RAGWITEK- ambrosia artemisiifolia pollen tablet
ALK-Abello A S

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RAGWITEK safely and effectively. See full prescribing information for RAGWITEK.

RAGWITEK® (Short Ragweed Pollen Allergen Extract)
Tablet for Sublingual Use
Initial U.S. Approval: 2014

WARNING: SEVERE ALLERGIC REACTIONS

See full prescribing information for complete boxed warning.

- **RAGWITEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (**5.1**)**
- **Do not administer RAGWITEK to patients with severe, unstable or uncontrolled asthma. (**4**)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (**5.1**)**
- **Prescribe auto-injectable epinephrine, instruct and train patients or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (**5.2**)**
- **RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (**5.2**)**
- **RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (**5.2**)**

RECENT MAJOR CHANGES

Indications and Usage (1) 04/2021

INDICATIONS AND USAGE

RAGWITEK is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen. RAGWITEK is approved for use in persons 5 through 65 years of age. (1)

DOSAGE AND ADMINISTRATION

For sublingual use only.

- One tablet daily. (2.1)
- Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. (2.2)
- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of RAGWITEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablet, 12 Amb a 1-Unit (Amb a 1-U) (3)

CONTRAINDICATIONS

- Severe, unstable or uncontrolled asthma. (4)
- History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. (4)
- A history of eosinophilic esophagitis. (4)
- Hypersensitivity to any of the inactive ingredients contained in this product. (4)

WARNINGS AND PRECAUTIONS

- Inform patients or parents/guardians of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)

- In case of oral inflammation or wounds, stop treatment with RAGWITEK to allow complete healing of the oral cavity. (**5.7**)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of adults were: throat irritation, oral pruritus, ear pruritus, oral paresthesia, mouth edema, and tongue pruritus. Adverse reactions reported in ≥5% of children and adolescents 5 through 17 years of age were: throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, swollen tongue, abdominal pain upper, stomatitis, and enlarged uvula. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc., a subsidiary of ALK-Abelló A/S, at 1-855-216-6497 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

- **RAGWITEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (**5.1**)**
- **Do not administer RAGWITEK to patients with severe, unstable or uncontrolled asthma. (**4**)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (**5.1**)**
- **Prescribe auto-injectable epinephrine, instruct and train patients or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (**5.2**)**
- **RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (**5.2**)**
- **RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (**5.2**)**

1 INDICATIONS AND USAGE

RAGWITEK® is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen. RAGWITEK is approved for use in persons 5 through 65 years of age.

RAGWITEK is not indicated for the immediate relief of allergic symptoms.

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

One RAGWITEK tablet daily.

2.2 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. If

the patient tolerates the first dose, the patient may take subsequent doses at home.

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 (or their parents/guardians) in the proper use of auto-injectable epinephrine *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

RAGWITEK is available as 12 Amb a 1-Unit (Amb a 1-U) tablets that are white to off-white, circular with a debossed double hexagon on one side.

4 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, mannitol, and sodium hydroxide] contained in this product *[see Description (11)].*

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

RAGWITEK can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, RAGWITEK can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening.

Allergic reactions may require treatment with epinephrine. Prescribe auto-injectable epinephrine to patients receiving RAGWITEK. Instruct patients or parents/guardians to recognize the signs and symptoms of a severe allergic reaction and in the proper use of auto-injectable epinephrine. Instruct patients or parents/guardians to seek immediate medical care and to stop treatment with RAGWITEK upon use of auto-injectable

epinephrine *[see Patient Counseling Information (17)]*. See Prescribing Information for epinephrine for complete information.

RAGWITEK may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or that may increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute); severe mast cell disorder; or cardiovascular disease including unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. In addition, RAGWITEK may not be suitable for patients who are taking medications that can potentiate or inhibit the effects of epinephrine (see Prescribing Information for epinephrine for information on drug interactions).

Administer the initial dose of RAGWITEK in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and prepared to manage a life-threatening systemic or local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of RAGWITEK.

5.2 Upper Airway Compromise

RAGWITEK can cause local reactions in the mouth or throat that could compromise the upper airway *[see Adverse Reactions (6.1)]*. Consider discontinuation of RAGWITEK in patients who experience persistent and escalating adverse reactions in the mouth or throat.

5.3 Eosinophilic Esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy *[see Contraindications (4)]*. Discontinue RAGWITEK and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

5.4 Asthma

Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid. RAGWITEK has not been studied in subjects with severe asthma.

Withhold immunotherapy with RAGWITEK if the patient is experiencing an acute asthma exacerbation. Reevaluate patients who have recurrent asthma exacerbations and consider discontinuation of RAGWITEK.

5.5 Concomitant Allergen Immunotherapy

RAGWITEK has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

5.6 Oral Inflammation

Stop treatment with RAGWITEK to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers, or thrush) or oral wounds, such as those following oral surgery or dental extraction.

