studies are needed to determine optimal dosing strategies.

In addition, several reviews of systematic reviews have been published. In 2011, de Bot and colleagues evaluated the quality of systematic reviews and meta-analyses on SLIT for treating allergic rhinitis in children. The investigators used the Assessment of Multiple Systematic Reviews (AMSTAR) quality evaluation tool to rate the reviews. The maximum score on the AMSTAR is 11; a score of 0-4 = low quality, 5-8 = moderate quality, and 9-11 = high quality. The authors identified 10 systematic reviews. None of these were rated as high quality; 6 were rated as moderate quality, and 4 as low quality. This analysis indicates that while there are numerous systematic reviews on SLIT, the methodologic quality remains suboptimal. This research suggests that SLIT for children could be promising, but methodologic flaws preclude definitive conclusions.

In 2009, Compalati and colleagues evaluated meta-analyses of RCTs on specific immunotherapy for respiratory allergy. They identified 7 meta-analyses of placebo-controlled RCTs using well-defined inclusion criteria, allergens, doses, and outcome measurement; 5 were on SLIT and 2 were on SCIT. Regarding evidence on SLIT, this analysis corroborated that there is evidence of efficacy compared to placebo but that questions remain, in particular regarding the optimal dose. This review highlighted the lack of consistent relationships between treatment dose, duration, and clinical efficacy.

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Representative meta-analyses are summarized briefly below.
A 2012 meta-analysis by Di Bona and colleagues focused on studies of immunotherapy in adults and children with seasonal allergic rhinitis. To be included in the meta-analysis, trials needed to be double-blind, placebo-controlled and evaluate natural grass pollen extracts for treating individuals with a history of grass pollen allergy. The authors identified 22 trials on SLIT versus placebo; 10 used sublingual drops and 12 used tablets. The authors also identified 14 studies on SCIT versus placebo. The investigators conducted an indirect meta-analysis, evaluating the impact of SLIT and SCIT, compared to placebo, on outcomes. The primary outcomes of the meta-analysis were reduction in symptoms and reduction in medication use. Because studies used different scoring symptoms, effect size was calculated as a standard mean difference (SMD). Compared to placebo, both SCIT and SLIT (drops and tablets) resulted in significantly greater reductions in symptom and medication scores. The effect size of SCIT versus placebo for the symptom score was -0.92 (95% confidence interval [CI]: -1.26 to -0.58). The effect size for SLIT administered via drops was SMD: -0.25, 95% CI: -0.45 to -0.05 and for SLIT administered by tablets was SMD: -0.40, 95% CI: -0.54 to -0.27. Results were similar for medication use. The investigators noted the larger effect sizes in their pooled analysis of studies comparing SCIT to placebo.

A 2011 Cochrane review addressed SLIT for treating allergic conjunctivitis in adults and/or children. A total of 57 trials met inclusion criteria, and 42 of these had data available for meta-analysis. All of the trials were conducted in countries other than the United States. The primary outcome of the meta-analysis was the total ocular symptom score. In a pooled analysis of data from 36 trials with a total of 3,399 participants, there was a significantly greater reduction in total ocular symptom scores in the SLIT group compared to placebo (SMD: -0.41, 95% CI: -0.53 to -0.28, $p < 0.0001$). This review supports the conclusion that SLIT is moderately effective in reducing ocular symptom scores compared to placebo but that concerns about the overall quality of the evidence base remain.

In 2011, Radulovic and colleagues published a meta-analysis of double-blind, placebo-controlled RCTs on SLIT for allergic rhinitis in adults and/or children. Sixty studies met inclusion criteria, and 49 (total n = 4,589) of these had efficacy data available suitable for meta-analysis. Most of the studies (n = 23) used grass pollen; other allergens used included ragweed, house dust mites, and trees. In a pooled analysis of study findings, there was a significantly greater reduction in symptom scores with active SLIT treatment compared to placebo (SMD: -0.49, 95% CI: -0.64 to -0.34, $p < 0.0001$). In addition, a pooled analysis found a significantly greater reduction in medication use scores with SLIT versus placebo (SMD: -0.32, 95% CI: -0.43 to -0.21, $p < 0.0001$).

Using Cochrane methodology, in 2006 Calamita and colleagues published a meta-analysis of SLIT in adults and children with asthma. Asthma parameters (n = 876) showed small but significant, improvements (using standardized mean difference). However, when just symptoms were analyzed (n = 303), there was a non-significant improvement using SLIT over placebo.

Sublingual immunotherapy compared to subcutaneous immunotherapy
Few published randomized trials have compared SLIT and SCIT head-to-head. A 2012 review by Bahceciler and Galip listed 8 RCTs comparing SLIT and SCIT. Sample sizes in individual studies ranged from 20 to 58 participants. Three of the studies were published in the 1990s and the other 5 were published

between 2004 and 2012. Pipet and colleagues reported that none of the studies from the 1990s found a statistically significant difference in efficacy between the 2 routes of administration. Three of the newer RCTs compared the efficacy of dust-mite specific SLIT and SCIT and were published by investigators in Turkey. Similar to the older studies, none of these RCTs found statistically significant differences between treatment with SLIT and SCIT in overall reduction of symptoms or medication use. For example, Eifan and colleagues published findings on 48 children with asthma or rhinitis who had been sensitized to house dust mites. Participants were randomized to receive treatment with SLIT (n = 16), SCIT (n = 16), or usual pharmacotherapy alone (n = 16). There was no significant difference in efficacy between the SLIT and SCIT groups. Compared to pharmacotherapy alone, both immunotherapy groups demonstrated significant reduction in rhinitis and asthma symptom scores and medication use scores.

