Short Ragweed *(Ambrosia artemisiifolia)* Pollen Allergen Extract (RAGWITEK®) National Drug Monograph April 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]	
Description/Mechanism of Action	Ragwitek® is a ragweed pollen allergen extract from the Short Ragweed plant (Ambrosia artemisiifolia) used in immunotherapy. While the exact mechanism of action is currently unknown, specific immunotherapy may adjust the T-cell response resulting in decreased production of inflammatory mediator cells such as eosinophils, mast cells, cytokines, and regulatory T lymphocytes which provides a decreased allergic response.
Indication(s) Under Review in this document (may include off label)	Ragwitek® is an allergen extract indicated 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 in adults 18 to 65 years of age.
Dosage Form(s) Under Review	Sublingual: One tablet once daily. How supplied: One tablet contains 12 Amb a 1-Unit (Amb a 1-U)
REMS	No REMS
Pregnancy Rating	Pregnancy Category C

Executive Summary	
Efficacy	• Two phase III clinical trials compared Ragwitek® at varying doses (1.5 Amb a1-U [1 trial], 6 Amb a1-U, and 12 Amb a 1-U) to placebo for improvement in self-reported Daily Symptom Score (DSS); Daily Medication Score (DMS) and Total Combined Score (TCS = DSS+DMS) in patients with confirmed allergic rhinitis to ragweed pollen, with or without conjunctivitis. • Varied doses of Ragwitek® improved symptoms of allergic rhinitis during peak and entire ragweed season ranging from 9% and 27% in TCS compared to placebo, with higher doses producing greater improvement in symptoms. • Outcome measures including TCS, DMS and visual analog scale (VAS) of symptom severity (0-no symptoms to 100-severe symptoms) were improved by >1 point with Ragwitek® vs. placebo during peak and entire ragweed season. • Ragwitek® is not indicated for and should not be used for immediate control of allergy symptoms. • Treatment is initiated at least 12 weeks before the anticipated onset of ragweed pollen season.
Safety	WARNING: SEVERE ALLERGIC REACTIONS (Boxed warning) • RAGWITEK® can cause life - threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. • Do not administer RAGWITEK® to patients with severe, unstable or uncontrolled asthma. • Observe patients in the office for at least 30 minutes following the initial dose.

	• Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. • RAGWITEK® may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. • RAGWITEK® may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. **Contraindications** • Use in severe, unstable or uncontrolled asthma. • History of any severe or systemic reaction or any severe local reaction to sublingual allergen immunotherapy. • A history of eosinophilic esophagitis. • Hypersensitivity to any of the inactive ingredients in the product. **Other** • The most common adverse events reported in clinical trials with Ragwitek® were local application-site reactions, these included: throat irritation (16.6%), oral pruritus (10.9%), ear pruritus (10.4%), paraesthesia oral (10%), mouth edema (6.1%), and tongue pruritus (5.1%) • Withdrawal from clinical trials was approximately 4.4% for Ragwitek® vs. 0.8% placebo.
Place in Therapy	• Consistent with more recent U.S. guidelines in the management of allergic rhinitis and due to safety considerations, therapy with Ragwitek® or other SLIT therapies can be considered in those patients (18-65 years of age) with an inadequate response to a therapeutic trial of intranasal corticosteroids and oral antihistamines. • The decision to prescribe sublingual immunotherapy (SLIT) or subcutaneous immunotherapy (SCIT) should be limited to VA Allergy/Immunology, Ear Nose and Throat specialists or locally designated experts. • The thirty minute "in office" observation of the initial dose in the second and subsequent ragweed allergy seasons or when restarting doses after interruptions of therapy for > 7 days is left to the discretion of the treating provider. However, it is prudent to perform this 30 minute "in office" observation in the second and subsequent allergy seasons and after prolonged interruptions in therapy unless there are extenuating circumstances that prevent this from taking place.
Potential Impact	• According to Arbes *et al*., over 26% of the population in the United States is sensitive to ragweed, which is the third most common allergy. • In patients who are identified as appropriate candidates for allergen immunotherapy, an advantage of SLIT over SCIT may be the ability for patients to self-administer the sublingual tablets at home, after the initial dose. • A physician or provider must supervise the patient taking the first dose of any SLIT therapy in a healthcare setting, in the event of a serious allergic or anaphylactic reaction. • All patients must be prescribed auto-injectable epinephrine and be instructed on its proper use for emergency self-administration.