6 ADVERSE REACTIONS

Adverse reactions reported in ≥5% of adults were: throat irritation, oral pruritus, ear pruritus, oral paresthesia, mouth edema, and tongue pruritus. Adverse reactions reported in ≥5% of children and adolescents 5 through 17 years of age were: throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, swollen tongue, abdominal pain upper, stomatitis, and enlarged uvula.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

In 4 placebo-controlled clinical trials, 1057 subjects 18 years of age and older with short ragweed pollen-induced rhinitis, with or without conjunctivitis, received at least one dose of RAGWITEK, of whom 327 (31%) completed at least 12 weeks of therapy. Of the subjects treated with RAGWITEK, 52% were male, 25% had mild asthma, and 82% were sensitized to other allergens in addition to ragweed pollen. The subject population was 83% White, 12% African American, and 2% Asian. Subject demographics in placebo-treated subjects were similar to the active group. The pooled analysis includes safety data from two 28-day safety studies and safety data from the first 28 days of two 52-week safety and efficacy studies. Adverse reactions reported in ≥1% of subjects in the 28-day pooled analysis treated with RAGWITEK are shown in Table 1.

The most common adverse reactions reported in subjects treated with RAGWITEK were throat irritation (16.6% vs 3.3% placebo), oral pruritus (10.9% vs 2.0%), ear pruritus (10.4% vs 1.1%), and oral paresthesia (10.0% vs 4.0%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to RAGWITEK or placebo was 4.4% and 0.8%, respectively. The most common adverse reactions that led to study discontinuation in subjects who were exposed to RAGWITEK were mouth edema, swollen tongue, and dysphagia.

One subject (1/1057; 0.1%) who received RAGWITEK experienced a treatment-related severe systemic allergic reaction that led to discontinuation of RAGWITEK. The subject had local reactions starting on Day 1 of treatment with RAGWITEK. On Day 6 symptoms progressed and included swelling of the throat, dyspnea, nausea, and lightheadedness. The subject fully recovered after treatment with epinephrine (self-administered), antihistamines, and oral corticosteroids.

Table 1: Adverse Reactions Reported in ≥1% of Adults Treated with RAGWITEK or Placebo (28-day pooled analysis)

Adverse Reaction	RAGWITEK (N=1057)	Placebo (N=757)
Ear and Labyrinth Disorders Ear pruritus	10.4%	1.1%

Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	16.6%	3.3%
Oropharyngeal pain	1.5%	0.7%
Throat tightness	1.3%	0.5%
Gastrointestinal Disorders		
Oral pruritus	10.9%	2.0%
Paresthesia oral	10.0%	4.0%
Mouth edema	6.1%	0.5%
Tongue pruritus	5.1%	0.5%
Lip swelling	3.0%	0.4%
Swollen tongue	2.9%	0.5%
Lip pruritus	1.5%	0.1%
Dry mouth	1.4%	0.7%
Tongue edema	1.3%	0.5%
Nausea	1.1%	0.3%
Palatal edema	1.1%	0%
Dysphagia	1.0%	0%
Skin and Subcutaneous Tissue Disorders		
Pruritus	1.8%	1.3%
General Disorders and Administration Site Conditions		
Chest discomfort	1.0%	0%

* 1036 subjects were 18 through 65 years of age and 21 subjects were older than 65 years of age.

† 746 subjects were 18 through 65 years of age and 11 subjects were older than 65 years of age.

The overall safety profile beyond Day 28 in the two 52-week trials was similar to that observed in the pooled 28-day analysis.

Children and Adolescents (5 through 17 years of age)

In 1 placebo-controlled clinical trial, 513 subjects 5 through 17 years of age with short ragweed pollen-induced rhinitis, with or without conjunctivitis, received at least one dose of RAGWITEK. Of the subjects treated with RAGWITEK, 63% were male, 43% had asthma, and 79% were sensitized to other allergens in addition to ragweed pollen. The subject population was 93% White, 3.1% African American, 2.3% multiple race, 1% Asian, 0.5% Native Hawaiian or Other Pacific Islander, and 0.1% American Indian or Alaska Native. Approximately 40% of subjects were children (5 through 11 years of age) and 60% of subjects were adolescents (12 through 17 years of age). Subject demographics in placebo-treated subjects were similar to the active treatment group.

In the trial in children and adolescents 5 through 17 years of age, parents/ guardians and/ or participants were provided SLIT report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following

treatment initiation with RAGWITEK or placebo (summarized in Table 2).

