PRODUCT MONOGRAPH

RAGWITEK®

Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*)

Sublingual Tablet, 12 Amb a 1-U

Allergy immunotherapy tablet

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral sublingual	Sublingual tablet / 12 Amb a 1-U	*For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

RAGWITEK® (Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*) Sublingual Tablet) is an allergy immunotherapy tablet for the treatment of the signs and symptoms of ragweed allergy. It is formulated as an orally disintegrating tablet designed to rapidly dissolve under the tongue. The active substance is a natural ragweed pollen extract which is purified and standardized from Short Ragweed. Each sublingual tablet has a strength of 12 Amb a 1-U.

INDICATIONS AND CLINICAL USE

RAGWITEK® (Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*) Sublingual Tablet) is indicated for reducing the signs and symptoms of moderate to severe seasonal short ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults and children 5 years of age or older confirmed by clinically relevant symptoms for at least one pollen season (age 6 or younger) or two pollen seasons (age 7 or older) and a positive skin prick test and/or a positive titre to *Ambrosia artemisiifolia* specific IgE, and who have responded inadequately, or are intolerant to conventional pharmacotherapy.

Treatment with RAGWITEK® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.

Geriatrics: The efficacy of RAGWITEK® has not been studied in patients over 50 years of age. There is no long term safety data for patients >50 years old (see **WARNINGS AND PRECAUTIONS / Geriatrics**).

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy

of RAGWITEK® have been established in pediatric patients 5 to 17 years of age (see **CLINICAL TRIALS**). The safety and efficacy of RAGWITEK® have not been studied in patients under 5 years of age (see **WARNINGS AND PRECAUTIONS / Pediatrics**).

CONTRAINDICATIONS

RAGWITEK® is contraindicated in patients who:

- Are hypersensitive to any of the excipients in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.
- Have previously had a severe systemic allergic reaction to short ragweed immunotherapy.
- Have unstable, severe chronic or severe seasonal asthma (FEV1 <70% of predicted value after adequate pharmacologic treatment).
- Are taking β-blockers, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction.
- Have active inflammatory conditions in the oral cavity, e.g., oral lichen planus with ulcerations, severe oral candidiasis, dental extraction (see also **WARNINGS AND PRECAUTIONS / Patients with Oral Conditions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Treatment with RAGWITEK® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.
- Systemic allergic reactions, including severe local allergic reactions, have been observed in patients receiving RAGWITEK®, and may require emergency administration of epinephrine, antihistamines, bronchodilators or systemic corticosteroids (see **WARNINGS AND PRECAUTIONS / Immune**).
- The first tablet of RAGWITEK® must be taken at the physician's office under medical supervision and the patient must be monitored for at least 30 minutes.

General

No data are available regarding the effect of vaccination in patients with RAGWITEK® treatment. Vaccination may be given without interrupting treatment with RAGWITEK® after medical evaluation of the patient's general condition.

Patients previously administered epinephrine used to treat a severe systemic allergic reaction, including anaphylactic shock, were not studied in clinical trials with RAGWITEK®. Effects of epinephrine may be potentiated in patients treated with tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

RAGWITEK® should not be initiated in pregnant women.

RAGWITEK® should be used with caution in patients who have had severe systemic reactions to any weed subcutaneous immunotherapy or severe local or systemic reactions to any weed immunotherapy taken by mouth.
As with other immunotherapy treatments, patients treated with RAGWITEK® may have local swelling which is severe or which may increase in severity over time. Because of the risk of upper airway compromise, treatment with RAGWITEK® should be discontinued in these patients.

Carcinogenesis and Mutagenesis
No carcinogenicity studies were conducted in animals with *Ambrosia artemisiifolia* extract. Based on *in vivo* assays for mutagenicity, no evidence of genotoxic risk was associated with *Ambrosia artemisiifolia* extract.

Gastrointestinal

Eosinophilic Esophagitis
Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. Discontinue RAGWITEK® and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

Immune

Systemic Allergic Reactions
As with other immunotherapy treatments, potentially life threatening systemic allergic reactions may occur. Signs and symptoms that may be associated with a systemic allergic reaction include syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, wheezing, bronchospasm, chest discomfort, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing and urticaria.

Systemic allergic reactions, including anaphylactic reactions and severe local allergic reactions, have occurred in clinical trial patients treated with RAGWITEK® (see **ADVERSE REACTIONS**). Treatment of severe allergic reactions may require the administration of epinephrine, antihistamines, inhaled bronchodilators and/or systemic corticosteroids.

The first dose of RAGWITEK® should only be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction. Patients should be observed for 30 minutes after first time administration of RAGWITEK®. Immediately discontinue RAGWITEK® in any patient developing clinical evidence of a severe systemic or severe local allergic reaction. In such cases, consider discontinuing treatment with RAGWITEK® permanently. Patients should be informed and educated about the symptoms of a severe allergic reaction, and instructed to discontinue RAGWITEK®, seek immediate medical care and contact their physician should any of these symptoms occur after taking RAGWITEK®.

Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the procedure of emergency self-injection of epinephrine (see **Serious Warnings and Precautions** Box). Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with RAGWITEK®.

Patients with Oral Conditions

In patients with oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush) or oral wounds, such as those following oral surgery, tooth loss or dental extraction, treatment with RAGWITEK® should be interrupted to allow healing of the oral cavity.

Respiratory

Patients with Asthma

Immunotherapy with RAGWITEK® is contraindicated in patients who have unstable or severe asthma (chronic or seasonal). During treatment with RAGWITEK®, instruct patients to stop treatment with RAGWITEK® and contact their physician immediately if they have difficulty breathing or if asthma becomes inadequately controlled (see **CONTRAINDICATIONS**).

Special Populations

Pregnant Women: No animal or clinical data are available for the use of RAGWITEK® during pregnancy. Immunotherapy with RAGWITEK® should not be initiated during pregnancy because severe systemic reactions may be detrimental to the mother or fetus.

Nursing Women: No clinical data are available for the use of RAGWITEK® during lactation. It is not known whether RAGWITEK® is excreted in human milk.

Pediatrics: Immunotherapy with RAGWITEK® has not been studied in pediatric patients below 5 years of age.

Geriatrics: The efficacy of RAGWITEK® has not been studied in patients over 50 years of age. Short term safety has been established in patients over 50 years of age in 28-day safety studies; however there was no long term safety data for patients in this age group.

Monitoring and Laboratory Tests

In clinical trials, evaluation of the laboratory values by treatment group revealed no clinically relevant changes in median values over the course of the studies.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Use of RAGWITEK® has been associated with systemic allergic reactions (see **WARNINGS AND PRECAUTIONS / Immune** and **Serious Warnings and Precautions** box).

In 6 clinical trials, 8/1067 (0.84%) adult patients and 3/513 (0.58%) pediatric patients treated with RAGWITEK® 12 Amb a 1-U experienced treatment-related symptoms consistent with a systemic allergic reaction.

- One (1) adult patient had a severe anaphylactic reaction in RAGWITEK 12 Amb a 1-U, onset Day 6, who self-administered epinephrine, and was subsequently treated with diphenhydramine, prednisone and ranitidine, then discontinued from the study.

