PRODUCT MONOGRAPH

GRASTEK®

Standardized Allergen Extract, Timothy Grass *(Phleum pratense)*

Sublingual Tablet, 2800 BAU

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 / 2800 BAU*	*For a complete listing see Dosage Forms, Composition and Packaging section.*

*Bioequivalent Allergy Units

DESCRIPTION

GRASTEK® (Standardized Allergen Extract, Timothy Grass *(Phleum pratense)* Sublingual Tablet) is an allergy immunotherapy tablet for the treatment of signs and symptoms of grass allergy. It is formulated as an orally disintegrating tablet designed to rapidly dissolve under the tongue. The active substance is a natural grass pollen extract which is purified and standardized from Timothy Grass. Each sublingual tablet has a strength of 2800 BAU.

INDICATIONS AND CLINICAL USE

GRASTEK® (Standardized Allergen Extract, Timothy Grass *(Phleum pratense)* Sublingual Tablet) is indicated for reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific IgE; and who have responded inadequately, or are intolerant to conventional pharmacotherapy.

Treatment with GRASTEK® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. For pediatric patients, physicians should have the corresponding training and experience with children.

Pediatrics (<5 years of age): Safety and efficacy in pediatric patients below 5 years of age have not been established.

Geriatrics (>65 years of age): There is limited experience with GRASTEK® in patients greater than 65 years of age (See **WARNINGS AND PRECAUTIONS / Geriatrics**).

CONTRAINDICATIONS

GRASTEK® 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 Timothy or related grass immunotherapy.
- Have unstable, severe chronic or severe seasonal asthma (FEV1 < 70% of predicted value after adequate pharmacologic treatment in adults; < 80% in children).
- 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 GRASTEK® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. In case of pediatric treatment, the physicians should have the corresponding training and experience in children.

- Systemic allergic reactions, including life-threatening anaphylactic shock, severe laryngopharyngeal restriction and severe local allergic reactions, have been observed in patients receiving GRASTEK®, and may require emergency administration of epinephrine, antihistamines, bronchodilators or systemic corticosteroids (see **WARNINGS AND PRECAUTIONS / Immune**)

- The first tablet of GRASTEK® must be taken at the physician's office under medical supervision and the patient must be monitored for at least 30 minutes.

- Extra precautions must be taken while treating pediatric patients, including: each administration of GRASTEK® must be given under direct adult supervision for at least 30 minutes.

General

No data are available regarding the effect of vaccination in patients with GRASTEK® treatment. Vaccination may be given without interrupting treatment with GRASTEK® 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 GRASTEK®. 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.

GRASTEK® should not be initiated in pregnant women.

GRASTEK® should be used with caution in patients who have had severe systemic reactions to any grass subcutaneous immunotherapy or severe local or systemic reactions to grass immunotherapy taken by mouth.

As with other immunotherapy treatments, patients treated with GRASTEK® 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 GRASTEK® should be discontinued in these patients.

Carcinogenesis and Mutagenesis

No carcinogenicity studies were conducted in animals with *Phleum pratense*. Based on *in vitro* assays for mutagenicity, no evidence of genotoxic risk was associated with *Phleum pratense*.

Reproductive studies in mice reveal no evidence of impaired fertility or harm to the fetus due to *Phleum pratense* (see **PART II: TOXICOLOGY**).

Gastrointestinal

Eosinophilic Esophagitis

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

Immune

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 may compromise breathing and be life-threatening. Signs and symptoms that may be associated with systemic allergic reaction may 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 GRASTEK® (See **ADVERSE REACTIONS**). The majority of these reactions occurred within minutes after receiving the first dose, but were also reported to occur after administration of subsequent doses. In postmarketing experience with Timothy Grass (*Phleum pratense)* tablets, rare cases of serious systemic allergic

reactions, including anaphylactic reactions, have also been reported (See **ADVERSE REACTIONS / Post Market Adverse Drug Reactions**). Treatment of severe allergic reactions may require the administration of epinephrine, antihistamines, inhaled bronchodilators or systemic corticosteroids.