Table 2: Solicited* Adverse Reactions occurring within 28 days of Initiation of Treatment with RAGWITEK or Placebo in Children and Adolescents 5 through 17 Years of Age

Adverse Reaction (Any Intensity)	RAGWITEK (N=513)	Placebo (N=509)
Ear and Labyrinth Disorders		
Itching in the ear	33.9%	6.3%
Gastrointestinal Disorders		
Itching in the mouth	47.8%	11.2%
Mouth pain	18.9%	4.5%
Swelling of the lips	13.8%	1.2%
Nausea	11.5%	3.3%
Swelling of the tongue†	11.3%	0.8%
Stomach pain	10.1%	4.5%
Swelling of the uvula/back of the mouth‡	9.9%	0.4%
Mouth ulcer/sore in the mouth	8.4%	2.2%
Tongue ulcer/sore on the tongue	6.8%	2.2%
Diarrhea	2.7%	1.2%
Vomiting	1.2%	0%
Nervous System Disorders		
Taste alteration/food tastes different	3.9%	2.0%
Respiratory, Thoracic and Mediastinal Disorders	48.3%	17.7%
Throat irritation/tickle	10.7%	1.6%
Throat swelling		

* Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy [SLIT]) were those solicited from subjects via SLIT report card within the first 28 days after treatment initiation.

† Of those subjects reporting any intensity of swelling of the tongue in the RAGWITEK group, 1 subject (0.2%) reported severe intensity of swelling of the tongue. Adverse reactions were categorised as severe according to the definition ‘incapacitating with inability to work or do usual activity’, as assessed by the investigator.

‡ The percentage of subjects reporting "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically at the back of the mouth).

In the clinical trial in children and adolescents, unsolicited adverse reactions occurring throughout the entire duration of the trial were recorded in electronic diaries or reported at study visits. Unsolicited adverse reactions reported by ≥1% of children and adolescents throughout the entire duration of the trial are shown in Table 3.

Table 3: Unsolicited Adverse Reactions occurring during the Entire Trial after Initiation of Treatment, Reported in ≥1% of Children and Adolescents 5 through 17 Years of Age Treated with RAGWITEK or Placebo

Adverse Reaction	RAGWITEK (N=513)	Placebo (N=509)
Ear and Labyrinth Disorders		
Ear pruritus	4.5%	0.2%
Gastrointestinal Disorders		
Oral pruritus	7.8%	1.0%
Tongue pruritus	4.5%	0.4%
Lip swelling	1.9%	-
Paresthesia oral	1.9%	0.4%
Mouth swelling	1.8%	-
Dysphagia	1.6%	0.2%
Nausea	1.6%	0.4%
Oral pain	1.6%	0.4%
Swollen tongue	1.4%	-
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	7.6%	1.6%
Oropharyngeal pain	1.8%	0.4%
Sneezing	1.6%	0.4%
Pharyngeal edema	1.2%	-
Rhinorrhea	1.2%	0.4%
Skin and Subcutaneous Tissue Disorders		
Pruritus	1.2%	0.2%

The percentage of subjects who discontinued from the clinical trial because of an adverse reaction while exposed to RAGWITEK or placebo was 3.9% and 1.0%, respectively. The most common adverse reaction that led to study discontinuation in subjects who were exposed to RAGWITEK was throat irritation.

Three subjects (0.6%) treated with RAGWITEK and one subject (0.2%) treated with placebo experienced treatment-related systemic allergic reactions [adverse reactions marked with an asterisk (*) were included in Table 3].

- One subject treated with RAGWITEK reported hypersensitivity events (skin/face/neck itching*, eye itching/swelling, sneezing*, runny*/itching nose, neck/abdomen redness) beginning on day 6 (i.e., outside the ragweed pollen season) that resolved by day 26. The events resolved within minutes to less than an hour. On two occasions, the subject was treated with antihistamine. This subject subsequently discontinued the trial on day 34 due to persistent local allergic symptoms (swollen tongue).
- The second subject treated with RAGWITEK reported hypersensitivity (generalized

rash on body and face) on day 26 (i.e., outside the ragweed pollen season). The event was treated with antihistamine and systemic corticosteroids and resolved in one week; the subject discontinued the trial due to the event.
- The third subject treated with RAGWITEK reported pruritus* (on cheeks, arms and legs) and dyspnea on day 1 (i.e., outside the ragweed pollen season) after administration of the first dose. Both adverse events resolved within 2 hours without treatment and did not reoccur upon restarting trial medication 1 week later. The subject subsequently completed the trial.
- The subject treated with placebo reported hypersensitivity (papular rash with itching on hands, body and lower limbs) on day 7 (i.e. outside the ragweed pollen season). The event was treated with an antihistamine and systemic corticosteroid and resolved in one week; the subject discontinued the trial due to the event.

One subject (0.2%) treated with RAGWITEK and no subjects on placebo, reported adverse reactions that were treated with epinephrine (any route).The one subject treated with RAGWITEK experienced severe laryngitis on day 126 (during the ragweed pollen season), for which the subject was hospitalized and treated with inhaled racemic epinephrine (i.e., not systemic epinephrine); the laryngitis resolved in 2 days.