Background

Purpose for review	FDA approval in April 2014 Issues to be determined: ✔ Does the evidence show that Ragwitek® provides effective relief from short ragweed pollen induced allergic rhinitis? ✔ Does Ragwitek® offer advantages over current VA National Formulary (VANF) agents?

✔ Who are the most appropriate patients for treatment with Ragwitek®?
✔ What additional safety issues need to be considered with the use of Ragwitek®?
✔ Does Ragwitek® have specific safety or efficacy characteristics needing management by the non-formulary process or criteria for use?

Other therapeutic options

Ragwitek® is intended for the treatment of patients with short ragweed pollen-induced allergic rhinitis that are either inadequately controlled or cannot tolerate conventional treatment for allergic rhinitis including intranasal steroids and oral antihistamines. The only direct alternative to this therapy are injectable formulations of standardized allergen extract of short ragweed (*Ambrosia artemisiifolia*). Formulary and non-formulary conventional treatment options are listed below.

Formulary Alternatives	**Other Considerations**	**CFU, Restrictions or Other Guidance**
Intranasal steroids • fluticasone		
Oral Antihistamines • chlorpheniramine • diphenhydramine • promethazine • hydroxyzine • cetirizine • cyproheptadine • loratadine		
Intranasal anticholinergic • Ipratropium		
Leukotriene Modifiers • Montelukast		Restricted – CFU
Non-formulary Alternatives	**Other Considerations**	
2nd Generation Antihistamines ▪ Fexofenadine		
Intranasal Steroids ▪ Beclomethasone ▪ Budesonide ▪ Flunisolide ▪ Mometasone ▪ Triamcinolone		
Intranasal Antihistamine ▪ Azelastine		
Leukotriene Receptor Antagonists ▪ Zafirlukast		
Ophthalmic Agents ▪ Azelastine ▪ Olopatadine ▪ Epinastine		
Subcutaneous Immunotherapy	Requires once weekly injections/then monthly	

Efficacy (FDA Approved Indications)

Literature Search Summary
A literature search was performed on PubMed/Medline (1966 to March 2016) using the search terms < Standardized Allergen Extract, Short Ragweed *(Ambrosia artemisiifolia*) > and <Ragwitek®>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials evaluating short ragweed sublingual tablets and published in English and in peer-reviewed journals were included. Trials of liquid immunotherapy were not included since liquid ragweed immunotherapy products are not approved for use in the United States.

Review of Efficacy
The efficacy and safety of Ragwitek® in the treatment of ragweed allergies was examined in two phase III clinical trials, which included 1,349 subjects. Of this population, 963 subjects received various doses of Ragwitek® while the others received placebo. Both trials were randomized, multicenter, double-blind, placebo-controlled and were approximately 52 weeks in duration. Although both studies evaluated increasing doses of Amb a 1-U (Ragwitek®), the only FDA approved dose is 12 Amb a 1-U as a sublingual tablet.

Outcomes Measured:
1. The average rhinoconjunctivitis Daily Symptom Score (DSS). The DSS is the sum of six rhinoconjunctivitis symptom scores with possible values of 0 (no symptoms) to 3 (severe symptoms). The six symptoms include: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. The maximum DSS is 18.
2. Medication use was measured using the average rhinoconjunctivitis Daily Medication Score (DMS). The DMS is the sum of scores that are assigned to use of specific rescue medications with a maximum score of 36.
3. The primary efficacy endpoint for both studies reviewed was the total combined score (TCS) through the peak of ragweed season. The TCS is the sum of DSS (maximum 18) and DMS (maximum 36). The maximum TCS is 54.
4. Symptoms were additionally analyzed utilizing a visual analog scale (VAS) with possible scores ranging from (0) no symptoms to (100) severe symptoms.