- Two (2) pediatric patients treated with RAGWITEK® 12 Amb a 1-U experienced treatment-related systemic allergic reactions. One patient experienced mild hypersensitivity and one patient reported moderate hypersensitivity (urticaria). None of these reactions required treatment with epinephrine.

- Two (2) adult patients received epinephrine for a severe event of throat tightness and a moderate event of mouth edema. Both patients discontinued treatment.

- There were 5 additional adult patients who had events that may be consistent with systemic allergic reactions and symptoms included local allergic reactions, dyspnea, urticarial, abdominal pain and diarrhea, respectively. Of these patients, all the events were mild; epinephrine and antihistamines were not used; 3 of the 5 patients discontinued treatment. There was one (1) additional pediatric patient who had events that may be consistent with systemic allergic reactions and symptoms included mild pruritus and moderate dyspnea. The events resolved without treatment.

Two (2) of 454 (0.44%) adult patients treated with RAGWITEK® 6 Amb a 1-U experienced allergic events. One patient with severe pharyngeal edema was treated with epinephrine and discontinued from the trial. The other patient had moderate and mild events; received an antihistamine and corticosteroid to treat the events; and continued in the trial.

Two (2) adult placebo patients of 757 (0.3%) experienced events consistent with a systemic allergic reaction. One patient developed urticarial, cough, dyspnea, pharyngeal pruritus, and thoracic pain; received 2 doses of epinephrine, antihistamine, corticosteroid, and albuterol. The second patient had dyspnea and vomiting that was not treated, and the patient continued in the trial. One (1) of 509 pediatric placebo patients (0.2%) experienced a treatment-related systemic allergic reaction, reported as moderate hypersensitivity (hives).

The percentage of adult patients who discontinued from the clinical trials because of a treatment-related adverse reaction while exposed to RAGWITEK® or placebo was 4.4% (46/1057) and 0.8% (6/757), respectively. The most common treatment related adverse reactions that led to study discontinuation in patients who were exposed to RAGWITEK® were mouth edema (16 of 1057 patients), swollen tongue (8/1057 patients) and dysphagia (5/1057 patients). The percentage of pediatric patients who discontinued from the clinical trials because of a treatment-related adverse reaction while exposed to RAGWITEK® or placebo was 3.3% (17/513) and 0.4% (2/509), respectively.

In clinical trials with RAGWITEK® in adults, epinephrine was administered 6 times in RAGWITEK® treated patients and 1 time in placebo treated patients. In RAGWITEK® treated

patients, three of the administrations were for treatment-related allergic events and 3 were for adverse experiences unrelated to RAGWITEK®. One additional epinephrine administration occurred for a treatment related allergic event in a patient administered a lower dose (6 Amb a 1-U). One (1) pediatric patient received inhaled racepinephrine for a severe event of laryngitis. The patient discontinued treatment.

In the 4 pooled adult clinical trials, there were 9 RAGWITEK® treated subjects (9/1057; 0.9%), and 8 placebo treated subjects (8/757; 1.1%), who had serious adverse events. None of the serious events in RAGWITEK® treated patients were assessed as treatment related by the investigators. In the pediatric trial, there were 7 RAGWITEK® treated subjects (7/513; 1.4%), and 9 placebo treated subjects (9/509; 1.8%), who had serious adverse events. Of those, 3 subjects treated with RAGWITEK® (0.6%) and 1 subject treated with placebo (0.2%) experienced serious events that were assessed as treatment related by the investigator.

In the pooled adult clinical trials, 22 RAGWITEK® treated subjects (22/1057; 2.1%) had treatment related severe adverse events. In placebo treated subjects, (3/757; 0.4%) had treatment related severe adverse events. In the pediatric clinical trial, 3 RAGWITEK®-treated subjects (3/513; 0.6%) had treatment related severe adverse events. In placebo-treated pediatric subjects no treatment related severe adverse events were reported.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult Efficacy and Safety studies (52-week studies)
The safety data described below are based on two, 52-week clinical trials which randomized 1348 patients 18 to 50 years of age with short ragweed pollen-induced rhinoconjunctivitis, including 381 patients who were exposed to at least one dose of RAGWITEK® (12 Amb a 1-U). Of the patients treated with RAGWITEK®, 21% had stable asthma and 82% were sensitized to other allergens in addition to short ragweed. The patient population was 85% Caucasian and 52% female. The mean age of patients was 36 years. Patient demographics in placebo treated patients were similar to the active group (see **Part II: CLINICAL TRIALS / Study demographics and trial design** for detailed demographics).

Adverse reactions reported in ≥1% of patients in the 52-week pooled analysis treated with RAGWITEK® that also occurred more commonly than in placebo-treated patients are shown in Table 1.

Table 1: Treatment Related Adverse Reactions Reported in ≥1% of Adult Patients with Short Ragweed Pollen Induced Rhinoconjunctivitis with or without Asthma Treated with RAGWITEK® and Occurring More Commonly than Placebo in two 52-week studies

Adverse Reaction	RAGWITEK® 12 Amb a 1-U (N=381) n (%)	PLACEBO (N=386) n (%)
Ear and Labyrinth Disorders	**57 (15.0)**	**6 (1.6)**
Ear pruritus	53 (13.9)	6 (1.6)
Eye Disorders	**16 (4.2)**	**7 (1.8)**
Eye pruritus	11 (2.9)	4 (1.0)
Gastrointestinal disorders	**160 (42.0)**	**37 (9.6)**
Oral pruritus	66 (17.3)	10 (2.6)
Paraesthesia oral	32 (8.4)	11 (2.8)
Mouth edema	35 (9.2)	2 (0.5)
Swollen tongue	32(8.4)	4 (1.0)
Tongue pruritus	24 (6.3)	3 (0.8)
Lip swelling	18 (4.7)	3 (0.8)
Lip pruritus	9 (2.4)	1 (0.3)
Tongue edema	11 (2.9)	2 (0.5)
Palatal edema	8 (2.1)	0 (0)
Glossitis	8 (2.1)	1 (0.3)
Lip edema	8 (2.1)	1 (0.3)
Dysphagia	7 (1.8)	0 (0)
Hypoesthesia oral	6 (1.6)	1 (0.3)
Tongue Disorder	7 (1.8)	2 (0.5)
Nausea	7 (1.8)	3 (0.8)
Dyspepsia	6 (1.6)	0 (0)
Glossodynia	4 (1.0)	1 (0.3)
General Disorders and Administration Site conditions	**17 (4.5)**	**5 (1.3)**
Chest discomfort	7 (1.8)	0 (0)
Sensation of foreign body	4 (1.0)	0 (0)
Infections and Infestations	**4 (1.0)**	**2 (0.5)**
Rhinitis	4 (1.0)	0 (0)
Nervous System Disorders	**21 (5.5)**	**11 (2.8)**
Headache	8 (2.1)	4 (1.0)
Paraesthesia	4 (1.0)	0 (0)
Sinus headache	4 (1.0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	**123 (32.3)**	**36 (9.3)**
Throat irritation	95 (24.9)	17 (4.4)
Cough	13 (3.4)	0 (0)
Pharyngeal edema	11 (2.9)	2 (0.5)
Throat tightness	10 (2.6)	2 (0.5)