6.2 Postmarketing Experience

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.
- *Ear and Labyrinth Disorders:* ear discomfort, ear pain
- *Gastrointestinal Disorders:* gastroesophageal reflux disease, glossodynia, dyspepsia, hypoesthesia oral
- *General disorder and administration site conditions:* sensation of foreign body
- *Immune System Disorders:* serious systemic allergic reactions, including anaphylaxis
- *Nervous System Disorders:* paresthesia
- *Respiratory, Thoracic and Mediastinal Disorders:* asthma exacerbation, cough, dry throat, dysphonia, pharyngeal erythema
- *Skin and Subcutaneous Tissue Disorders:* angioedema, urticaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available human data do not establish the presence or absence of RAGWITEK-associated risks during pregnancy.

In an embryo/fetal developmental toxicity study, RAGWITEK subcutaneously administered to mice during gestation at doses up to approximately 3 times the human sublingual dose did not reveal adverse developmental outcomes in fetuses *(see 8.1 Data)*.

Data

Animal Data

In a developmental toxicity study, the effect of RAGWITEK on embryo/fetal development was evaluated in mice. Animals were administered RAGWITEK subcutaneously daily from day 6 to day 15 of the gestation period at doses approximately 1 to 3 times the human sublingual dose of 12 Amb a 1-U. There were no RAGWITEK-related post-implantation losses, fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether RAGWITEK is excreted in human milk. Data are not available to assess the effects of RAGWITEK on the breastfed child or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RAGWITEK and any potential adverse effects on the breastfed child from RAGWITEK or from the underlying maternal condition.

8.4 Pediatric Use

Efficacy and safety of RAGWITEK have been established in children and adolescents 5 through 17 years of age. The efficacy and safety in pediatric patients below 5 years of age have not been established.

8.5 Geriatric Use

RAGWITEK is not approved for use in patients over 65 years of age because safety and efficacy have not been established.

11 DESCRIPTION

RAGWITEK tablets contain pollen allergen extract from Short Ragweed (*Ambrosia artemisiifolia*). RAGWITEK is a sublingual tablet that dissolves within 10 seconds.

RAGWITEK is available as a tablet of 12 Amb a 1-U of short ragweed pollen allergen extract.

Inactive ingredients: gelatin NF (fish source), mannitol USP, and sodium hydroxide NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy are not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed in animals to evaluate the carcinogenic potential

of RAGWITEK.

There were no positive findings in a combined *in vivo* Comet and micronucleus assay in rats using Short Ragweed (*Ambrosia artemisiifolia*) pollen allergen extract.

Fertility studies have not been performed with Short Ragweed pollen allergen extract.

14 CLINICAL STUDIES

Adults

The efficacy of RAGWITEK in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, was investigated in two double-blind, placebo-controlled clinical trials in adults 18 through 50 years of age. Subjects received RAGWITEK or placebo for approximately 12 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season.

The subject population was 86% White, 9% African American, and 3% Asian. The subject population was almost equally divided between males and females. Overall, the mean age of subjects was 36 years. Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Approximately 16% of subjects had mild asthma at baseline.

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). Subjects 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. 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) which was averaged over the peak ragweed pollen season. Also, in each study, the average TCS over the entire ragweed season was assessed. Other endpoints in both studies included the average DSS during the peak and entire ragweed season, and the average DMS during the peak ragweed season.

Trial 1

The first study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing RAGWITEK (n=187) and placebo (n=188) administered as a sublingual tablet daily. In this trial, approximately 22% of subjects had mild asthma and 85% were sensitized to other allergens in addition to short ragweed. Subjects with asthma who participated in this trial had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Subjects with a clinical history of symptomatic allergies to non-short ragweed pollen allergens that required treatment during the ragweed pollen season were excluded from the trial. The subject population was 78% White, 12% African American, and 8% Asian, and almost equally divided between males and females. The mean age of subjects in this study was 35.4 years. The

two treatment groups were balanced with regard to baseline characteristics. The results of this study are shown in Table 4.

Trial 2

The second study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing RAGWITEK (n=194) and placebo (n=198) administered as a sublingual tablet daily. Approximately 17% of subjects had mild asthma and 78% were sensitized to other allergens in addition to short ragweed. Subjects with asthma who participated in this trial had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Subjects with a clinical history of symptomatic allergies to non-short ragweed pollen allergens that required treatment during the ragweed pollen season were excluded from the trial. The subject population was 88% White, 8.9% African American, 2% Asian, and almost equally divided between males and females. The mean age of subjects in this study was 36.4 years. The two treatment groups were balanced with regard to baseline characteristics. The results of this study are shown in Table 5.

A decrease in TCS during the peak ragweed season for subjects treated with RAGWITEK compared to placebo-treated subjects was demonstrated in both trials. Subjects treated with RAGWITEK also showed a decrease in the average TCS from the start of and throughout the entire ragweed pollen season. Similar decreases were observed in subjects treated with RAGWITEK for other endpoints (see Tables 4 and 5).

