Ragwitek
(short ragweed pollen allergen extract)

STRENGTH	DOSAGE FORM	ROUTE	GPID
12 units	Tablet	Sublingual	36402

MANUFACTURER

Merck Sharp & Dohme Corp

INDICATION(S)

Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis confirmed by a positive skin prick test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen in adults 18 years through 65 years of age

DRUG CLASS
ALLERGY; ALLERGENIC EXTRACTS, THERAPEUTICS

PLACE IN THERAPY

Ragwitek is one of the newest FDA-approved sublingual immunotherapy (SLIT) products for the treatment of pollen-induced allergic rhinitis (AR), specifically short ragweed pollen. For over a century, allergen immunotherapy has been administered subcutaneously (commonly known as allergy shots), and in recent years the administration of these allergen serums via sublingual drops has grown in popularity. However, this method is considered off-label and generally not covered by insurance companies. Ragwitek, on the other hand, is an oral tablet that is approved for dissolution under the tongue.

The treatment of AR typically consists of patient education, allergen avoidance, and pharmacotherapy. Immunotherapy is reserved for patients with demonstrable specific IgE antibodies to relevant allergens who continue to have moderate to severe AR symptoms despite pharmacotherapy. Other factors that would justify consideration of immunotherapy include intolerable side effects to medications, the patient's desire to limit cost burden associated with chronic medication use, and the presence of comorbid conditions. Unlike pharmacotherapy, the clinical benefits of immunotherapy may be sustained for years after discontinuation of treatment for some patients. Immunotherapy can potentially modify the disease such that the immune system no longer reacts to the allergen.

Ragwitek provides an alternative to subcutaneous immunotherapy with minimal risk for systemic allergic reactions, decreased burden of office visits, and elimination of injection site discomfort. Ragwitek has been shown to be effective in reducing allergic symptoms and the use of allergy medications. Currently there are only two other immunotherapy agents with FDA-approval for sublingual use, Oralair and Grastek. Unfortunately, patients who exhibit an allergic response to allergens not specified in these novel products will still need to rely on customary allergy shots.

EFFICACY

The efficacy of Ragwitek was based on two double-blind, placebo-controlled, multi-centered studies (P05233 and P05234) conducted in the US, Canada, and Europe. Subjects 18 to 50 years of age took placebo or Ragwitek for approximately 52 weeks, beginning roughly 12 weeks prior to the ragweed season. The primary efficacy endpoints for each study was the total combined score (TCS), a summation of the daily symptom score (DSS) and daily medication score (DMS), over the peak of ragweed season. Daily symptoms were measured on a scale of 0 (none) to 3 (severe) which included runny nose, stuffy nose, sneezing, itchy nose, gritty/itchy eyes, and watery eyes. Subjects were allowed to take symptom-relieving medications such as systemic/topical antihistamines and oral/topical corticosteroids as needed. Each class of medication was assigned a predefined value, with antihistamines given the lowest score, and oral corticosteroids given the highest score.

Study P05233 included 560 subjects randomized to receive placebo, Ragwitek 12 Amb a 1-U, or Ragwitek 6 Amb a 1-U. Study P05234 consisted of 783 subjects and was designed in a similar fashion, except it included an additional study arm, Ragwitek 1.5 Amb a 1-U. In both trials, the primary endpoint was the TCS in each group during the peak ragweed season. The results of the primary and secondary endpoints for the 12 Amb a 1-U group were statistically significant (see Table 1 and 2).

Table 1. Study P05233 Primary and Secondary Endpoints

	N	Adjusted Mean	Treatment Difference (RAGWITEK – Placebo) (95% CI)[a]	% difference relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	159	6.2	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
Placebo	164	8.4	-	---	---
TCS entire ragweed season					
12 Amb a 1-U	160	5.2	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
Placebo	166	7.0	-	---	---
DSS peak ragweed season					
12 Amb a 1-U	159	4.6	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
Placebo	164	5.5	-	---	---
DSS entire ragweed season					
12 Amb a 1-U	160	4.0	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
Placebo	166	4.8	-	---	---
DMS peak ragweed season					
12 Amb a 1-U	159	1.5	-1.30 (-1.95, -0.64)	-45.28 (-65.39, -26.99)	0.0001

a: Adjusted means, treatment differences, confidence intervals and p-values were based on an ANOVA model with baseline asthmatic condition, pollen region and treatment group as fixed effects;
b. Percent reduction in ragweed AIT group compared to placebo: 100 x [(AIT-placebo)/placebo] Confidence intervals were obtained using the bootstrap method.