Adverse Reaction	RAGWITEK® 12 Amb a 1-U (N=381) n (%)	PLACEBO (N=386) n (%)
Oropharyngeal pain	8 (2.1)	3 (0.8)
Sneezing	8 (2.1)	4 (1.0)
Dry throat	5 (1.3)	1 (0.3)
Pharyngeal erythema	5 (1.3)	2 (0.5)
Oropharyngeal discomfort	4 (1.0)	0 (0)
Dyspnoea	5 (1.3)	2 (0.5)
Skin and Subcutaneous Tissue Disorders	**16 (4.2)**	**3 (0.8)**
Pruritus	6 (1.6)	3 (0.8)
Urticaria	5 (1.3)	4 (1.0)

The most common treatment related adverse events reported in the 52-week trials in patients treated with RAGWITEK® were reactions of local swelling and itching involving the mouth and ears. Oropharyngeal swelling (including swelling and/or edema of the lips, mouth, palate, tongue, and pharynx) was reported in 49.3% RAGWITEK® treated patients vs. 8.5% of placebo treated patients. Oropharyngeal pruritus (including pruritus of the mouth, tongue, lips and ears) was reported in 29.9% of RAGWITEK® treated patients vs. 4.5% of placebo treated patients. Throat irritation was reported in 24.9% of patients treated with RAGWITEK® vs. 4.4% of placebo treated patients.

Treatment related adverse events for local application site reactions were 202/381 (53.0%) patients in the RAGWITEK® group vs. 52/386 (13.5%) patients in the placebo group.

Treatment-related adverse reactions were reported by 233 (61.2%) of RAGWITEK® treated patients and 98 (25.4%) of patients treated with placebo. The most common adverse reactions (deemed by the investigators to be causally related to treatment) reported in patients treated with RAGWITEK® were throat irritation (24.9% vs. 4.4% placebo), oral pruritus (17.3% vs. 2.6%), ear pruritus (13.9% vs. 1.6%) and mouth edema (9.2% vs. 0.5%). Most (91%) treatment related adverse reactions occurred within the first 28 days of treatment.

In these trials, 31 (8.1%) of patients treated with RAGWITEK® and 6 (1.6%) of placebo-treated patients discontinued from the trial due to a treatment-related adverse reaction.

Severe treatment-related adverse reactions were reported by 16 of 391 (4.2%) of RAGWITEK® treated patients and 3 of 386 (0.8%) of patients treated with placebo. These events included mouth edema and swollen tongue. Local swelling assessed as severe occurred in 6 patients treated with RAGWITEK®. The events self-resolved in 2 patients, and 4 patients were treated with an antihistamine.

Mild or moderate local reactions were most common on the first day of treatment; however, some patients experienced their first treatment-related reaction up to 391 days after their first dose. Most treatment-related reactions lasted for 1–10 days; however, some mild or moderate reactions recurred up to 376 days in some patients e.g. lip swelling, throat irritation, glossodynia, oral pruritus, mouth edema and paraesthesia oral, lip oedema, swollen tongue and tongue oedema.

There were 8 (2.1%) patients in the 12 Amb a 1-U group, and 2 (0.5%) patients in the placebo group that had study treatment interrupted due to a TRAE. The treatment interruption was due to adverse events in the mouth for 6 patients in the 12 Amb a 1-U group and 2 in the placebo group.

No patient treated with RAGWITEK® in the two trials had a treatment-related systemic allergic reaction.

Pediatric Efficacy and Safety study (28-weeks)

Safety data are based on one clinical trial which randomized and exposed 1022 subjects between 5 and 17 years of age with short ragweed pollen-induced rhinoconjunctivitis, including 513 patients who were exposed to at least one dose of RAGWITEK® (12 Amb a 1-U). See **Part II: CLINICAL TRIALS / Study demographics and trial design** for detailed demographics. In the trial, solicitation of predefined local adverse events took place during the first 28 days of treatment.

The safety profile in pediatric patients was largely similar to that previously observed in adult clinical trials. Most frequent treatment-related adverse reactions occurred at or near the administration site. Most treatment-related adverse reactions were seen with a similar frequency as in adults. However, the following treatment-related adverse reactions reported ≥1% in pediatric patients were observed more frequently than those reported in Table 1 in adult patients: throat irritation (48.5% vs. 24.9%), lip swelling (12.5% vs. 4.7%), glossodynia (12.3% vs. 0.5%), oral pain (11.7% vs. 0%), pharyngeal edema (10.9% vs. 2.9%), swollen tongue (10.7% vs. 8.4%), stomatitis (6.4% vs. 0.5%), enlarged uvula (6.2% vs. 0%), dysgeusia (3.9% vs. 0.5%), tongue ulceration (2.3% vs. 0.3%), mouth ulceration (1.2% vs. 0.5%), nausea (11.7% vs. 1.8%) and diarrhea (2.7% vs. 0.5%). Most of these treatment-related adverse reactions are local application site reactions.

Other treatment-related adverse reactions that were observed in ≥1% of pediatric patients but in <1% of adult patients in clinical trials included abdominal pain (1.4%), abdominal pain upper (9.4%), aphthous ulcer (1.6%), enlarged uvula (6.2%) and vomiting (1.6%).

About 65% of the pediatric patients in the RAGWITEK® group experienced predefined local application site reaction(s). These reactions included adverse events related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus.

Other Safety Clinical Studies
In two, 28-day studies, a total of 676 adult patients received RAGWITEK® and 371 received placebo. The following treatment related adverse reactions were reported in addition to those reported in Table 1: dry mouth (1.9% vs. 0.5%), nasal congestion (1.2% vs. 0.5%), nasal discomfort (1.2% vs. 0.3%) and rhinorrhea (1.5 vs. 0.8%).

In these trials, one (1) patient treated with RAGWITEK® had a treatment-related systemic allergic reaction on the sixth day of dosing characterized by throat swelling, shortness of breath, nausea and light-headedness which occurred within 30 minutes after dosing. The subject self-

administered epinephrine, and was then treated in a medical setting with antihistamines and corticosteroids. The subject recovered and discontinued from the trial.

Overall, the adverse reaction profile in the 28-day studies was consistent with what was reported in the 52-week studies.