Table 4: Adult Trial 1: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season (Adults 18 through 50 Years of Age)

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(159) 6.22	(164) 8.46	-2.24	-26% (-38.7, -14.6)
TCS Entire Season	(160) 5.21	(166) 7.01	-1.80	-26% (-37.6, -13.5)
DSS Peak Season	(159) 4.65	(164) 5.59	-0.94	-17% (-28.6, -4.6)
DSS Entire Season	(160) 4.05	(166) 4.87	-0.82	-17% (-28.5, -4.5)
DMS Peak Season	(159) 1.57	(164) 2.87	-1.30	-45% (-65.4, -27.0)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily

Medication Score.

* Parametric analysis using analysis of variance model for all endpoints.

† Number of subjects in analyses.

‡ The estimated group means are reported and difference relative to placebo is 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 10,000 bootstrap samples.

¶ Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

Table 5: Adult Trial 2: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season (Adults 18 through 50 Years of Age)

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(152) 6.41	(169) 8.46	-2.04	-24% (-36.5, -11.3)
TCS Entire Season	(158) 5.18	(174) 7.09	-1.92	-27% (-38.8, -14.1)
DSS Peak Season	(152) 4.43	(169) 5.37	-0.94	-18% (-29.2, -4.5)
DSS Entire Season	(158) 3.62	(174) 4.58	-0.96	-21% (-31.6, -8.8)
DMS Peak Season	(152) 1.99	(169) 3.09	-1.10	-36% (-55.8, -14.6)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

* Parametric analysis using analysis of variance model for all endpoints.

† Number of subjects in analyses.

‡ The estimated group means are reported and difference relative to placebo is 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 10,000 bootstrap

samples.

¶ Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

Children and Adolescents (5 through 17 years of age)

The efficacy of RAGWITEK in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, was investigated in a double-blind, placebo-controlled clinical trial in children and adolescents 5 through 17 years of age comparing RAGWITEK (n= 512) and placebo (n= 510) administered as a sublingual tablet daily. Subjects received RAGWITEK or placebo 12-20 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season. The subject population was 63% male, 93% White, 3.1% African American, 2.3% multiple race, 1% Asian, 0.5% Native Hawaiian or Other Pacific Islander, and 0.1% American Indian or Alaska Native. Approximately 40% of subjects were children (5 through 11 years of age) and 60% of subjects were adolescents (12 through 17 years of age). Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a medium dose of an inhaled corticosteroid. 43% of subjects had asthma at baseline. Treatment groups were balanced with regard to baseline characteristics.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS) using a similar methodology to the adult trials.

The sums of the DSS and DMS were combined into the Total Combined Score (TCS) which was averaged over the peak ragweed pollen season. The average TCS over the entire ragweed season was also assessed.

A decrease in TCS during the peak ragweed season for subjects treated with RAGWITEK compared to placebo-treated subjects was demonstrated. Subjects treated with RAGWITEK also showed a decrease in the average TCS from the start of and throughout the entire ragweed pollen season. Similar decreases were observed in subjects treated with RAGWITEK for other endpoints (see Table 6).

Table 6: Pediatric Trial: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season for Children and Adolescents 5 through 17 Years of Age

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(460) 4.39	(487) 7.12	-2.73	-38% (-46.0, -29.7)
TCS Entire Season	(466) 3.88	(491) 5.75	-1.86	-32% (-40.7, -23.3)
DSS Peak Season	(468) 2.55	(494) 3.95	-1.40	-35% (-43.2, -26.1)

DMS Peak Season	(460) 2.01	(487) 3.85	-1.84	-48% (-59.8, -32.5)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

* Parametric analysis using analysis of variance model for all endpoints.

† Number of subjects in analyses.

‡ The estimated group means are reported and difference relative to placebo is 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 10,000 bootstrap samples.

¶ Primary endpoint (pre-specified criteria for success for primary endpoint: a treatment difference relative to placebo of at least -15% and the associated upper bound of the 95% confidence interval (CI) for this difference of at least -10%); peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

Note: All statistical analyses for the 4 endpoints included fixed effects of treatment, baseline asthma status (yes, no), age group (5 through 11 years of age, 12 through 17 years of age), pollen season, and pollen region nested within pollen season.

The average DSS during the entire season was 2.27 (RAGWITEK group) and 3.26 (placebo group) (treatment difference of -0.99) with a relative treatment difference of -30% (95% CI -38.6, -20.7) and the average DMS during the entire season was 1.61 (RAGWITEK group) and 2.48 (placebo group) (treatment difference of -0.87) with a relative treatment difference of -35% (95% CI -45.5, -22.7).

16 HOW SUPPLIED/STORAGE AND HANDLING

RAGWITEK 12 Amb a 1-U tablets are white to off-white, circular sublingual tablets with a debossed double hexagon on one side.

RAGWITEK is supplied as follows:

3 blister packages of 10 tablets (30 tablets total). NDC 52709-1601-3

Store at controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF). Store in the original package until use to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients or parents/guardians to read the FDA-approved patient labeling (Medication Guide) and to keep RAGWITEK and all medicines out of the reach of children.

