SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY (cont.)

Description:

Allergy or hypersensitivity disorders may be manifested by localized or systemic reactions. Reactions may be acute, subacute or chronic, immediate or delayed, and caused by numerous allergens including pollen, venomous stinging insects (insects from the Hymenoptera family), foods, drugs, fur, mold, dust, animal dander and mites. The offending allergen can be diagnosed/identified by history, physical exam and various types of allergy testing.

Treatment is provided by immunotherapy, medication or avoidance. The goal of immunotherapy is to reduce symptoms by administering regular injections of the offending allergen. Therapy begins with low doses which gradually increase as immunity develops.

Sublingual (under the tongue) immunotherapy (SLIT) has been investigated as an alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy for a variety of allergic disorders. In April 2014, Oralair® allergen extract, Grastek® Timothy grass pollen (Phleum pretense) allergen extract and Ragwitek® short ragweed pollen allergen extract were approved by the U.S Food and Drug Administration (FDA) for the treatment of pollen-induced allergic rhinitis with or without conjunctivitis.

Pharmacological treatments of pollen-induced allergic rhinitis/rhinoconjunctivitis may include allergen avoidance, individualized symptom specific treatment plans and measurements to increase treatment adherence.

Criteria:

For sublingual immunotherapy as an alternate intervention, see BCBSAZ Medical Coverage Guideline #O164, "Complementary and Alternative Medicine".

- Sublingual immunotherapy using FDA approved dosage of, Grastek, Oralair or Ragwitek for the treatment of an individual with pollen-induced allergic rhinitis is considered medically necessary with documentation of ALL of the following:

  1. History of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure
  2. Positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test
  3. Symptoms are not adequately controlled by appropriate pharmacotherapy (see Description section)
  4. Does not have severe, unstable or uncontrolled asthma
  5. No history of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy
  6. No history of eosinophilic esophagitis
  7. Does not have a hypersensitivity to any of the inactive ingredients contained in this product.
SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY (cont.)

Criteria: (cont.)

➢ Sublingual immunotherapy for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

Treatments/immunotherapy include, but are not limited to:

▪ Sublingual treatment/immunotherapy with EP-3
▪ Sublingual treatment/immunotherapy administered subcutaneously (SQ)

Resources:

Literature reviewed 05/12/15. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 04/02/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


Resources: (cont.)

FDA Product Approval Information for Grastek:

- FDA-approved indication: An allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. For use in persons 5 through 65 years of age.

<table>
<thead>
<tr>
<th>Dosage and Administration</th>
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<tbody>
<tr>
<td>For sublingual use only</td>
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<tr>
<td></td>
</tr>
<tr>
<td>• One tablet daily</td>
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<tr>
<td>• Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK may be taken daily for three consecutive years</td>
</tr>
<tr>
<td>• Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute</td>
</tr>
<tr>
<td>• Administer the first dose of GRASTEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose</td>
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</tbody>
</table>

FDA Product Approval Information for Oralair:

- FDA-approved indication: An allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product. For use in persons 10 through 65 years of age.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>For sublingual use only</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Day 1</td>
</tr>
<tr>
<td>10-17</td>
<td>100 IR</td>
</tr>
<tr>
<td>18-65</td>
<td>300 IR</td>
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</table>

Administration

- Initiate treatment 4 months before the expected onset of each grass pollen season and continue treatment throughout the season
- Place the tablet under the tongue for at least 1 minute, until complete dissolution and then swallow
- Administer the first dose of ORALAIR under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions. Observe the patient for at least 30 minutes
SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY (cont.)

Resources: (cont.)

FDA Product Approval Information for Ragwitek:

- FDA-approved indication: An allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen. For use in adults 18 through 65 years of age.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>For sublingual use only</td>
</tr>
<tr>
<td>▪ One tablet daily</td>
</tr>
<tr>
<td>▪ Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season.</td>
</tr>
<tr>
<td>▪ Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute</td>
</tr>
<tr>
<td>▪ Administer the first dose of RAGWITEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose</td>
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</table>

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SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah nilinigií Blue Cross Blue Shield of Arizona haadá yilt'éego bina’ííldidíígo éi doodago Háída bi já níiíyéediílíigo beehaaz'áníí hóóhdíí díí tá háaadák'ehjí háa’íí doódowolgo be haa’íí díí bááq bíí bááq ilíinígóó. Atl' hálée'ígíí kojí bích'íí hodilíiííh 877-475-4799.

Chinese: 如果您, 或是您正在協助的對象, 有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題, 您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員, 請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.
SUBLINGUAL IMMUNOTHERAPY AS A TECHNIQUE OF ALLERGEN-SPECIFIC THERAPY (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay maa rin iting maaaring puanti, tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makasap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 언제든 한국어 또는 한글로 질문이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면, 질문하는 내용의 도움과 정보를 취하기 전에 한국어로 이용 부담없이 알 수 있는 권리가 있습니다. 그렇게 통역사와 예기하기 위해서는 877-475-4799로 전화하시는 것을 추천드립니다.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳をお話される場合、877-475-4799までお電話ください。

Farsi:
اغر تهیه، یا کسی که شما به او کمک می‌کند، سوال در مورد اطلاعات به زبان خود را به مدارک دریافت نمایید 877-475-4799.

Assyrian:

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคนที่เคารพคุณถามคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ได้รับการช่วยเหลือและข้อมูลภาษา ของคุณโดยไม่มีค่าใช้จ่าย ติดต่อที่ โทร 877-475-4799