Less Common Clinical Trial Adverse Reactions in adults (<1%):
Blood and Lymphatic System Disorders: lymphadenopathy, palpitations
Cardiac Disorders: palpitations
Ear and Labyrinth Disorders: auricular swelling, ear congestion, ear discomfort, ear pain, hyperacusis
Endocrine Disorders: hyperthyroidism
Eye Disorders: abnormal sensation in eye, conjunctivitis, eye discharge, eye irritation, eye swelling, eyelid edema, lacrimation increased, ocular hyperaemia, vision blurred
Gastrointestinal Disorders: abdominal discomfort, chapped lips, cheilitis, diarrhea, dyspepsia, epigastric discomfort, flatulence, gastritis, gastroesophageal reflux, gingival blister, gingival erythema, gingival edema, gingival pain, gingival pruritus, glossitis, lip blister, lip disorder, lip pain, lip ulceration, mouth hemorrhage, mouth ulceration, odynophagia, oesophageal pain, oral discomfort, oral disorder, oral mucosal blistering, oral mucosal eruption, oral mucosal erythema, oral mucosal exfoliation, oral pain, oral papule, palatal disorder, retching, saliva altered, salivary gland enlargement, salivary hypersecretion, stomatitis, tongue blistering, tongue discoloration, tongue disorder, tongue exfoliation, tongue ulceration
General Disorders and Administration Site Conditions: chills, fatigue, nodule, mucosal hyperaemia, feeling cold, irritability, oedema mucosal, pre-existing condition improved, pyrexia, sensation of foreign body, sensation of pressure
Immune System Disorders: allergy to animal, hypersensitivity, perfume sensitivity, laryngitis, nasopharyngitis, rhinitis, sialadentitis, skin infection, viral upper respiratory tract infection
Investigations: blood alkaline phosphate increased
Metabolism and Nutrition Disorders: decreased appetite
Musculoskeletal and Connective Tissue Disorders: myalgia, neck pain, rheumatoid arthritis
Nervous System Disorder: dizziness, dysgeusia, hypoaesthesia, sinus headache, migraine, somnolence, speech disorder, tension headache
Psychiatric Disorders: anxiety
Respiratory, Thoracic and Mediastinal Disorders: allergic cough, asthma, dry throat, dysphonia, epistaxis, oropharyngeal swelling, pharyngeal disorder, pharyngeal inflammation, rhinalgia, snoring, tonsillolith, upper airway cough
Skin and Subcutaneous Tissue Disorders: angioedema, circumoral edema, erythema, papule, petechiae, pruritus generalised, rash papular, solar dermatitis, umbilical erythema
Vascular Disorders: hot flush

Adverse Drug Reactions of Special Interest in Controlled Clinical Trials;

- Hypersensitivity Reactions (systemic reactions): There were 3 subjects with systemic allergic reactions who were exposed to RAGWITEK®. In 2 of the 3 subjects, the systemic allergic reaction was attributed to triggers unrelated to RAGWITEK® use.
- Serious and Severe Local Reactions and progression of oral reactions to the throat: There were no subjects exposed to RAGWITEK® who developed serious local allergic swellings or

airway compromise. Severe reactions that affected the throat included throat tightness (n=3), pharyngeal edema (n=2) and oropharyngeal swelling (n=1).
- Acute Asthma: There were no serious treatment related asthma exacerbations in the clinical development program.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of RAGWITEK®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: glossodynia.

DRUG INTERACTIONS

Overview

Interactions with other drugs have not been established.

Co-administration of RAGWITEK® with subcutaneous allergen immunotherapies has not been studied.

Potential Drug-Drug Interactions

Interactions with other drugs have not been established.
- See **CONTRAINDICATIONS** for potential drug-drug interactions with beta-blockers.
- See **WARNINGS AND PRECAUTIONS / General** for potential drug-drug interactions with MAOIs or Tricyclic anti-depressants.

Drug-Food Interactions

Interactions with food have not been studied.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

Drug-Lifestyle Interactions

If dizziness or fatigue is experienced by the patient they should be advised not to drive or operate machinery until these effects have passed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The first dose of RAGWITEK® should only be administered 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, the patient should be kept under observation for 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the first dose is adequately tolerated, subsequent doses may be taken at home.
- Initiate treatment with RAGWITEK® at least 12 weeks prior to the ragweed season and maintain dosing throughout the season.
- In patients with a history of ragweed allergy, methods of determining the presence of short ragweed specific IgE should also include skin prick testing or serum testing for specific IgE against *Ambrosia artemisiifolia*.

Recommended Dose

- The recommended dose of RAGWITEK® for adults and children 5 years of age or older is 1 sublingual tablet (12 Amb a 1-U) daily.
- Efficacy and safety of RAGWITEK® tablets beyond one year have not been established.

Missed Dose

The patient should not take more than one sublingual tablet daily. Advise a patient who misses taking a dose of RAGWITEK® to return to their normal schedule the next day.

Administration

- RAGWITEK® is a sublingual tablet. The tablet should be taken from the blister unit after carefully removing the foil with dry hands.
- The tablet should be placed under the tongue immediately where it will dissolve in seconds.
- Do not take the tablet with food or beverage. Swallowing should be avoided for about 1 minute. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after handling the tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The risk of side effects may increase with doses above 12 Amb a 1-U. In the event of an overdose, any adverse effects should be treated symptomatically. In clinical trials, local and systemic reactions such as oral swelling, periorbital edema, chest discomfort and chest pain were observed with doses up to 50 Amb a 1-U.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The immune system is the target of immunotherapy. The aim is to prevent or suppress allergic symptoms, such as allergic rhinitis, through repeated administration of the allergen. The effect of sublingual immunotherapy is thought to be mediated through local and systemic

immunomodulatory mechanisms (immune deviation) including changes in allergen specific antibodies and regulatory T-cells leading to long-term tolerance development.

Pharmacodynamics

The immune system is the target for the pharmacodynamic effect. The aim is to induce an immune response against the allergen with which the patient is treated. In a 1-year study in which immunologic parameters were assessed, a significant increase in short ragweed-specific IgG4 (blocking antibody) occurred in patients treated with RAGWITEK® relative to placebo. The increase in IgG4 level occurred shortly after treatment initiation and was sustained throughout the treatment. The clinical significance of this finding has not been established.

Pharmacokinetics

No pharmacokinetic studies in animals or clinical studies investigating the pharmacokinetic profile and metabolism of *Ambrosia artemisiifolia* have been conducted.

STORAGE AND STABILITY

Store at room temperature (15 to 30 °C).
Store in the original package until use to protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

RAGWITEK® is a white to off-white circular sublingual tablet with a debossed double hexagon on one side. RAGWITEK® is a sublingual tablet designed to dissolve rapidly under the tongue.

Composition

Each RAGWITEK® tablet contains 12 Amb a 1-U of standardized natural ragweed pollen extract of Short Ragweed (*Ambrosia artemisiifolia*). RAGWITEK® is free of lactose.
The active substance is a standardized allergen extract derived from short ragweed. RAGWITEK® contains the following inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF.

Packaging

RAGWITEK® sublingual tablets are packaged in 10 tablet aluminum blister packs composed of a blister film and a lidding foil. The lidding foil has been designed to be peeled back from the blister film to allow the removal of the tablets.

The trade size is a box of 30 tablets (3 blisters packs with 10 tablets each).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

The potency (in Amb a 1 Units) of RAGWITEK® is determined by standardization against reference extracts and reference serum pools distributed by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration. The potency of the standard is based on quantitative skin testing.

Proper name: Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia)*

Molecular formula and molecular mass: A complex mixture of proteins and other biologically derived substances extracted from natural ragweed pollen that is partially purified. Detailed structural information is not available.

Physicochemical properties: Greenish light brown to greenish dark brown non-adhesive frozen droplets that are soluble in a range of buffers and water.

Product Characteristics

The drug substance (DS) is prepared by extraction of Short ragweed pollen, which is then purified by filtration and stabilized into frozen droplets before incorporation in the final dosage form. The characterization of the major allergenic components includes identification of the relevant allergen.