Severe Allergic Reactions

Advise patients or parents/guardians that RAGWITEK may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients or parents/guardians about the signs and symptoms of these allergic reactions *[see Warnings and Precautions (5.1)]*. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.

Ensure that patients (or their parents/guardians) have auto-injectable epinephrine and instruct patients or parents/guardians in its proper use. Instruct patients (or their parents/guardians) who experience a severe allergic reaction to seek immediate medical care, discontinue RAGWITEK, and resume treatment only when advised by a physician to do so *[see Warnings and Precautions (5.1)].*

Advise patients or parents/guardians to read the patient information for epinephrine.

Inform patients or parents/guardians that the first dose of RAGWITEK must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of life-threatening systemic or local allergic reaction *[see Warnings and Precautions (5.1)]*.

Because of the risk of upper airway compromise, instruct patients (or their parents/guardians) with persistent and escalating adverse reactions in the mouth or throat to discontinue RAGWITEK and to contact their healthcare professional *[see Warnings and Precautions (5.2)].*

Because of the risk of eosinophilic esophagitis, instruct patients (or their parents/guardians) with severe or persistent symptoms of esophagitis to discontinue RAGWITEK and to contact their healthcare professional *[see Warnings and Precautions (5.3)].*

Asthma

Instruct patients (or their parents/guardians) with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking RAGWITEK and contact their healthcare professional immediately *[see Warnings and Precautions (5.4)]*.

Administration Instructions

Instruct patients (or their parents/guardians) to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve. Also instruct patients (or their parents/guardians) to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet *[see Dosage and Administration (2.2)].*

Manufactured for: ALK-Abelló A/S

ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

U.S. License No. 1292

Manufactured by:

Catalent Pharma Solutions Limited, Blagrove,

Swindon, Wiltshire, SN5 8RU UK

MEDICATION GUIDE

RAGWITEK® (RAG-wi-tek)

(Short Ragweed Pollen Allergen Extract)

Carefully read this Medication Guide before you or your child start taking RAGWITEK® and each time you get a refill. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk with your doctor or pharmacist if there is something you do not understand or if you want to learn more about RAGWITEK.

What is the Most Important Information I Should Know about RAGWITEK?

RAGWITEK can cause severe allergic reactions that may be life-threatening. Stop taking RAGWITEK and get medical treatment right away if you or your child have any of the following symptoms after taking RAGWITEK:

- Trouble breathing
- Throat tightness or swelling
- Trouble swallowing or speaking
- Dizziness or fainting
- Rapid or weak heartbeat
- Severe stomach cramps or pain, vomiting, or diarrhea
- Severe flushing or itching of the skin

For home administration of RAGWITEK, your doctor will prescribe auto-injectable epinephrine, a medicine you can inject if you or your child have a severe allergic reaction after taking RAGWITEK. Your doctor will train and instruct you on the proper use of auto-injectable epinephrine.

Talk to your doctor or read the epinephrine patient information if you have any questions about the use of auto-injectable epinephrine.

What is RAGWITEK?

RAGWITEK is a prescription medicine used for sublingual (under the tongue) immunotherapy to treat ragweed pollen allergies that can cause sneezing, runny or itchy nose, stuffy or congested nose, or itchy and watery eyes. RAGWITEK may be prescribed for persons 5 through 65 years of age who are allergic to ragweed pollen.

RAGWITEK is taken for about 12 weeks before ragweed pollen season and throughout ragweed pollen season.

RAGWITEK is NOT a medication that gives immediate relief for symptoms of ragweed allergy.

RAGWITEK is not approved for use in children younger than 5 years of age or in adults older than 65 years of age.

Who Should Not Take RAGWITEK?

You or your child should not take RAGWITEK if:

- You or your child have severe, unstable or uncontrolled asthma
- You or your child had a severe allergic reaction in the past that included any of these symptoms:
  - ○ Trouble breathing
  - ○ Dizziness or fainting
  - ○ Rapid or weak heartbeat
- You or your child have ever had difficulty with breathing due to swelling of the throat or upper airway after using any sublingual immunotherapy before.
- You or your child have ever been diagnosed with eosinophilic esophagitis.
- You or your child are allergic to any of the inactive ingredients contained in RAGWITEK. The inactive ingredients contained in RAGWITEK are: gelatin, mannitol, and sodium hydroxide.

What Should I Tell My Doctor Before Taking RAGWITEK?