Clinical significance of findings:
- The Agency for Health Research and Quality (AHRQ) has indicated that: 1) a 30% improvement vs. placebo is clinically meaningful.[2]
- The World Allergy Organization (WAO) recognizes a 20% difference as the standardization of efficacy for clinical trials with allergen-specific immunotherapy for respiratory allergy.[3-4]
- Cohen, et al. criteria for significance in clinical practice is not met for differences of <1 point.[5]

TABLE 1. CLINICAL TRIALS OF SHORT RAGWEED *(AMBROSIA ARTEMISIIFOLIA*) SUBLINGUAL TABLET, 12 AMB A 1-U (RAGWITEK®)

Clinical Trial	Treatments	Population	Results
Nolte 2013[6]	Randomized to 12 Amb a 1-U, 6 Amb 1-U or Placebo 52 weeks TX 8 week FU Total 52 weeks Phase II/III efficacy and	**Adults ages 18-50 from US and Canada** N=565 Mean age 35.4 years 22% had asthma (severe asthmatics excluded) 85% sensitized to

	Placebo	6 Amb vs placebo	12 Amb vs placebo
Peak Season			
TCS	8.46	-1.76	-2.24
DMS	2.87	*	-1.30
DSS	5.59	-0.78	-0.94
VAS	26.36	-1.48	-6.38

	safety study	other allergens 78% Caucasian 49% male	***Entire Season*** **TCS** 7.01 -1.09 -1.80 **DMS** 2.15 -0.63 -1.16 **DSS** 4.87 * -0.82 **VAS** 23.02 * -5.65 *Only significant differences presented
Creticos 2013[7]	Randomized to 12 Amb a 1-U, 6 Amb 1-U, 1.5 Amb 1-U or Placebo 52 week TX Patients treated a mean of 15.9 weeks prior to ragweed season Phase III efficacy and safety study	**Adults 18-50 years with ragweed allergy for at least 2 years. Multi-national trial** N=784 Mean age 36.4 years Participants required prior treatment for ragweed allergy Severe asthmatics ($FEV_1 \leq 70\%$) excluded	**Dose** / **Reduction in TCS (Peak)** / **95% Confidence Interval** 1.5-Amb a 1-U — 9% — -0.76 (95% CI -1.98 to 0.45) 6-Amb a 1-U — 19% — -1.58 (95% CI -2.80 to -0.36) 12-Amb a 1-U — 24% — -2.04 (95% CI -3.30 to -0.79) Improvements were also noted during the entire season with 1.5, 6 and 12-AMB a 1-U improving symptoms by 12%, 18% and 27%, respectively versus placebo.

Summary of Evidence

- In the study by Nolte, et al., 565 patients with confirmed allergic rhinitis to ragweed pollen were randomized in a 1:1:1 ratio to 6 or 12 Amb a 1 unit of Ragwitek® or placebo. All baseline characteristics were well balanced between groups. The study took place before, during, and after ragweed season. The primary endpoint was the Total Combined Score (TCS) during peak season. The study included patients 18-50 years of age with a mean age of 35.4 years. The population was divided equally between males and females and 78% of participants were white. Peak season was defined as the 15 consecutive days with the highest moving average pollen counts during the entire pollen season. During peak ragweed season, the TCS for patients taking 6 and 12 Amb a 1 Unit of Ragwitek® therapy improved by 21% and 27%, respectively ($P < 0.05$) when compared to placebo. The difference between groups in TCS for the entire ragweed season was similar to the peak season outcomes and superior for both active groups vs. placebo. The DSS and DMS scores were also statistically improved after using either dose of Ragwitek® during the peak season ($P < 0.05$). For DSS, statistically significant improvement versus placebo was observed in all but the 6-Amb a 1 unit over the entire season. Ragwitek® was well tolerated with only mild, oral reactions being most commonly reported and no anaphylactic reactions were reported. Only 1 patient in this study needed administration of epinephrine injection at an emergency department for pharyngeal edema after receiving 6-Amb a 1 unit.

