Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

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

GRASTEK® (Timothy Grass Pollen Allergen Extract)
Tablet for Sublingual Use
Initial U.S. Approval: 2014

WARNING: SEVERE ALLERGIC REACTIONS
See full prescribing information for complete boxed warning.

- **GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer GRASTEK 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 on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **GRASTEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

----------INDICATIONS AND USAGE----------
GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. (1)

---------- DOSAGE AND ADMINISTRATION ----------
For sublingual use only. (2)

- One tablet daily. (2.1)
- Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK may be taken daily for three consecutive years. (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 GRASTEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablet, 2800 Bioequivalent Allergy Units (BAUs) (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 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 GRASTEK to allow complete healing of the oral cavity. (5.7)

---------- ADVERSE REACTIONS ----------

- Adverse reactions reported in ≥5% of patients were: ear pruritus, oral pruritus, tongue pruritus, mouth edema, throat irritation. (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: 03/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

- **GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer GRASTEK 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 on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **GRASTEK 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

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

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

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

One GRASTEK tablet daily.

2.2 Administration

Administer the first dose of GRASTEK 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 GRASTEK, 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.

Administer GRASTEK to children under adult supervision.

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 each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK may be taken daily for three consecutive years (including the intervals between the grass pollen seasons). 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 GRASTEK are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.

Prescribe auto-injectable epinephrine to patients prescribed GRASTEK and instruct them in the proper use of emergency self-injection of epinephrine *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

GRASTEK is available as 2800 Bioequivalent Allergy Unit (BAU) tablets that are white to off-white, circular with a debossed round detail on one side.

4 CONTRAINDICATIONS

GRASTEK 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

GRASTEK can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, GRASTEK can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening. Educate patients to recognize the signs and symptoms of these allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. Allergic reactions may require treatment with epinephrine. *[See Warnings and Precautions (5.2).]*

Administer the initial dose of GRASTEK 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 GRASTEK.

5.2 Epinephrine

Prescribe auto-injectable epinephrine to patients receiving GRASTEK. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with GRASTEK. *[See Patient Counseling Information (17).]*

See the epinephrine package insert for complete information.

GRASTEK may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or 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), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

GRASTEK may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

Beta-adrenergic blockers: Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

Alpha-adrenergic blockers, ergot alkaloids: Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors and certain antihistamines: The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

Cardiac glycosides, diuretics: Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

5.3 Upper Airway Compromise

GRASTEK can cause local reactions in the mouth or throat that could compromise the upper airway *[see Adverse Reactions (6.1 and 6.2)]*. Consider discontinuation of GRASTEK in patients who experience persistent and escalating adverse reactions in the mouth or throat.

5.4 Eosinophilic Esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy *[see Contraindications (4) and Adverse Reactions (6.2)]*. Discontinue GRASTEK and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

5.5 Asthma

GRASTEK has not been studied in subjects with moderate or severe asthma or any subjects who required daily medication to treat asthma.

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

5.6 Concomitant Allergen Immunotherapy

GRASTEK 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.

5.7 Oral Inflammation

Stop treatment with GRASTEK 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 patients were: ear pruritus, oral pruritus, tongue pruritus, mouth edema, and throat irritation.

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

The safety data described below are based on 6 clinical trials which randomized 3589 subjects 18 through 65 years of age with Timothy grass pollen induced rhinitis with or without conjunctivitis, including 1669 subjects who were exposed to at least one dose of GRASTEK. Of the subjects treated with GRASTEK, 25% had mild asthma and 80% were sensitized to other allergens in addition to grass. The subject population was 88% White, 7% African American, and 3% Asian. Subjects were 52% male, and 88% of subjects were between 18 and 50 years of age. Subject demographics in placebo-treated subjects were similar to the active group.

The most common adverse reactions reported in subjects treated with GRASTEK were oral pruritus (26.7% vs 3.5% placebo), throat irritation (22.6% vs 2.8%), ear pruritus (12.5% vs 1.1%) and mouth edema (11.1% vs 0.8%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK or placebo was 4.9% and 0.9%, respectively. The most

common adverse reactions that led to study discontinuation in subjects who were exposed to GRASTEK were pharyngeal edema and oral pruritus.

Seven adult subjects (7/1669; 0.4%) who received GRASTEK experienced treatment-related systemic allergic reactions that led to discontinuation of GRASTEK in four out of the seven subjects.