Your doctor may decide that RAGWITEK is not the best treatment if:

- You or your child have asthma, depending on how severe it is.
- You or your child suffer from lung disease such as chronic obstructive pulmonary disease (COPD)
- You or your child suffer from heart disease such as coronary artery disease, an irregular heart rhythm, or you have hypertension that is not well controlled.
- You or your daughter are pregnant, plan to become pregnant during the time you will be taking RAGWITEK, or are breast-feeding.
- You or your child are unable or unwilling to administer auto-injectable epinephrine to treat a severe allergic reaction to RAGWITEK.
- You or your child are taking certain medicines that enhance the likelihood of a severe reaction, or interfere with the treatment of a severe reaction. These medicines include:
  - ○ beta blockers and alpha-blockers (prescribed for high blood pressure)
  - ○ cardiac glycosides (prescribed for heart failure or problems with heart rhythm)
  - ○ diuretics (prescribed for heart conditions and high blood pressure)
  - ○ ergot alkaloids (prescribed for migraine headache)
  - ○ monoamine oxidase inhibitors or tricyclic antidepressants (prescribed for depression)
  - ○ thyroid hormone (prescribed for low thyroid activity).
- You or your child are receiving allergy shots or other immunotherapy under the tongue. Use of more than one of these types of medicines together may increase the likelihood of a severe allergic reaction.

You should tell your doctor if you or your child are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal supplements. Keep a list of them and show it to your doctor and pharmacist each time you get a new supply of RAGWITEK. Ask your doctor or pharmacist for advice before taking RAGWITEK.

Are there any Reasons to Stop Taking RAGWITEK?

Stop RAGWITEK and contact your doctor if you or your child have any of the following after taking RAGWITEK:

- Any type of a serious allergic reaction
- Throat tightness that worsens or swelling of the tongue or throat that causes trouble

speaking, breathing, or swallowing
- Asthma or any other breathing condition that gets worse
- Dizziness or fainting
- Rapid or weak heartbeat
- Severe stomach cramps or pain, vomiting, or diarrhea
- Severe flushing or itching of the skin
- Heartburn, difficulty swallowing, pain with swallowing, or chest pain that does not go away or worsens

Also, stop taking RAGWITEK following: mouth surgery procedures (such as tooth removal), or if you develop any mouth infections, ulcers or cuts in the mouth or throat.

How Should I Take RAGWITEK?

Take RAGWITEK exactly as your doctor tells you.

RAGWITEK is a prescription medicine that is placed under the tongue.
- Take the tablet from the blister package 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.
- Do not take RAGWITEK with food or beverage. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after taking the tablet.

Take the first tablet of RAGWITEK in your doctor’s office. After taking the first tablet, you or your child will be watched for at least 30 minutes for symptoms of a serious allergic reaction.

If you tolerate the first dose of RAGWITEK, you or your child will continue RAGWITEK therapy at home by taking one tablet every day. Children should be given each tablet of RAGWITEK by an adult who will watch for any symptoms of a serious allergic reaction.

Take RAGWITEK as prescribed by your doctor until the end of the treatment course. If you forget to take RAGWITEK, do not take a double dose. Take the next dose at your normal scheduled time the next day. If you miss more than one dose of RAGWITEK, contact your healthcare provider before restarting.

What are the Possible Side Effects of RAGWITEK?

In children and adults, the most commonly reported side effects were throat irritation, itching in the mouth or ears, swelling of the lips, mouth or throat, mouth ulcer/sore in the mouth, mouth pain, stomach pain, nausea.

RAGWITEK can cause severe allergic reactions that may be life-threatening. Symptoms of allergic reactions to RAGWITEK include:
- Trouble breathing
- Throat tightness or swelling
- Trouble swallowing or speaking
- Dizziness or fainting
- Rapid or weak heartbeat
- Severe stomach cramps or pain, vomiting, or diarrhea
- Severe flushing or itching of the skin

For additional information on the possible side effects of RAGWITEK talk with your doctor or pharmacist. You may report side effects to the U.S. Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch.

How Should I Store RAGWITEK?

Keep RAGWITEK out of the reach of children.

Throw away any unused RAGWITEK after the expiration date which is stated on the carton and blister pack after “EXP.”

Store RAGWITEK in a dry place at room temperature, 15ºC to 30ºC (59ºF to 86ºF), in the original package.

General Information about RAGWITEK

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RAGWITEK for a condition for which it was not prescribed. Do not give RAGWITEK to other people, even if they have the same symptoms. It may harm them.

This Medication Guide summarizes the most important information about RAGWITEK. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about RAGWITEK that was written for healthcare professionals. For more information, go to: www.ragwitek.com or call 1-855-782-9323 (toll-free).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

U.S. License No. 1292

Manufactured by:

Catalent Pharma Solutions Limited, Blagrove,

Swindon, Wiltshire, SN5 8RU UK

Revised: 04/2021

PRINCIPAL DISPLAY PANEL

NDC 52709-1601-3
This carton contains 30 sublingual tablets in three 10-Tablet blister cards