The first dose of GRASTEK® 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 GRASTEK®. Immediately discontinue GRASTEK® in any patient developing clinical evidence of a severe systemic or severe local allergic reaction. In such cases, consider discontinuing treatment with GRASTEK® permanently. Patients should be informed and educated about the symptoms of a severe allergic reaction, and instructed to discontinue GRASTEK® and contact their physician or seek immediate medical care should any of these symptoms occur after taking GRASTEK®.

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

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, dental extraction, or tooth loss, treatment with GRASTEK® should be interrupted to allow healing of the oral cavity.

Respiratory

Patients with Asthma

Immunotherapy with GRASTEK® is contraindicated in patients who have unstable or, severe asthma (chronic or seasonal) (see **CONTRAINDICATIONS**).

Post-marketing experience indicates that it is important that a patient's asthma is controlled when treated with GRASTEK®. During treatment with GRASTEK®, instruct patients to stop treatment with GRASTEK® and contact their physician immediately if they have difficulty breathing or if asthma becomes inadequately controlled.

Special Populations

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

Animal reproductive studies have revealed no evidence of impaired fertility or harm to the fetus (see PART II: **TOXICOLOGY**).

Nursing Women: No clinical data are available for the use of GRASTEK® during lactation. It is unknown whether GRASTEK® is excreted in human milk.
Pediatric (< 5 years of age): Immunotherapy with GRASTEK® has not been studied in pediatric patients below 5 years of age.

Geriatrics (> 65 years of age): Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Monitoring and Laboratory Tests
In the 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 GRASTEK® has been associated with systemic allergic reactions (see **WARNINGS AND PRECAUTIONS / Immune** and **"Serious Warnings and Precautions"** box).

In clinical trials with GRASTEK®, treatment-related systemic allergic reactions were reported in 0.5% (7/1669) of patients treated with GRASTEK® and no patients treated with placebo. Signs and symptoms associated with a systemic allergic reaction included sneezing, rhinorrhea, light-headedness, pruritus of the mouth, tongue and throat, edema of the lips and throat, throat irritation, dysphagia, dyspnea and chest tightness.

The percentage of adult patients who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK® or placebo was 4.9% (81/1669) and 0.9% (15/1645), respectively. The most common adverse reactions that led to study discontinuation in patients who were exposed to GRASTEK® were oral pruritus (12 patients), pharyngeal edema (11 patients), mouth edema (7 patients), and swollen tongue (6 patients).

The percentage of pediatric patients who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK® or placebo was 6.3% (28/447) and 0.7% (3/434), respectively.

In 3 North American clinical trials in which it was co-prescribed, epinephrine was administered 10 times by a healthcare provider in GRASTEK® treated patients and 3 times in placebo treated patients. Eight of these administrations were for treatment-related allergic events and 5 were for adverse experiences unrelated to GRASTEK®. In a European trial, one patient was administered epinephrine in an emergency department by a health care provider. Epinephrine was self-administered on three occasions; once for a treatment-related event and twice for events unrelated to GRASTEK®.

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.

Adults

The safety data described below are based on 6 clinical trials which randomized 3589 patients 18 years of age and older with grass pollen induced rhinoconjunctivitis, including 1669 patients who were exposed to at least one dose of GRASTEK® (2800 BAU). Of the patients treated with GRASTEK®, 25% had asthma and 80% were sensitized to other allergens in addition to grass. The patient population was 88% white, 52% male and 88% of patients were between 18 and 50 years of age. 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).

Table 1 - Treatment-related Adverse Reactions Reported in ≥1% of Adult Patients with Grass Pollen Induced Rhinoconjunctivitis with or without Asthma Treated with GRASTEK® and Occurring More Commonly than Placebo