- Five of the seven subjects had reactions on Day 1 of treatment with GRASTEK. Symptoms included swelling of lips/mouth; oral/pharyngeal itching; ear itching, sneezing, rhinorrhea, throat irritation, dysphonia, dysphagia, chest discomfort, and rash. Three of the five subjects received treatment with epinephrine and antihistamines, and one of the three also received oral corticosteroids. One of the five subjects who had a reaction on Day 1 of treatment with GRASTEK also had a reaction on Day 2 of treatment with GRASTEK. Symptoms on Day 2 included oral burning sensation; rhinorrhea; and throat irritation.
- One of the seven subjects had a reaction on Day 2 after tolerating treatment with GRASTEK on Day 1. Symptoms included edema of the lower lip, epigastric discomfort and dizziness.
- One of the seven subjects developed chest tightness and shortness of breath on Day 42 of treatment with GRASTEK.

Adverse reactions reported in ≥1% of subjects treated with GRASTEK are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥1% of Adults Treated with GRASTEK

Adverse Reaction	**GRASTEK (N=1669)**	**PLACEBO (N=1645)**
Nervous System Disorders		
Headache	2.1%	1.3%
Ear and Labyrinth Disorders		
Ear pruritus	12.5%	1.1%
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	22.6%	2.8%
Pharyngeal edema	3.4%	0.1%
Dry throat	1.7%	0.4%
Oropharyngeal pain	1.6%	1.0%
Nasal discomfort	1.6%	1.0%
Throat tightness	1.4%	0.2%
Dyspnea	1.1%	0.4%
Gastrointestinal Disorders		
Oral pruritus	26.7%	3.5%
Mouth edema	11.1%	0.8%
Paresthesia oral	9.8%	2.0%
Tongue pruritus	5.7%	0.5%
Lip swelling	4.0%	0.2%
Swollen tongue	2.8%	0.1%
Dyspepsia	2.3%	0.1%
Hypoesthesia oral	2.3%	1.0%
Nausea	1.9%	0.6%
Oral discomfort	1.6%	0.3%
Oral mucosal erythema	1.5%	0.6%
Lip edema	1.3%	0.1%

Glossitis	1.3%	0.1%
Stomatitis	1.1%	0.3%
Tongue disorder	1.1%	0.2%
Tongue edema	1.1%	0.4%
Glossodynia	1.0%	0.3%
Dysphagia	1.0%	0.2%
Palatal edema	1.0%	0.1%
Skin and Subcutaneous Tissue Disorders		
Pruritus	2.4%	1.0%
Urticaria	1.7%	0.9%
General Disorders and Administration Site Conditions		
Chest discomfort	1.6%	0.5%
Fatigue	1.4%	0.4%

Adverse reactions of interest that occurred in ≤1% of GRASTEK recipients include abdominal pain and gastroesophageal reflux.

Pediatrics

Safety data are based on 3 clinical trials which randomized 881 subjects between 5 and 17 years of age with grass pollen induced rhinitis with or without conjunctivitis. Overall, 445 subjects received at least one dose of GRASTEK. Of the subjects treated with GRASTEK, 31% had mild asthma and 86% were sensitized to other allergens in addition to grass. The subject population was 86% White, 7% African American and 3% multi-racial. The majority (66%) of subjects were male. The mean age of subjects was 11.7 years. Subject demographics in placebo-treated subjects were similar to the active group.

The most common adverse reactions in pediatric subjects treated with GRASTEK were oral pruritus (24.4% vs 2.1% placebo), throat irritation (21.3% vs 2.5%) and mouth edema (9.8% vs 0.2%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK or placebo was 6.3% and 0.7%, respectively.

One pediatric subject (1/447; 0.2%) who received GRASTEK experienced a treatment-related systemic allergic reaction consisting of lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough which was of moderate intensity on Day 1. The subject was treated with epinephrine, recovered, and was discontinued from the trial.