CLINICAL TRIALS

Ragweed Induced Rhinitis with or without Conjunctivitis - Adults

The safety and efficacy of RAGWITEK® (12 Amb a 1-U) in adults were demonstrated in two randomized, double-blind, parallel group, multicenter clinical trials of approximately 52 weeks treatment duration involving 1349 patients 18 to 50 years of age, with or without asthma. Patients had a history of ragweed induced rhinoconjunctivitis and sensitivity to short ragweed as determined by specific testing (IgE). In the two studies combined, patients were treated with 1.5 Amb a 1-U, 6 Amb a 1-U, 12 Amb a 1-U or placebo.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). Daily rhinoconjunctivitis symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose), and two ocular symptoms (gritty/itchy eyes and watery eyes). The rhinoconjunctivitis symptoms were measured on a scale of 0 (none) to 3 (severe). Patients in clinical trials were allowed to take symptom relieving medications (including systemic and topical antihistamines and topical and oral corticosteroids) as needed. The daily medication score measured the use of standard open-label allergy medications. Predefined values were assigned to each class of medication to represent the symptomatic relief provided by the rescue medication. Generally, systemic and topical antihistamines were given the lowest score, topical steroids an intermediate score and oral corticosteroids the highest score.

The sums of the DSS and DMS were combined into the Total Combined Score (TCS). The TCS provides an estimate of symptomatic treatment benefit adjusted for symptom relief provided by rescue medications. Each study used the TCS during the peak ragweed season as the primary efficacy endpoint. By focusing on peak season, the treatment effect of RAGWITEK® was evaluated during the time when patients were most symptomatic. In each study, the average TCS over the entire ragweed season was assessed as a key secondary endpoint. Other key secondary endpoints in both studies included the average DSS during the peak and entire ragweed season, and the average DMS during the peak ragweed season (RS).

All subjects were co-prescribed self-injectable epinephrine. There were 2 patients who self-administered epinephrine for treatment related adverse events.

Clinical Trial P05233

Study demographics and trial design

Table 2: Summary of patient demographics for RAGWITEK® clinical trial

Study #/ Sites	**Trial design** *Primary Endpoint(s)*	**Dosage and Duration**	**No. of Subjects**	**Age Range (mean)[b]** *Male/Female*
P05233[a] North America	Phase 3: Efficacy and Safety R, MC, DB, PG, PC *TCS averaged over the peak RS*	12 Amb a 1-U 6 Amb a 1-U Placebo Approx. **52 weeks**	187 190 188 (Total=565)	18–50 (35.4) *279/286*

DB = double blind; MC = Multicenter; PC = placebo-controlled; PD = pharmacodynamic; PG = parallel-group; R = randomized
TCS = Total combined score; RS = ragweed season
[a]Includes Canadian population.
[b]Age range represents age at screening

This approximately 52-week, placebo-controlled trial evaluated 565 patients 18 to 50 years of age treated with RAGWITEK® (n=187), 6 Amb a 1-U (n=190) and placebo (n=188) administered as a sublingual tablet daily. In this trial, approximately 22% of patients had asthma and 85% were sensitized to other allergens in addition to ragweed. The patient population was 78% Caucasian and almost equally divided between males and females. The mean age of patients in this study was 35.4 years. Patients with severe asthma were excluded from the trial. All treatment groups were balanced with regard to baseline characteristics.

Study results

Based on an analysis using the longitudinal data analysis model on the repeated measurement of daily scores, patients treated with RAGWITEK® had significant relief of nasal and ocular symptoms and reduction in standard allergy medication use as measured by improvement in TCS during the peak ragweed season. A similar significant improvement in the average TCS from the start and throughout the entire ragweed season was observed in patients treated with RAGWITEK® compared to placebo treated patients. Treatment with RAGWITEK® also resulted in a significant improvement in the average DSS during the peak and entire season compared to placebo. Additionally, RAGWITEK® significantly improved the individual DMS compared to placebo during the peak season (see Table 3).

Table 3: Total Combined Score, Rhinoconjunctivitis Daily Symptom Scores, and Daily Medication Scores During the Ragweed Pollen Season

Average RPS duration: 44 days Average Peak RPS pollen count: 204 grains/m^3 Average Entire RPS pollen count: 122 grains/m^3							
Endpoint*	**RAGWITEK® (N)† Score‡**	**Placebo (N)† Score‡**	**Treatment Difference (RAGWITEK® – Placebo)**			**Difference Relative to Placebo§**	
			Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**
TCS Peak Season	(159) 6.22	(164) 8.44	-2.22	(-3.37, -1.06)	0.0002	-26%	(-39%, -14%)
TCS Entire Season	(160) 6.11	(166) 8.32	-2.21	(-3.37, -1.05)	0.0002	-27%	(-39%, -15%)
DSS Peak Season	(159) 4.65	(164) 5.59	-0.94	(-1.69, -0.19)	0.0140	-17%	(-29%, -5%)
DSS Entire Season	(160) 4.60	(166) 5.51	-0.92	(-1.66, -0.17)	0.0162	-17%	(-29%, -4%)
DMS Peak Season	(159) 1.56	(164) 2.82	-1.26	(-1.91, -0.61)	0.0001	-45%	(-65%, -26%)

RPS = Ragweed Pollen Season; TCS = Total Combined Score (DSS + DMS); DSS = Daily Symptom Score; DMS = Daily Medication Score.

* Parametric analysis using longitudinal data analysis model for all endpoints.

† Number of subjects included in analyses.

‡ The estimated group means are reported and difference relative to placebo was based on estimated group means.

§ Difference relative to placebo computed as: (RAGWITEK® - placebo)/placebo x 100. The 95% CI was based on the 2.5^{th} and 97.5^{th} percentiles of the 5,000 bootstrap samples.

Note: For the peak RPS, analysis model on daily score included treatment, day, and treatment- by- day interaction as fixed effects, and pollen region and baseline asthmatic condition as covariates, with a Toeplitz covariance structure. For the entire RPS, analysis model on daily score included treatment, pollen region and baseline asthmatic as fixed effects, and subject as random effect, with an AR(1) covariance structure.

During the peak ragweed pollen season and based on a longitudinal data analysis model, the difference in TCS for patients who received RAGWITEK® compared to placebo was -2.22, which corresponds to a relative difference of -26%. The peak season was defined as maximum 15 days with the highest moving average pollen counts during the entire pollen season.

Clinical Trial P05234

Study demographics and trial design

Table 4: Summary of patient demographics for RAGWITEK® clinical trial

Study # / Sites	Trial design *Primary Endpoint(s)*	Dosage and Duration	No. of Subjects	Age Range (mean)[b] *Male/Female*
P05234[a] North America and Europe	Phase 3: Efficacy and Safety R, MC, DB, PG, PC *TCS averaged over the peak RS*	12 Amb a 1-U 6 Amb a 1-U 1.5 Amb a 1-U Placebo Approx. **52 weeks**	194 195 197 198 (Total=784)	18–50 (36.4) *384/400*

DB = double blind; MC = Multicenter; PC = placebo-controlled; PD = pharmacodynamic; PG = parallel-group; R = randomized
TCS = Total combined score; RS = ragweed season
[a]Includes Canadian population.
[b]Age range represents age at screening

This placebo-controlled trial of approximately 52 weeks duration evaluated 784 patients 18 to 50 years of age treated with RAGWITEK® (n=194), 6 Amb a 1-U (n=195), 1.5 Amb a 1-U (197) or placebo (n=198) administered as a sublingual tablet daily. Approximately 17% of patients had asthma and 78% were sensitized to other allergens in addition to ragweed. The patient population was 88% Caucasian and almost equally divided between males and females. The mean age of patients in this study was 36.4 years. Patients with severe asthma were excluded from the trial. All treatment groups were balanced with regard to baseline characteristics.