- In the study by Creticos et al. patients were randomized in a 1:1:1:1 ratio to receive doses of 1.5, 6, and 12 Amb a 1-U or placebo to determine the efficacy and tolerability of SCH 39641/MK-3641 (also known as Ragwitek®) in the treatment of ragweed-induced allergic rhinitis with or without conjunctivitis. All baseline characteristics were balanced between groups and included an equal representation of males and females and less than 20% of patients had a co-morbid diagnosis of asthma. Similar to the study by Nolte et al, patients reported an improvement in symptoms of allergic rhinitis with use of Ragwitek® through a total combined daily symptom/medication score (TCS) compared to placebo. Allergen immunotherapy (or AIT) with Ragwitek® was also well tolerated when treating patients with a ragweed allergy. There was a dose response relationship

observed, thus higher doses of AIT improved symptoms to a greater degree compared to placebo. A reduction of allergy symptoms of 9%, 19% and 24% was observed during peak ragweed season in the 1.5, 6, and 12 Amb A 1-U groups, respectively when compared to placebo. Similar differences were reported during the entire allergy season. Allergy immunotherapy supplying 12 Amb a 1-U daily produced the greatest improvement in the primary outcome of TCS but was associated with an increase in adverse effects compared to the lowest dose and placebo. The percentage of patients who experienced AEs during the trial were 23%, 40%, 52%, or 54% for placebo, 1.5, 6, and 12 Amb A 1-U groups, respectively. No deaths or life-threatening anaphylactic events were observed and most AEs were local reactions. Three to eight percent of patients withdrew due to adverse events, most commonly due to tongue edema. There was no increase in AEs in asthmatic compared to non-asthmatic patients.

- In the trial by Nolte, et al., improvements of >1 point were reported in symptom assessments including TCS, DMS and VAS but not in the DSS using the FDA approved dose of Ragwitek® of 12 AMB A 1-U.

- In the trial by Creticos, et al., improvement in allergic rhinitis symptoms during peak or entire ragweed season was generally less than 30% compared to placebo with any dose of Ragwitek®.

Potential Off-Label Use

- At this time there are no studies examining the safety and efficacy of Ragwitek® for indications other than ragweed pollen-induced allergic rhinitis. Therefore, off-label use of Ragwitek® is not recommended.

Safety
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	WARNING: SEVERE ALLERGIC REACTIONS • RAGWITEK® can cause life - threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. • Do not administer RAGWITEK® to patients with severe, unstable or uncontrolled asthma. • Observe patients in the office for at least 30 minutes following the initial dose. • Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. • RAGWITEK® may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. • RAGWITEK® may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.
Contraindications	RAGWITEK® is contraindicated in patients with: • Severe, unstable or uncontrolled asthma • A history of any severe systemic allergic reaction • A history of any severe local reaction after taking any sublingual allergen immunotherapy • A history of eosinophilic esophagitis • Hypersensitivity to any of the inactive ingredients [gelatin NF (fish source), mannitol USP and sodium hydroxide NF] contained in this product