Adverse reactions reported in ≥1% of subjects treated with GRASTEK are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥1% of Pediatric Subjects Treated with GRASTEK

Adverse Reaction	**GRASTEK (N=447)**	**PLACEBO (N=434)**
Nervous System Disorders		
Headache	3.4%	1.8%
Ear and Labyrinth Disorders		
Ear pruritus	7.2%	0.5%
Eye Disorders		

Eye pruritus	3.4%	2.1%
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	21.3%	2.5%
Oropharyngeal pain	4.0%	1.4%
Pharyngeal erythema	3.6%	0.7%
Pharyngeal edema	2.9%	0%
Cough	2.7%	1.2%
Dyspnea	2.0%	0.5%
Nasal discomfort	1.6%	0.9%
Nasal congestion	1.6%	0.5%
Sneezing	1.6%	0.7%
Gastrointestinal Disorders		
Oral pruritus	24.4%	2.1%
Mouth edema	9.8%	0.2%
Tongue pruritus	9.2%	0.9%
Lip swelling	7.2%	0.5%
Paresthesia oral	5.4%	1.2%
Oral mucosal erythema	4.9%	0.9%
Lip pruritus	2.9%	0.2%
Swollen tongue	2.5%	0%
Dysphagia	2.0%	0%
Nausea	1.6%	0.5%
Oral discomfort	1.6%	0.2%
Stomatitis	1.3%	0%
Hypoesthesia oral	1.1%	0.2%
Glossodynia	1.1%	0.2%
Skin and Subcutaneous Tissue Disorders		
Urticaria	1.8%	0.2%
General Disorders and Administration Site Conditions		
Chest discomfort	2.0%	0.5%

6.2 Postmarketing Experience

Postmarketing Safety Studies

In European post-approval studies which included 1,666 patients treated with GRASTEK (marketed under the name GRAZAX), reported serious adverse reactions assessed as related to GRASTEK use included anaphylactic reaction, asthma exacerbation, hoarseness, laryngitis, oral ulceration, and ulcerative colitis exacerbation.

Spontaneous Postmarketing Reports

The following adverse reactions have been identified during post-approval use of GRASTEK (marketed under the name GRAZAX in Europe). 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. These include:

- Ear and Labyrinth Disorders*:* ear discomfort, ear swelling
- Eye Disorders: eye swelling

- Gastrointestinal Disorders: cheilitis, diarrhea, dry mouth, enlarged uvula, eosinophilic esophagitis, gastritis, lip blister, oral pain, salivary hypersecretion, vomiting
- General disorder and administration site conditions: chest pressure, face edema, sensation of foreign body, swelling of neck
- Immune System Disorders: serious systemic allergic reactions, including anaphylaxis, anaphylactic shock
- Infections and Infestations: pneumonia
- Investigations: heart rate increased, heart rate irregular, oxygen saturation decreased, peak expiratory flow rate decreased
- Nervous System Disorders: altered state of consciousness, dizziness, drowsiness, dysgeusia, paresthesia, tremor, difficulty speaking, paresthesia (including hypoesthesia and burning sensation in extremities)
- Respiratory, Thoracic and Mediastinal Disorders: asthma exercise induced, bronchospasm, hyperventilation, laryngeal discomfort, respiratory distress, status asthmaticus, stridor, throat pruritus, wheezing
- Skin and Subcutaneous Tissue Disorders: angioedema, erythema, erythema facial, rash
- Vascular Disorders: hypotension.

Eosinophilic esophagitis has been reported following treatment with GRASTEK (marketed under the name GRAZAX). The clinical details of some postmarketing reports are consistent with a drug-induced effect, including at least one case with resolution of symptoms upon discontinuation of GRASTEK, relapse after resuming GRASTEK and resolution again after discontinuation of GRASTEK.

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 GRASTEK-associated risks during pregnancy.

In two reproductive and developmental toxicity studies mice were administered Timothy grass pollen extract daily by buccal cavity at doses approximately 6.7 times the human sublingual dose. In one study doses were administered during gestation and lactation. In the other study doses were administered prior to mating and during gestation. These studies revealed no evidence of harm to the mother or the fetus due to GRASTEK *(see 8.1 Data)*.

Data

Animal Data

A pre- and postnatal developmental study and a combined fertility/developmental toxicity study were conducted in mice. In these studies, the effect of Timothy grass (*Phleum pratense*) pollen allergen extract, the active component of GRASTEK, on embryo-fetal development was evaluated. In the pre- and postnatal developmental toxicity study female mice were administered Timothy grass pollen allergen extract by buccal cavity daily from day 6 of gestation to day 17 of lactation at doses approximately 6.7 times the human sublingual dose. In the combined fertility/developmental toxicity study, female mice were administered Timothy grass pollen allergen extract daily by buccal cavity administration from 14 days prior to mating and until day 15 of the gestation period (male animals were administered the same dose daily for 4 weeks before pairing and during pairing) at doses approximately 6.7 times the human sublingual dose. Fertility was normal and there were no treatment-related post-implementation losses, fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known if GRASTEK is excreted in human milk. Data are not available to assess the effect of GRASTEK on milk production or on the breast-fed child. The developmental and health benefits of

breastfeeding should be considered along with the mother's clinical need for GRASTEK and any potential adverse effects on the breast-fed child from GRASTEK or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

There is no clinical trial experience with GRASTEK in patients over 65 years of age.