Study results

Based on an analysis using the longitudinal data analysis model on the repeated measurement of daily scores, the results of Trial P05233 were replicated in Trial P05234. An improvement in TCS during the peak ragweed season for patients treated with RAGWITEK® compared to placebo treated patients was similar to the result in Trial P05233. Patients treated with RAGWITEK® also showed significant improvement in the average TCS throughout the entire ragweed pollen season. Similar improvement was observed in patients treated with RAGWITEK® for all other key secondary endpoints (see Table 5).

Table 5: Total Combined Score, Rhinoconjunctivitis Daily Symptom Scores, and Daily Medication Scores During the Ragweed Pollen Season

Average RPS duration: 46 days Average Peak RPS pollen count: 228 grains/m^3 Average Entire RPS pollen count: 127 grains/m^3							
Endpoint*	**RAGWITEK® (N)† Score‡**	**Placebo (N)† Score‡**	**Treatment Difference (RAGWITEK® – Placebo)**			**Difference Relative to Placebo§**	
			Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**
TCS Peak Season	(152) 6.45	(169) 8.46	-2.01	(-3.25, -0.76)	0.0016	-24%	(-36%, -11%)
TCS Entire Season	(158) 6.30	(174) 7.60	-2.02	(-3.27, -0.78)	0.0015	-24%	(-36%, -12%)
DSS Peak Season	(152) 4.46	(169) 5.40	-0.94	(-1.67, -0.21)	0.0115	-17%	(-29%, -4%)
DSS Entire Season	(158) 4.39	(174) 5.32	-0.93	(-1.66, -0.20)	0.0122	-18%	(-29%, -5%)
DMS Peak Season	(152) 2.00	(169) 3.10	-1.10	(-1.87, -0.32)	0.0055	-35%	(-56%, -14%)

RPS = Ragweed Pollen season; TCS = Total Combined Score (DSS + DMS); DSS = Daily Symptom Score; DMS = Daily Medication Score.

* Parametric analysis using longitudinal analysis model for all endpoints.

† Number of subjects included in analyses.

‡ The estimated group means are reported and difference relative to placebo was based on estimated group means.

§ Difference relative to placebo computed as: (RAGWITEK® - placebo)/placebo x 100. The 95% CI was based on the 2.5th and 97.5th percentiles of the 5,000 bootstrap samples.

Note: For the peak RPS, analysis model on daily score included treatment, day, and treatment- by- day interaction as fixed effects, and pollen region and baseline asthmatic condition as covariates, with a Toeplitz covariance structure. For the entire RPS, analysis model on daily score included treatment, pollen region and baseline asthmatic as fixed effects, and subject as random effect, with an AR(1) covariance structure.

During the peak ragweed pollen season and based on a longitudinal data analysis model, the difference in TCS for patients who received RAGWITEK® compared to placebo was -2.01, which corresponds to a relative difference of -24%.

Ragweed Induced Rhinitis with or without Conjunctivitis – Pediatrics

The safety and efficacy of RAGWITEK® (12 Amb a 1-U) in children and adolescents ages 5-17 years were demonstrated in one randomized, double-blind, parallel group, multicenter clinical trial of approximately 28 weeks treatment duration involving 1022 patients, with or without asthma. Patients had a history of ragweed induced rhinoconjunctivitis and sensitivity to short ragweed as determined by specific testing (IgE). Patients received RAGWITEK® (12 Amb a 1-U) or placebo.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). Daily rhinoconjunctivitis symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose), and two ocular symptoms (gritty/itchy eyes and watery eyes). The rhinoconjunctivitis symptoms were measured on a scale of 0 (none) to 3 (severe). Patients in clinical trials were allowed to take symptom relieving medications (including systemic and topical antihistamines and topical corticosteroids) as

needed. The daily medication score measured the use of standard open-label allergy medications. Predefined values were assigned to each class of medication to represent the symptomatic relief provided by the rescue medication. Generally, systemic and topical antihistamines were given the lowest score and topical steroids the highest score.

The sums of the DSS and DMS were combined into the Total Combined Score (TCS). The TCS provides an estimate of symptomatic treatment benefit adjusted for symptom relief provided by rescue medications. TCS during the peak ragweed season was the primary efficacy endpoint. By focusing on peak season, the treatment effect of RAGWITEK® was evaluated during the time when patients were most symptomatic. The average TCS over the entire ragweed season was assessed as a key secondary endpoint. Other key secondary endpoints were the average DSS and the average DMS during the peak ragweed season (RS). The peak season was defined as maximum 15 days with the highest moving average pollen counts during the entire pollen season.

Clinical Trial P008

Study demographics and trial design

Table 6: Summary of patient demographics for RAGWITEK® clinical trial

Study #/ Sites	**Trial design** *Primary Endpoint(s)*	**Dosage and Duration**	**No. of Subjects**	**Age Range (mean)[b]** *Male/Female*
P008[a] North America and Europe	Phase 3: Efficacy and Safety R, MC, DB, PG, PC *TCS averaged over the peak RS*	12 Amb a 1-U Placebo Approx. **28 weeks**	512 510 (Total=1022)	5-17 (12.1) *643/379*

DB = double blind; MC = Multicenter; PC = placebo-controlled; PG = parallel-group; R = randomized
TCS = Total combined score; RS = ragweed season
[a]Includes Canadian population.
[b]Age range represents age at screening

This approximately 28-week, placebo-controlled trial evaluated 1022 patients 5 to 17 years of age treated with RAGWITEK® 12 Amb a 1-U (n=512) and placebo (n=510) administered as a sublingual tablet daily. In this trial, approximately 43% of patients had asthma and 79% were sensitized to other allergens in addition to ragweed. The patient population was 93% Caucasian and 63% male. Approximately 40% were children (5-11 years) and 60% were adolescents (12-17 years). All treatment groups were balanced with regard to baseline characteristics.

Study results

Patients treated with RAGWITEK® had significant relief of nasal and ocular symptoms and reduction in standard allergy medication use as measured by improvement in TCS during the peak ragweed season. A significant improvement in the average TCS from the start and throughout the entire ragweed season was observed in patients treated with RAGWITEK® compared to placebo treated patients. Treatment with RAGWITEK® also resulted in a significant improvement in the average DSS and the average DMS during the peak season compared to placebo (see Table 7).

Table 7: Total Combined Score, Rhinoconjunctivitis Daily Symptom Scores, and Daily Medication Scores During the Ragweed Pollen Season

Average RPS duration: 50 days Average Peak RPS pollen count: 184 grains/m^3 Average Entire RPS pollen count: 84 grains/m^3							
Endpoint*	**RAGWITEK® (N=512)† Score**	**Placebo (N=510)† Score**	**Treatment Difference (RAGWITEK® – Placebo)**			**Difference Relative to Placebo**	
			Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**
TCS Peak Season	4.81	7.15	-2.33	(-3.09, -1.57)	<0.0001	-33%	(-24%, -42%)
TCS Entire Season	4.15	5.74	-1.59	(-2.20, -0.98)	<0.0001	-28%	(-18%, -37%)
DSS Peak Season	2.72	3.95	-1.23	(-1.65, -0.81)	<0.0001	-31%	(-22%, -40%)
DMS Peak Season	2.05	3.18	-1.13	(-1.57, -0.68)	<0.0001	-35%	(-24%, -47%)

RPS = Ragweed Pollen Season; TCS = Total Combined Score (DSS + DMS); DSS = Daily Symptom Score; DMS = Daily Medication Score.