Warnings/Precautions

- Severe Allergic Reactions:
  - Ragwitek® can cause systemic allergic reactions including anaphylaxis, which may be life threatening. It can also cause severe local reactions, including laryngopharyngeal swelling, which can also be life threatening. Administer the initial dose in a healthcare setting under the supervision of a physician qualified to diagnose and treat allergic ailments. Observe patient for at least 30 minutes after the initial dose.
- Epinephrine
  - Auto-injectable epinephrine should be prescribed to all patients receiving Ragwitek®. Educate patient on recognition of signs and symptoms of allergic reactions, epinephrine use, and to seek immediate medical attention and discontinue Ragwitek® upon administration of epinephrine.
  - Patients with medical conditions such as impaired lung function, cardiac conditions, and uncontrolled hypertension may not be appropriate candidates for Ragwitek® therapy, due to possible reduced survival in the event of serious allergic reactions.
  - Patients taking medications that may alter the effects of epinephrine (eg. Tricyclic antidepressants, MAOIs, beta-blockers, and alpha-blockers, ergot alkaloids, levothyroxine, cardiac glycosides, diuretics, and certain antihistamines) may not be appropriate candidates for Ragwitek® therapy.
- Upper Airway Compromise
  - Reactions involving the mouth or throat that may compromise the upper airway can occur with Ragwitek® use. Ragwitek should be discontinued in patients in whom this reaction is persistent and escalating.
- Eosinophilic Esophagitis
  - Discontinue Ragwitek® in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.
- Asthma
  - Ragwitek® has not been studied in subjects with moderate or severe asthma. Do not administer Ragwitek® if patient is experiencing an acute exacerbation and consider discontinuing Ragwitek® in patients who have recurrent asthma exacerbations.
- Concomitant allergen immunotherapy
  - The use of Ragwitek® with concomitant allergen immunotherapy has not been studied and may increase the possibility of adverse reactions.
- Oral Inflammation
  - Discontinue treatment with Ragwitek® in subjects with oral inflammation or wounds to allow healing.

Safety Considerations/Adverse Reactions:

The safety of Ragwitek® was reviewed by the Allergenic Products Advisory Committee (APAC) in January of 2014.[9] The committee evaluated data from 4 trails which included Phase 2 and 3 studies.

- All 4 studies were multicenter, double blind, parallel group, placebo controlled, randomized designs.
- Treatment related adverse events occurred more often in the study subjects in the Ragwitek® treatment groups in all studies.

- 2 studies conducted for 28 weeks outside of ragweed pollen season + data from first 28 days of 52 week studies below
  - Adverse events – 12 Amb a 1-U vs placebo:
    Oral pruritus (11% Ragwitek®, 2% placebo)
    Ear pruritus (10.7% Ragwitek®, 1.1% placebo)
    Throat irritation (17% Ragwitek®, 3.8% placebo)
    Mouth edema (6.1% Ragwitek®, 0.5% placebo)
    Similar frequency of events with 6 Amb a 1-U dosing
  - Study discontinuation – 90 subjects discontinued study therapy
    0.9% of placebo group
    2% of Ragwitek® 1.5 Amb a 1-U group
    5.3% of Ragwitek® 6 Amb a 1-U group
    5.2% of Ragwitek® 12 Amb a 1-U group
- 2 studies conducted for 52 weeks (16 weeks prior to, during, and following ragweed pollen season)
  - Adverse events – 12 Amb a 1-U vs placebo:
    Oral pruritus (17.3% Ragwitek®, 2.6% placebo)
    Ear pruritus (14.2% Ragwitek®, 1.6% placebo)
    Throat irritation (25.2% Ragwitek®, 5.4% placebo)
    Mouth edema (9.7% Ragwitek®, 0.5% placebo)
    Eye pruritus (3.9% Ragwitek®, 1.3% placebo)
    Similar frequency of events with 6 Amb a 1-U dosing
  - Study discontinuation – 67 subjects discontinued study therapy
    1.6% of placebo group
    2% of Ragwitek® 1.5 Amb a 1-U group
    6.8% of Ragwitek® 6 Amb a 1-U group
    8.1% of Ragwitek® 12 Amb a 1-U group
- The most common adverse events leading to withdrawal from these trials were dysphagia, lip swelling, mouth edema, oral pruritus, palatal edema, swollen tongue, tongue edema, pharyngeal edema, throat irritation, throat tightness, chest discomfort, lip edema, oral paresthesia, and pharyngeal erythema.
- Although Ragwitek's® safety profile seems to reflect acceptable tolerability in most subjects, there are some adverse effects of concern: anaphylaxis, severe throat tightness, lip swelling, platal edema, mild wheezing and dyspnea. A total of 5 subjects in these trials required administration of 1 or more epinephrine injections, due to reaction to the study medication. It is imperative every patient receiving Ragwitek® therapy have an epinephrine injection with them at all times.