11 DESCRIPTION

GRASTEK tablets contain pollen allergen extract from Timothy grass (*Phleum pratense*). GRASTEK is a sublingual tablet.

GRASTEK is available as a tablet of 2800 BAU of Timothy grass 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 GRASTEK.

There were no positive findings in the *in vitro* mouse lymphoma and the bacterial reverse mutation assays for mutagenicity using Timothy grass (*Phleum pratense*) pollen allergen extract.

A combined fertility/developmental toxicity study in male and female mice revealed no evidence of impaired fertility due to Timothy grass pollen allergen extract administered daily prior to mating and during gestation at approximately 6.7 times the human sublingual dose *(see 8.1 Data).*

14 CLINICAL STUDIES

The efficacy of GRASTEK in the treatment of allergic rhinitis with or without conjunctivitis in Timothy grass pollen allergic subjects 5 years of age and older, with or without mild asthma, was evaluated during the first grass pollen season in two trials of approximately 24 weeks treatment duration. The sustained effect of GRASTEK was evaluated in one trial conducted over 5 grass pollen seasons. All three trials were randomized, double-blind, parallel group, multicenter clinical trials. Subjects had a history of grass pollen induced rhinitis with or without conjunctivitis and sensitivity to Timothy grass pollen as determined by specific testing (IgE). In these three studies, subjects initiated GRASTEK or placebo approximately 12 weeks prior to the pollen season. In the long-term study, subjects received GRASTEK or placebo daily for 3 consecutive years and were followed for 2 years without treatment.

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 entire grass pollen season.

14.1 First Season Efficacy

Adults and Children

This placebo-controlled trial evaluated 1501 subjects 5 through 65 years of age (approximately 80% were 18 years and older) comparing GRASTEK (N=752) and placebo (N=749) administered as a sublingual tablet daily for approximately 24 weeks. The subject population was 84% White, 9% African American and 4% Asian. The majority of subjects were male (52%). In this study, approximately 25% of subjects had mild, intermittent asthma and 85% of all subjects were sensitized to other allergens in addition to grass pollen. Subjects with a clinical history of symptomatic allergies to non-grass pollen allergens that required treatment during the grass pollen season were excluded from the studies. All treatment groups were balanced with regard to baseline characteristics.

Subjects treated with GRASTEK had a decrease in the TCS throughout the grass pollen season compared to placebo-treated subjects. Similarly, the DSS and DMS were decreased in subjects treated with GRASTEK compared to placebo throughout the grass pollen season, and the TCS was decreased compared to placebo during the peak grass pollen season (see Table 3).

Table 3: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Grass Pollen Season

Endpoint*	GRASTEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Entire Season	(629) 3.24	(672) 4.22	-0.98	-23% (-36.0, -13.0)
TCS Peak Season	(620) 3.33	(663) 4.67	-1.33	-29% (-39.0, -15.0)
DSS Entire Season	(629) 2.49	(672) 3.13	-0.64	-20% (-32.0, -10.0)
DMS Entire Season	(629) 0.88	(672) 1.36	-0.48	-35% (-49.3, -20.8)

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

***** Non-parametric analysis for TCS and DSS endpoints: Parametric analysis using zero-inflated log-normal model for DMS.

† Number of subjects in analyses.

‡ For TCS and DSS endpoints the group medians are reported, treatment difference and that relative to placebo is based on group medians. For DMS, the group means are reported and difference relative to placebo is based on estimated group means.

§ Difference relative to placebo computed as: (GRASTEK - placebo)/placebo x 100.

Children

This double-blind clinical trial of approximately 24 weeks duration evaluated 344 pediatric subjects 5 to 17 years of age who were treated with either GRASTEK or placebo once daily. The subject population was 88% White, 7% African American, and 2% Asian. The majority (65%) of subjects were male. The mean age of subjects was 12.3 years. In this study, 26% of subjects had mild intermittent asthma and most subjects (89%) were sensitized to other allergens in addition to grass pollen. Subjects with a clinical history of symptomatic allergies to non-grass pollen allergens that required treatment during the grass pollen season were excluded from the studies. All treatment groups were balanced with regard to baseline characteristics.