Obtained from the Ragwitek FDA briefing Jan 28, 2014

Table 8. Study P05234 Primary and Secondary Endpoints

	N	Adjusted Mean	Treatment Difference (RAGWITEK – Placebo) (95% CI)[a]	% difference relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	152	6.41	-2.04 (-3.30, -0.79)	-24.16 (-36.47, -11.31)	0.0015
Placebo	169	8.46	-	---	---
TCS entire ragweed season					
12 Amb a 1-U	158	5.18	-1.92 (-2.95, -0.88)	-27.01 (-38.75, -14.07)	0.0003
Placebo	174	7.09	-	---	---
DSS peak ragweed season					
12 Amb a 1-U	152	4.43	-0.94 (-1.67, -0.21)	-17.51 (-29.20, -4.48)	0.0118
Placebo	169	5.37	-	---	---
DSS entire ragweed season					
12 Amb a 1-U	158	3.62	-0.96 (-1.57, -0.35)	-21.00 (-31.62, -8.81)	0.0021
Placebo	174	4.58	-	---	---
DMS peak ragweed season					
12 Amb a 1-U	152	1.99	-1.10 (-1.89, -0.32)	-35.73 (-55.82, -14.63)	0.0058
Placebo	169	3.09	-	---	---
DMS entire ragweed season					
12 Amb a 1-U	158	1.56	-0.95 (-1.57, -0.33)	-37.99 (-57.62, -16.39)	0.0026
Placebo	174	2.51	-	---	---

a: Adjusted means, treatment differences, confidence intervals and p-values were based on an ANOVA model with baseline asthmatic condition, pollen region and treatment group as fixed effects;
b. Percent reduction in ragweed AIT group compared to placebo: 100 x [(AIT-placebo)/placebo] Confidence intervals were obtained using the bootstrap method.

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SAFETY

Ragwitek carries the following black box warnings:

- 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

Discontinuation rates were 4.4% in the Ragwitek group and 0.8% in the placebo group. The most common adverse events leading to withdrawal in the Ragwitek group included mouth edema, swollen tongue, and dysphagia. The most common adverse events were throat irritation (16.6% Ragwitek, 3.3% placebo), oral pruritus (10.9% Ragwitek, 2.0% placebo), ear pruritus (10.4% Ragwitek, 1.1% placebo), and oral paresthesia (10.1% Ragwitek, 4.0% placebo). One subject (1/1057, 0.1%) who received Ragwitek experienced anaphylaxis which led to discontinuation from the trial. The subject fully recovered after treatment with epinephrine, antihistamines, and oral corticosteroids.

Ragwitek is Pregnancy Category C. It should be used during pregnancy only if clearly needed, since systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy.

DOSAGE

The recommended dosage of Ragwitek is 1 tablet (12 Amb a 1-U) daily in patients 18-65 years of age. Ragwitek is not approved for use in pediatric patients because safety and efficacy have not been established.

Ragwitek should be initiated 12 weeks prior to the expected onset of each ragweed pollen season and continued throughout the season.

COST

Drug	Cost/unit	Maximum Cost per 30 Days
Ragwitek	AWP $9.90	$297
Grastek 2800 BAU*	AWP $9.90	$297
Oralair 300 IR*	AWP $12	$360

*For the treatment of grass pollen-induced allergic rhinitis

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Ragwitek to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Ragwitek [Prescribing Information]. Whitehouse Station, NJ, Merck Sharp & Dohme Corp., Apr 2014.

- Sur DK, Scandale S. Treatment of Allergic Rhinitis. Am Fam Physician, 2010 Jun; 81(12):1440-6.
- Wallace DV, Dykewicz MS, et al. The diagnosis and management of rhinitis: An updated practice parameter. J Allergy Clin Immunol, 2008 Aug; 122:S1-84.
- FDA Briefing Document - Biologic License Application (BLA) for Ragwitek Sublingual Tablet for Oral Use. Accessed on Mar 2014 at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/allergenicproductsadvisorycommittee/ucm382841.pdf