Adverse Reactions

Common adverse reactions	Adverse reactions >5% of patients: throat irritation, oral pruritus, ear pruritus, oral paraesthesia, mouth edema, and tongue pruritus.
Death/Serious adverse reactions	Severe systemic allergic reaction was reported in 1 patient: swelling of the throat, dyspnea, nausea, and lightheadedness. No deaths reported.
Discontinuations due to adverse reactions	Ragwitek® discontinuation: 4.4% vs Placebo discontinuation: 0.8%

Combined Safety Data[9]

Treatment-related adverse events of 12 Amb a 1-U dose at 28 days of treatment versus placebo		
Adverse Event	**Ragwitek® (N=1707) %**	**Placebo (N=757) %**
Oral Pruritus	**11**	**2**
Ear Pruritus	**10.7**	**1.1**
Throat Irritation	**17**	**3.8**
Mouth Edema	**6.1**	**0.5**

Treatment-related adverse events of 12 Amb a 1-U dose at 52 weeks of treatment versus placebo		
Adverse Event	**Ragwitek® (N=381) %**	**Placebo (N=386) %**
Oral Pruritus	**17.3**	**2.6**
Ear Pruritus	**14.2**	**1.6**
Throat Irritation	**25.2**	**5.4**
Mouth Edema	**9.7**	**0.5**
Eye Pruritus	**3.9**	**1.3**

Drug Interactions

Drug-Drug Interactions

- Concomitant allergen immunotherapy. Use with other allergen immunotherapy may increase the possibility of adverse reactions.

Drug-food Interactions

- Avoid food or beverage for 5 minutes following administration.

Drug-Lab Interactions

- None

Risk Evaluation

As of October 08, 2015

	Comments
Sentinel event advisories	• None to date • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List) • Ragweed Pollen Allergen Extract SL tab: Grass Pollen Allergen Extract (Timothy Grass), Grass Pollen Allergen Extract (5 grass extract) • Ragwitek® 12-Amb U: Grastek, Rilutek

Other Considerations

- A meta-analysis of four studies evaluated the safety and tolerability of Ragwitek® in patients with confirmed allergy to ragweed and treated for up to one year in duration.[8] From this meta-analysis, Ragwitek was found to be beneficial in the treatment of ragweed allergies, improving allergy symptoms by approximately 25% versus placebo. However, treatment led to an increase in local side effects. Limitations of the clinical trials evaluating Ragwitek® include a patient population of males and females between the ages of 18 and 50 years. Since the Veteran population is predominantly older and male, the safety and efficacy of Ragwitek® in patients older than 50 years of age is unknown.
- Based on the National Center for Veterans Analysis and Statistics, 45.82% of veterans are aged 65 and older as of September 2015.[10] Thus, caution should be used if Ragwitek® is used in patients older than

65 years since safety has not been evaluated in this patient population. Also, use of SLIT in patients with perennial allergic rhinitis is less well established.

- Administration issues and special monitoring center around the risk of anaphylaxis upon initiation of immunotherapy; therefore, the first dose of Ragwitek® must be administered in a clinician's office and the patient must be observed for at least 30 minutes. Ragwitek® is not regulated using a REMS program, but a medication guide should be dispensed with the medication.
- Because Ragwitek® has a limited treatment window, compliance is vitally important to establish efficacy.
- Ragwitek® must be stored in the original blister packages until used as moisture can degrade the medication product. Blister packages can be stored at room temperature and should not be administered if packaging has been compromised.

Dosing and Administration

Dose:

One sublingual tablet daily (12 Amb a 1-U)

Administration:

Administer the first dose of Ragwitek® in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of Ragwitek®, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction.

- Take the tablet from the blister unit after carefully removing the foil with dry hands.
- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved.
- Do not swallow for at least 1 minute.
- Wash hands after handling the tablet.
- Do not take the tablet with food or beverage. Food or beverage should not be taken for the following 5 minutes after taking the tablet.
- Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. The safety and efficacy of initiating treatment in season have not been established.
- Data regarding the safety of restarting treatment after missing a dose of Ragwitek® are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.
- Prescribe auto-injectable epinephrine to patients prescribed Ragwitek® and instruct them in the proper use of emergency self-injection of epinephrine.