Pediatric subjects treated with GRASTEK had a decrease in TCS throughout the grass pollen season compared to placebo treated subjects (see Table 4). Similarly, the DSS and DMS were decreased in GRASTEK compared to placebo throughout the grass pollen season.

Table 4: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS) and Daily Medication Scores (DMS) During the Entire Grass Pollen Season

Endpoint*	GRASTEK (N=149)† Score‡	Placebo (N=158)† Score‡	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS	4.62	6.25	-1.63	-26% (-38.2, -10.1)
DSS	3.71	4.91	-1.20	-24% (-36.4, -9.1)
DMS	0.91	1.33	-0.42	-32% (-57.7, 4.0)

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: (GRASTEK - placebo)/placebo x 100.

14.2 Sustained Effect

Adult Subjects 18 Years and Older

The sustained effect of GRASTEK was measured in a 5-year double-blind study. The study included 634 randomized subjects between 18 and 65 years of age. The subject population was 96% White, 2% Asian and 1% African American. The majority (59%) of subjects were male. The mean age of subjects was 34 years. Subjects received either GRASTEK or placebo daily for 3 consecutive years and were then observed for 2 subsequent years during which they did not receive study drug. Subjects treated with GRASTEK had a decrease in TCS throughout the grass pollen season during the three years of active treatment. This effect was sustained during the grass pollen season in the first year after discontinuation of GRASTEK (see Table 5), but not in the second year.

Table 5: Rhinoconjunctivitis Total Combined Score (TCS), Daily Symptom Score (DSS), and Daily Medication Score (DMS) During the Entire Grass Pollen Season from the 5-Year Study

	Difference Relative to Placebo* (95% CI)			
Endpoint	**Treatment Year 1 N=568†**	**Treatment Year 2‡ N=316†**	**Treatment Year 3 N=287†**	**Post Treatment Year 1 N=257†**
TCS	-34.2% (-42.0%, -26.3%)	-40.9% (-51.8%, -29.5%)	-34.0% (-45.5%, -21.4%)	-27.2% (-39.9%, -12.4%)
DSS	-31.2% (-38.8%, -23.4%)	-36.2% (-46.5%, -26.2%)	-29.0% (-40.3%, -16.3%)	-26.2% (-37.6%, -12.2%)
DMS	-38.4%	-45.5%	-40.1%	-28.6%

	(-49.8%, -26.5%)	(-60.4%, -28.2%)	(-55.4%, -21.2%)	(-46.3%, -6.0%)

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

***** Difference relative to placebo computed as: (GRASTEK - placebo)/placebo x 100.

† Number of subjects in analyses.

‡ Study extended from 1 to 5 years (site closures, subject unwillingness to participate beyond 1 year).

16 HOW SUPPLIED/STORAGE AND HANDLING

GRASTEK 2800 BAU tablets are white to off-white, circular sublingual tablets with a debossed round detail on one side.

GRASTEK is supplied as follows:

3 blister packages of 10 tablets (30 tablets total). NDC 52709-1501-3

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

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide) and to keep GRASTEK and all medicines out of the reach of children.

Severe Allergic Reactions

Advise patients that GRASTEK may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients 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 have auto-injectable epinephrine and instruct patients in its proper use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue GRASTEK, and resume treatment only when advised by a physician to do so. *[See Warnings and Precautions (5.2).]*

Advise patients to read the patient information for epinephrine.

Inform patients that the first dose of GRASTEK 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 a life-threatening systemic or local allergic reaction *[see Warnings and Precautions (5.1)].*

Because of the risk of upper airway compromise, instruct patients with persistent and escalating adverse reactions in the mouth or throat to discontinue GRASTEK and to contact their healthcare professional. *[See Warnings and Precautions (5.3).]*

Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue GRASTEK and to contact their healthcare professional. *[See Warnings and Precautions (5.4).]*

Inform parents/guardians that GRASTEK should only be administered to children under adult supervision *[see Dosage and Administration (2.2)]*.

Asthma

Instruct patients with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking GRASTEK and contact their healthcare professional immediately *[see Warnings and Precautions (5.5)]*.

Administration Instructions

Instruct patients 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 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).]*

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