* Missing values in both treatment groups were imputed from the observed data of the endpoint in the placebo group using the method of unrestricted random sampling. Rubin's multiple imputation strategy is used with 1000 values sampled for each missing value.

† Number of subjects in Full Analysis Set (FAS).

Note: The analysis is based on an analysis of variance (ANOVA) model, which included fixed effects of treatment, baseline asthma status (yes, no), age group (<12 years, ≥12 years), pollen season, and pollen region nested within pollen season.

The control for multiplicity of the type I error rate is done by hierarchical testing.

DETAILED PHARMACOLOGY

Pharmacokinetic and pharmacodynamic studies in animals or humans have not been conducted.

TOXICOLOGY

A conventional general toxicity study with *Ambrosia artemisiifolia* extract in mice dosing up to 1 month revealed no safety concerns for humans at doses up to 70 Amb a 1-U/day which is 6-fold greater than the human dose of 12 Amb a 1-U.

Carcinogenesis

No studies have been performed to evaluate the carcinogenic potential of *Ambrosia artemisiifolia* extract.

Mutagenesis

Based on *in vivo* assays for mutagenicity, *Ambrosia artemisiifolia* extract does not pose a genotoxic risk in male rats.

Impairment of Fertility

Reproductive studies have not been performed with *Ambrosia artemisiifolia* extract.

REFERENCES

1. Nolte H, Hébert J, Berman G, Gawchik S, White M, Kaur A, Liu N, Lumry W, Maloney J. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. Ann Allergy Asthma Immunol 110 (2013) 450-456.

2. Creticos P, Maloney J, Bernstein, D, Casale T, Kaur A, Fisher R, Liu N, Murphy K, Nékam K, Nolte H. Randomized controlled trial of ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013 May; 13(5):1342-1349.

3. Nolte H, Bernstein DI, Nelson HS, Ellis AK, Kleine-Tebbe J, Lu S. Efficacy and safety of ragweed SLIT-tablet in children with allergic rhinoconjunctivitis in a randomized, placebo-controlled trial. J Allergy Clin Immunol Pract 2020; 8: 2322-2331.

PART III: CONSUMER INFORMATION

RAGWITEK®

(Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*) Sublingual tablet, 12 Amb a 1-U)

This leaflet is part III of a three-part "Product Monograph" published when RAGWITEK® was authorised for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RAGWITEK®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RAGWITEK® (RAG-wih-tek) is used for the treatment of adults and children 5 to 65 years of age with a history of allergy to ragweed pollen. Ragweed pollen allergy is characterized by rhinitis (sneezing, runny or itchy nose, stuffed up nose) with or without conjunctivitis (itchy, burning, red or watery eyes).

Before you begin treatment with RAGWITEK®, your allergy will be confirmed by a doctor who will perform skin and/or blood tests.

RAGWITEK® has not been tested in patients younger than 5 years of age.

What it does:
RAGWITEK® is a tablet that treats your allergy caused by ragweed. It contains an allergen extract that helps to make you less sensitive to the ragweed pollens you are allergic to.

When it should not be used:
Do not take RAGWITEK® if you:
- have severe or difficult to control asthma;
- have ever had a serious allergic reaction to ragweed allergy shots, tablets or drops;
- are taking beta-blockers (a medicine for heart conditions, such as high blood pressure);
- have any swelling or sores in your mouth;
- are allergic (hypersensitive) to any of the other ingredients of RAGWITEK® (see What the non-medicinal ingredients are).

What the medicinal ingredient is:
The active substance is Standardized allergen extract, Short Ragweed *(Ambrosia artemisiifolia)*.

What the non-medicinal ingredients are:
Fish gelatin, mannitol, sodium hydroxide.

What dosage form it comes in:
RAGWITEK® is a prescription tablet that you take once a day by placing it under your tongue.

Each tablet contains 12 Amb a 1-U of Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

- RAGWITEK® is to be given only by doctors experienced in treating allergies.
- It is very common (in 35% (one-third) of patients) for patients to have mild local allergic reactions with RAGWITEK® (for example: mouth swelling, throat itching or burning, itching in the mouth or ears).
- The first tablet of RAGWITEK® must be taken at the doctor's office. Your doctor will also tell you to stay for at least 30 minutes to check you for possible allergic reactions.

Serious allergic reactions that require immediate medical attention have happened in patients treated with RAGWITEK®. They are most common early in treatment, but can happen even if patients have been taking RAGWITEK® for months. If you experience serious allergic reactions such as:
- swelling in the throat
- trouble swallowing
- wheezing or trouble breathing
- changes in your voice
- hives
- feeling faint or anxious
- nausea, vomiting, diarrhea or stomach cramps,

contact your doctor immediately and get emergency treatment. Stop treatment until your doctor tells you to start taking it again

Once you start taking RAGWITEK® at home, your doctor may prescribe some medications to have with you in case of emergency.

Stop treatment and get emergency medical treatment right away if you have any of the following symptoms after taking RAGWITEK®:
- dizziness, fainting, fast or weak heartbeat, feeling nervous or feeling of "impending doom"
- throat tightness or swelling of the tongue or throat that causes trouble speaking, breathing or swallowing
- wheezing, shortness of breath, cough, chest tightness or trouble breathing
- stomach cramps, vomiting or diarrhea
- skin rash, itching, flushing or hives

Stop treatment with RAGWITEK® if you have any of the following symptoms that do not go away or that worsen:
- heartburn, difficulty swallowing, pain with swallowing, or chest pain

Before you take RAGWITEK®, tell your doctor if you:

- have ever had a serious allergic reaction to allergy shots, tablets or drops
- have worsening asthma symptoms or breathing problems
- have recently had any mouth injury or mouth surgery (such as a tooth removal)
- are pregnant or could become pregnant
- are breastfeeding or plan to breastfeed. It is not known if RAGWITEK® will pass into breast milk
- have diseases which affect the immune system, such as autoimmune diseases, including Multiple Sclerosis (MS), lupus or Rheumatoid Arthritis, or immune deficiency such as HIV/AIDS, or if you had your spleen removed
- have cancer

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Your doctor will tell you if it is safe to take other medications while you are using RAGWITEK®. **No drug interaction studies have been done in patients taking** RAGWITEK®**.**

PROPER USE OF THIS MEDICATION

The first dose of RAGWITEK® should only be taken in the doctor's office. After taking the first dose, you will be watched for 30 minutes by a healthcare professional for symptoms of a serious allergic reaction.

Your doctor may prescribe medicines for you to take in case you have a serious allergic reaction.

After the first dose, you may take RAGWITEK® at home.