Special Populations (Adults)

	Comments
Elderly	• Not approved for use in patients over 65 years of age, because safety and efficacy have not been established.
Pregnancy	• Animal reproduction studies have not been performed with Ragwitek®. It is also not known whether Ragwitek® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. • Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, Ragwitek® should be used during pregnancy only if clearly needed.
Lactation	• It is not known if Ragwitek® is excreted in human milk.

		Because many drugs are excreted in human milk, caution should be exercised when Ragwitek® is administered to a nursing woman.
Renal Impairment	•	No data identified.
Hepatic Impairment	•	No data identified.
Pharmacogenetics/genomics	•	No data identified.

Projected Place in Therapy

- Allergic rhinitis (AR) is an inflammatory, IgE-mediated disease characterized by nasal congestion, rhinorrhea (nasal drainage), sneezing, and/or nasal itching. Examples of the symptoms of AR are sneezing, stuffy nose, runny nose, postnasal drip, and itchy eyes, ears and soft palate. Allergic rhinitis can be classified by temporal pattern of exposure triggering allergen: seasonal, perennial/year-round, or episodic (environmental from exposures not normally encountered in the patient's environment). Allergic rhinitis can also be classified by frequency: intermittent or persistent and severity of symptoms: mild or more severe.
- Allergic rhinitis is one of the most common diseases affecting adults, is the most common chronic disease in children in the United States today, and is the fifth most common chronic disease in the United States overall.[11-13] It is estimated to affect nearly 1 in every 6 Americans and generates $2 to $5 billion in direct health expenditures annually. It can impair quality of life and, through loss of work and school attendance, is responsible for as much as $2 to $4 billion in lost productivity annually. [14-15]
- Ragweed is a common inhalant allergen and a cause of rhinoconjunctivitis. According to Arbes *et al.*, over 26% of the population in the United States is sensitive to ragweed, which is the third most common allergy.[16]
- In February of 2015, the American Academy of Otolaryngology (AAO) – Head and Neck Surgery Foundation released updated clinical practice guidelines for allergic rhinitis.[17] There are no VA DoD guidelines on the treatment of allergic rhinitis. Per the AAO guidelines, clinicians can offer to refer outpatients with allergic rhinitis for immunotherapy (SLIT or SCIT) for those patients who failed to have an adequate response to traditional pharmacotherapies. Allergen-specific immunotherapy modifies the disease process through repetitive dosing of allergen(s) to increase the immune tolerance of the allergen(s). Traditionally, this has been achieved through subcutaneous injection of allergen-specific serums. Subcutaneous immunotherapy (SCIT) has proven efficacy in treating allergic rhinitis, but requires regular injections at a physician's office and serious local or systemic allergic reactions are a recognized risk.
- Identification of appropriates candidates for immunotherapy is necessary for the safe and effective use of such therapy and involves determining the causal allergen or trigger by considering a combination of factors including clinical history and skin and/or blood testing for allergen specific IgE. Routes of administration for this type of treatment include subcutaneous and sublingual allergy immunotherapy. Since clinical trials directly comparing SCIT to SLIT (as sublingual tablets) are not available, the comparative effectiveness is unknown. One advantage of SLIT over SCIT is the ability for patients to self-administer the sublingual tablets at home, after the initial dose. A physician or provider must supervise the patient taking the first dose of Ragwitek® in a healthcare setting and monitor for 30 minutes, in the event of a serious allergic or anaphylactic reaction.
- Consistent with more recent U.S. guidelines in the management of allergic rhinitis and due to safety considerations, therapy with Ragwitek® or other SLIT therapies can be considered in those patients (18-65 years of age) with an inadequate response to a therapeutic trial of intranasal corticosteroids and oral antihistamines. The decision to prescribe SLIT or SCIT should be limited to VA Allergy /Immunology, Ear Nose and Throat specialists or locally designated experts.

References

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