Short Ragweed Pollen Allergen Extract,
Ragwitek® Tablet for sublingual use

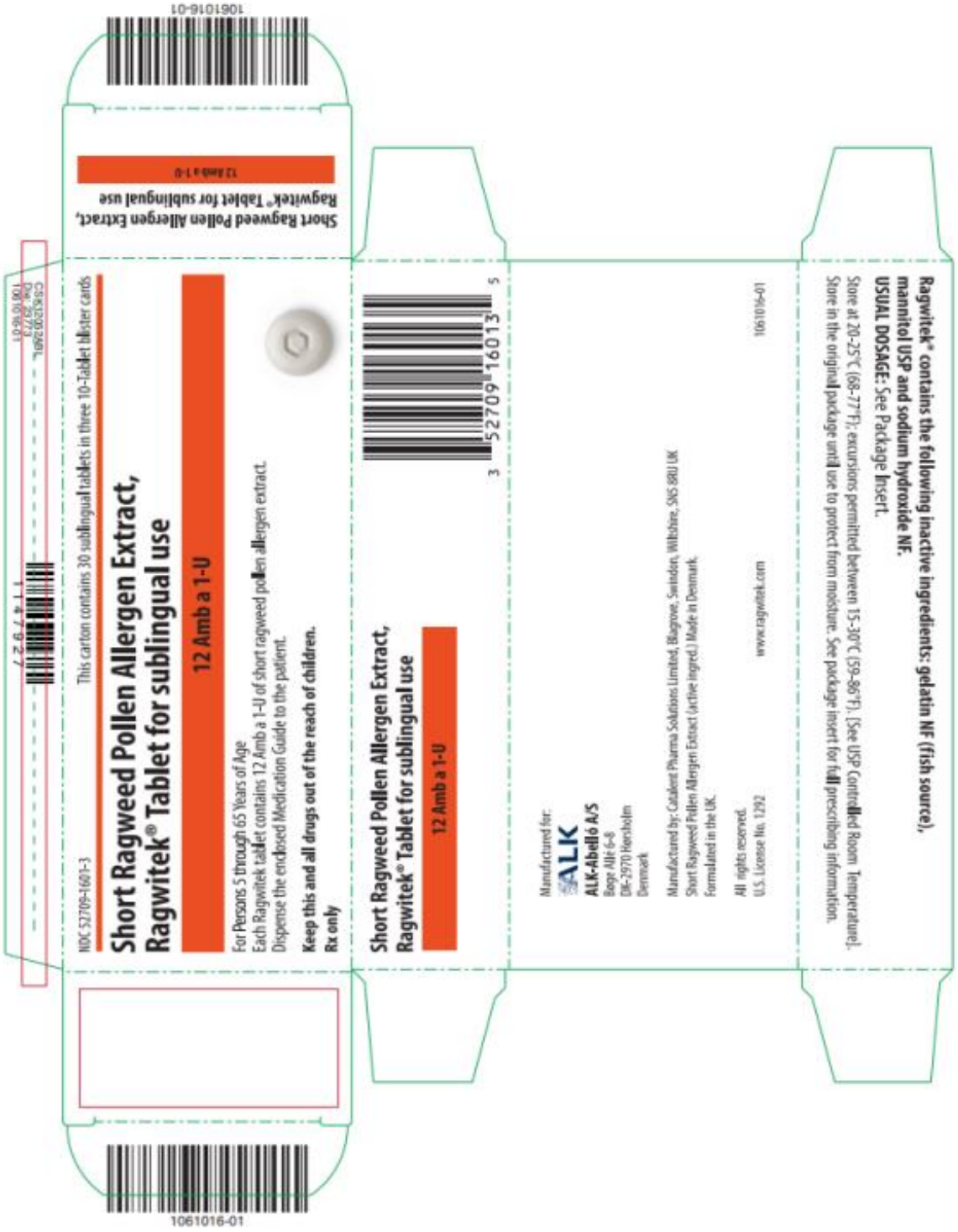
12 Amb a 1-U

For Persons 5 through 65 Years of Age
Each Ragwitek tablet contains 12 Amb a 1-U of short ragweed pollen allergen extract.

Dispense the enclosed Medication Guide to the patient.

Keep this and all drugs out of the reach of children.

Rx only



RAGWITEK

ambrosia artemisiifolia pollen tablet

Product Information			
Product Type	STANDARDIZED ALLERGENIC	**Item Code (Source)**	NDC:52709-1601

Route of Administration	SUBLINGUAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMBROSIA ARTEMISIIFOLIA POLLEN (UNII: K20Y81ACO3) (AMBROSIA ARTEMISIIFOLIA POLLEN - UNII:K20Y81ACO3)	AMBROSIA ARTEMISIIFOLIA POLLEN	12 [Amb'a'1'U]

Inactive Ingredients

Ingredient Name	Strength
MARINE COLLAGEN, SOLUBLE (UNII: 8JC99XGU4W)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Product Characteristics

Color	white (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52709-1601-3	3 in 1 CARTON		
1	NDC:52709-1601-1	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:52709-1601-5	1 in 1 CARTON		
2		5 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125478	04/17/2014	

Labeler - ALK-Abello A S (306020926)