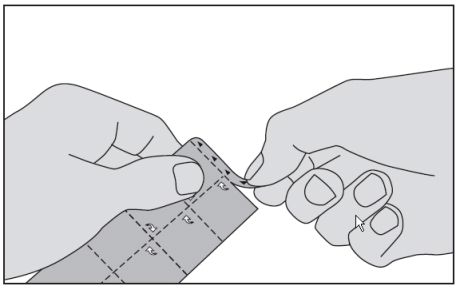
Usual dose:
You should start taking RAGWITEK® at least 12 weeks before the ragweed pollen season usually begins. Take RAGWITEK® exactly as your doctor tells you to take it, usually until the end of the ragweed pollen season.

How should I take RAGWITEK®?

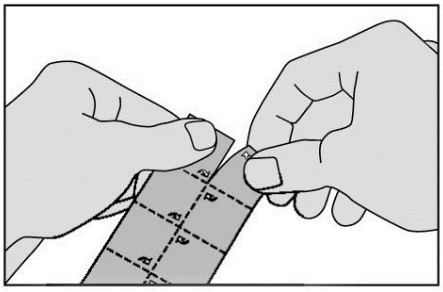
1. Do not use food or water to take the tablet.
2. Remove the tablet from the package with dry hands by carefully removing the foil. (If your hands are wet or damp, the tablet will break or dissolve too soon.)
3. Place the tablet under the tongue right away. It will dissolve in seconds.
4. Do not swallow for about 1 minute.
5. Do not drink or eat for 5 minutes after taking the tablet.
6. Wash your hands after handling the tablet.

Detailed Instructions

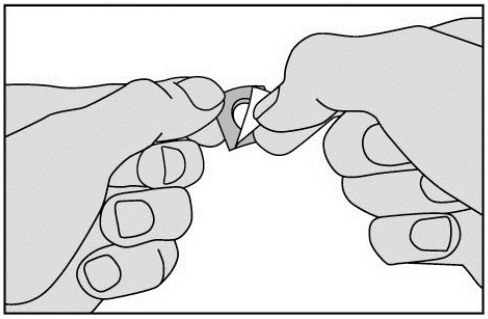
1. Tear off the strip marked with triangles.

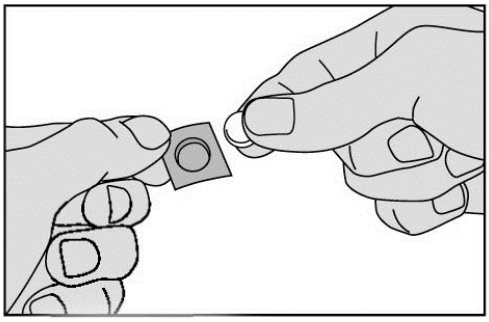


2. Tear a square off the blister pack along the perforated lines.

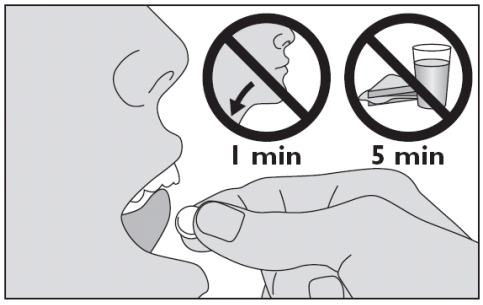


3. Remove the tablet carefully from the foil (*do not force the tablet through the foil. It may become damaged as it easily breaks. Instead, fold back the marked corner of the foil and then pull it off*). Take it immediately.





4. Place the tablet under the tongue. Allow it to remain there for a few seconds until it dissolves. Do not swallow during the first minute. Do not eat or drink for 5 minutes. Wash hands after handling the tablet.



General information about the safe and effective use of RAGWITEK®

This medicine has been prescribed for you. Do not give it to anyone else. It may harm them, even if their symptoms are the same as yours.

Your doctor may also prescribe medications to treat the possible allergic reactions from RAGWITEK® treatment.

Missed Dose:

- If you miss a dose, do not take a double dose to make up for the forgotten dose.
- Increased doses can cause severe allergic reactions.

Overdose:

Taking more than one RAGWITEK® tablet in one day can cause severe allergic reactions.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, RAGWITEK® can cause side effects, including **serious side effects.** The side effects usually happen early in treatment, but can happen even if you have been taking RAGWITEK® for months.

The most common side effects of RAGWITEK® include:

- throat irritation
- itching of the mouth ears or eyes
- swelling or numbness of the mouth

Severe allergic reactions to RAGWITEK® occurred in 2% of patients in clinical trials. Symptoms include:

- swelling of the throat, mouth or tongue
- difficulty swallowing or breathing
- asthma attack/wheezing
- hives/itchy rash
- voice changes (hoarse voice or trouble speaking)

If you experience these symptoms, contact your doctor immediately and get emergency treatment. Do not take any more doses until your doctor tells you to.

Side effects reported by adult patients who were treated with RAGWITEK® in clinical studies include:

Very common [in more than 10% of patients (1 in 10)]:

- **Mouth:** tingling and/ or itching
- **Throat:** irritation in the throat
- **Ear:** itching in the ear

Common [in 1-10% of patients (more than 1 in 100 but less than 1 in 10)]:

Mouth: numbness and/or inflammation, swelling at the roof of the mouth
Tongue: itching, swelling, inflammation
Lips: itching, swelling
Throat: difficulty swallowing, pain and/or swelling and/or redness
Nose: sneezing, runny nose
Eyes: itching
Other:

- headache
- chest discomfort
- cough
- nausea
- itching

Uncommon [in less than 1% of patients (less than 1 in 100)]:

Mouth: mouth discomfort and/or redness and/or burning and/or dryness, inflammation of the mouth, oral discomfort
Tongue: pain, tongue disorder
Lips: inflammation
Throat: tightness, dryness
Nose: congestion, uncomfortable feeling
Eyes: watery
Other:

- shortness of breath
- upset stomach
- itch
- rash
- hives
- change in voice
- asthma

The side effects observed in children were similar to those in adults. The following side effects were reported in addition or more often in children compared to adults:
Mouth: burning (very common), pain (very common), ulcers (common), inflammation of the mouth (common), uvula swelling (common)
Tongue: swelling (very common), ulcers (common)
Lips: swelling (very common)
Throat: irritation (very common), swelling (very common)
Other: nausea (very common), change in taste (common), diarrhea (common), vomiting (common), stomach ache (very common)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor
		Only if severe	In all cases	
Common	Swelling in the mouth	√		
	Swollen tongue	√		
	Swelling in the throat	√		
	Trouble swallowing			√
	Chest discomfort			√
	Itching all over your body	√		
	Throat tightness			√
	Hives all over your body	√		
	Trouble breathing			√
Rare	Severe allergic reactions or asthma Shortness of breath			Seek emergency help immediately

This is not a complete list of side effects. For any unexpected effects while taking RAGWITEK® contact your doctor or pharmacist.

HOW TO STORE IT

- Store at room temperature (15 to 30 °C).
- Store in the original package and protect from moisture.
- Keep out of reach of children.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect
- By calling 1-866-234-2345
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about RAGWITEK®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or ALK-Abelló A/S website *www.alk.net* or by calling ALK-Abelló, Inc. at 1-800-325-7354 (for English) or at 1-800-663-0972 (for French)

To report an adverse event related to RAGWITEK®, please contact 1-800-325-7354 (for English) or at 1-800-663-0972 (for French).

This leaflet was prepared by ALK-Abelló A/S.

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