The 2013 AHRQ comparative effectiveness review, discussed above, identified 8 RCTs comparing sublingual and SCIT. The report stated that only 1 study was considered to be at low risk of bias and most of the studies had biases related to improper concealment of allocation to the interventions, unblinded interventions and incomplete reporting of missing data. The authors were unable to pool study findings because of heterogeneity. Regarding the question of comparative effectiveness of SLIT and SCIT, the report concluded that there was low-grade evidence that SCIT is more effective than SLIT at controlling allergy symptoms and dust mite allergy symptoms. Moreover, the report concluded that there was moderate-grade evidence that SCIT provides better symptom control for allergic nasal and/or eye symptoms than SLIT.

Also in 2013, Dretzke and colleagues published a systematic review that included an indirect comparison of SCIT and SLIT using data from placebo-controlled trials. Several outcomes were examined. For symptom score, the overall standardized score difference (SSD) was 0.35 (95% CI: 0.13 to 0.59), a statistically significant result that favored SCIT. The overall SSD for medication score was 0.27 (95% CI: 0.03 to 0.53) which was statistically significant in favor of SCIT. The authors noted that there was substantial heterogeneity among trials and that it is difficult to draw conclusions about the clinical significance of the difference in outcomes between SCIT and SLIT.

In 2011, Sieber and colleagues published a meta-analysis of individual patient data from 4 observational studies on treatment of allergic rhinitis. A total of 665 patients were treated with SLIT and 182 with SCIT. The median rhinitis symptom score decreased from 3.00 to 2.00 (range 1.00 to 4.00) in both treatment groups; $p < 0.001$ for changes within-group. The median conjunctivitis symptom score decreased from 2.00 to 1.00 (range 0.00-3.00) in each group; $p < 0.001$ for changes within-group. In addition, the median asthma symptom score decreased from 3.00 to 2.00 (range 1.00-4.00) in each group; $p < 0.001$ for changes within-group. There were no significant differences in symptom scores when the SLIT group was compared to the SCIT group.

In terms of the relative safety of SCIT and SLIT, the 2009 Pipet review cites reports of fatalities after SCIT, although subsequent examination of 13 deaths occurring between 1992 and 1996 suggested that unstable asthma was a major risk factor. It is generally believed that SCIT is safe when performed with proper patient selection and established security principles. A 2012 review of SLIT for allergic rhinitis stated that no SLIT-related fatalities have been reported. There may be a larger number of mild-to-moderate adverse effects

with SLIT than SCIT. The 2012 meta-analysis by Di Bona and colleagues included 22 placebo-controlled studies on SLIT and 14 on SCIT The investigators identified a total of 960 adverse events (AEs) in patients who received SCIT (0.86 AE per patient) and 4,046 AEs in patients who received SLIT (2.13 AEs per patient). Most of the AEs were modest in severity. The authors did not report the total number of serious AEs. However, they stated that there were 12 episodes of anaphylaxis requiring epinephrine treatment in patients treated with SCIT and only 1 in patients treated with SLIT. There were also 2 reported episodes of anaphylaxis in patients treated with placebo in the SCIT studies.

Ongoing Clinical Trials

Long-Term Effects of Sublingual Grass Therapy (NCT01335139): This double-blind trial is randomizing adults with seasonal allergic rhinitis to treatment with SCIT and placebo SLIT or SLIT and placebo SCIT. The primary outcome is nasal response to an allergen challenge and secondary outcomes include use of rescue medication, quality of life and hay fever severity. The estimated completion date is September 2014.

Summary

Sublingual immunotherapy is a potential alternative to SCIT for providing allergen-specific therapy. Despite multiple placebo-controlled studies evaluating SLIT, questions remain about the optimal dosing, duration of treatment, and the use of multiple allergens. Moreover, there are few head-to-head studies comparing SLIT to SCIT. The limited number of comparative trials tended not to find statistically significant differences in outcomes with SLIT versus SCIT. Sample sizes were generally small and the studies likely had limited statistical power. Thus, conclusions cannot be drawn from these data about the relative efficacy of the 2 treatment approaches. There are also insufficient data to draw firm conclusions about the relative safety of SLIT versus SCIT. A recent meta-analysis of placebo-controlled trials suggests there may be more mild-to-moderate AEs with SLIT than SCIT, but there are only data on a small number of serious AEs. Because of the above limitations in the evidence and the absence of any FDA-approved allergy extracts for SLIT, this treatment is considered investigational.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	95199
HCPCS	J3590
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

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B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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