APPENDIX to Sublingual Immunotherapy for Allergen-Specific Therapy Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

This policy is based on a 2003 Blue Cross Blue Shield Technology Evaluation Center (TEC) Assessment of sublingual immunotherapy (SLIT) which offered the following observations and conclusions:

- Data from 21 placebo-controlled trials suggested 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. Evidence on whether SLIT may also reduce use of rescue medications was conflicting and inconclusive. Most of the trials had small sample sizes.
- Whether SLIT improves health outcomes when compared with injection allergen-specific immunotherapy could not be determined from the available evidence. The results of two trials that directly compared SLIT with subcutaneous immunotherapy were insufficient to permit conclusions; patient groups in each trial were small (10 to15 patients per arm), and each was of short duration.

Due to the paucity of studies comparing the gold standard of subcutaneous injection immunotherapy to SLIT, and the lack of U.S. Food and Drug Administration (FDA)-approved agents for use in SLIT, use of SLIT for allergen immunotherapy was considered investigational.

Sublingual Immunotherapy Compared to Placebo

Since the TEC Assessment, numerous placebo-controlled and meta-analyses of randomized controlled trials (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 subcutaneous immunotherapy (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 to 4 equaled low quality, 5 to 8 equaled moderate quality, and 9 to 11 equaled high quality. The authors identified 10 systematic reviews. None of these were rated as high quality; six were rated as moderate quality, and four 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 seven meta-analyses of placebo-controlled RCTs using well-defined inclusion criteria, allergens, doses, and outcome measurement; five were on SLIT and two 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.

Summary of Representative Meta-Analyses

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 (Calderon et al., 2011). 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, $p<0.0001$]).

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 eight 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 five were published between 2004 and 2012. Pipet and colleagues (2009) reported that none of the studies from the 1990s found a statistically significant difference in efficacy between the two 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 (Eifan et al., 2010; Keles

et al., 2011; Yukselen et al., 2011). 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 (2010) 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 eight RCTs comparing sublingual and subcutaneous immunotherapy (Lin et al., 2013). The report stated that only one 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 sublingual immunotherapy for allergic rhinitis stated that no SLIT-related fatalities have been reported (Wise & Schlosser, 2012). 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 one in patients treated with SLIT. There were also two reported episodes of anaphylaxis in patients treated with placebo in the SCIT studies.

Practice Guidelines and Position Statements

In 2013, the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology published a consensus report on allergy immunotherapy (Burks et al., 2013). The report summarized the literature and current practices in the United States and Europe; it did not include clinical recommendations. The authors concluded:

> AIT (allergy immunotherapy) is effective in reducing symptoms of allergic asthma and rhinitis, as well as venom-induced anaphylaxis. In addition, AIT modifies the underlying course of disease. However, AIT remains a niche treatment secondary to symptomatic drugs because of its cost, long duration of treatment and concerns regarding safety and effectiveness...

In 2011, a joint task force of the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology issued updated practice parameters for allergen immunotherapy. The document stated that RCTs of SLIT for individuals with allergic rhinitis and asthma have demonstrated significant improvement in symptoms. The authors note that there are no FDA approved extract formulations for a non-injection route of immunotherapy.

The Centers for Medicare and Medicaid Services (CMS) has established a National Coverage Decision (NCD) regarding sublingual immunotherapy (110.9). The NCD states that sublingual allergy therapy has not been proven to be safe and effective. Antigens are covered only if they are administered by injection (CMS, 2012).

Summary

Sublingual immunotherapy (SLIT) is a potential alternative to subcutaneous immunotherapy (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 trial tended to have small sample sizes and were likely underpowered. Several 2013 systematic reviews tended to find better outcomes with SCIT than with SLIT, but findings are not conclusive due to the limited number of trials and variability in study design. 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 adverse events with SLIT than SCIT, but there are only data on a small number of serious adverse events. Because of the above limitations in the evidence and the absence of any FDA-approved allergy extracts for sublingual immunotherapy, this treatment is considered investigational.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	95199	Unlisted allergy/clinical immunologic service or procedure [when specified as sublingual immunotherapy]
HCPC	None	
ICD9 Procedure	99.12	Immunization for allergy [when specified as sublingual immunotherapy]
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Allergy Testing

Key / Related Searchable Words

- Allergies
- Allergy immunotherapy
- Immunotherapy
- Sublingual immunotherapy

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
12/7/2006	BCBSA Medical Policy adoption	Medical Policy Committee

Effective Date	Action	Reason
1/7/2011	Policy title change from Sublingual Immunotherapy as a Technique of Allergen Specific Therapy Policy revision without position change	Medical Policy Committee
8/6/2013	Policy revision without position change. Policy placed on No Further Routine Literature Review and Update status.	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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