	GRASTEK® N= 1669 n (%)	**PLACEBO N= 1645 n (%)**
Ear and Labyrinth Disorders	**216 (12.9)**	**21 (1.3)**
Ear pruritus	208 (12.5)	18 (1.1)
Nervous System Disorders	**76 (4.6)**	**44 (2.7)**
Headache	35 (2.1)	22 (1.3)
Eye Disorders	**99 (5.9)**	**46 (2.8)**
Eye pruritus	50 (3.0)	29 (1.8)
Lacrimation increased	19 (1.1)	8 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	**525 (31.5)**	**149 (9.1)**
Throat irritation	378 (22.6)	46 (2.8)
Pharyngeal edema	56 (3.4)	2 (0.1)
Sneezing	34 (2.0)	23 (1.4)
Rhinorrhea	34 (2.0)	27 (1.6)
Cough	30 (1.8)	18 (1.1)
Dry throat	29 (1.7)	6 (0.4)
Oropharyngeal pain	26 (1.6)	16 (1.0)

Nasal Discomfort	26 (1.6)	17 (1.0)
Throat tightness	24 (1.4)	4 (0.2)
Dyspnea	19 (1.1)	7 (0.4)
Gastrointestinal Disorders	**889 (53.3)**	**197 (12.0)**
Oral pruritus	446 (26.7)	57 (3.5)
Mouth edema	186 (11.1)	13 (0.8)
Paresthesia oral	164 (9.8)	33 (2.0)
Tongue pruritus	95 (5.7)	8 (0.5)
Lip swelling	67 (4.0)	3 (0.2)
Swollen tongue	46 (2.8)	2 (0.1)
Dyspepsia	39 (2.3)	1 (0.1)
Hypoesthesia oral	38 (2.3)	17 (1.0)
Lip pruritus	39 (2.3)	7 (0.4)
Nausea	31 (1.9)	10 (0.6)
Oral discomfort	27 (1.6)	5 (0.3)
Oral mucosal erythema	25 (1.5)	10 (0.6)
Lip edema	22 (1.3)	1 (0.1)
Glossitis	21 (1.3)	2 (0.1)
Stomatitis	19 (1.1)	5 (0.3)
Tongue disorder	18 (1.1)	3 (0.2)
Tongue edema	19 (1.1)	6 (0.4)
Glossodynia	17 (1.0)	5 (0.3)
Dysphagia	17 (1.0)	4 (0.2)
Palatal edema	17 (1.0)	2 (0.1)
Skin and Subcutaneous Tissue Disorders	**98 (5.9)**	**47 (2.9)**
Pruritus	40 (2.4)	16 (1.0)
Urticaria	29 (1.7)	15 (0.9)

General Disorders and Administration Site Conditions	**85 (5.1)**	**27 (1.6)**
Chest discomfort	26 (1.6)	9 (0.5)
Fatigue	24 (1.4)	7 (0.4)

The most common adverse reactions (deemed by the investigators to be causally related to treatment) reported in patients 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%). Most local allergic events were mild and transient. Recurrent symptoms generally resolved over time.

Treatment-related severe adverse events were reported in 48 of 1669 (2.9%) patients in the GRASTEK® group vs. 16 of 1645 (1.0%) of patients in the placebo group. These events included oropharyngeal edema, swollen tongue and throat tightness, and were more common in the first month of treatment."

Adults and Pediatrics – P08067

In this North American study, a total of 752 patients (adult: n = 608, pediatric: n = 144) received GRASTEK®, and 749 received placebo (adult: n = 610, pediatric: n = 129). The following treatment-related adverse reactions were reported in addition to those reported in Table 1: lymphadenopathy (1.6% vs 0.8%), lip pruritus (3.2% vs 0.4%) and nasal congestion (1.3% vs. 1.2%).

Treatment-related adverse reactions were reported by 441 (58.6%) of GRASTEK® treated patients and 178 (23.9%) of patients treated with placebo. The most common were local reactions in the mouth, throat, and ear. These included throat irritation (23.2% GRASTEK® vs. 3.5% placebo), oral pruritus (18.5% vs. 2.8%), mouth edema (13% vs. 1.2%), and ear pruritus (12.1% vs. 1.5%).

In this trial, 46 (6.1%) of patients treated with GRASTEK® and 10 (1.3%) of placebo-treated patients discontinued from the trial due to a treatment-related adverse reaction.

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 183 days after their first dose. Most treatment-related reactions lasted for 2-3 days; however, some mild or moderate reactions recurred up to 230 days in some patients.

Severe treatment-related adverse reactions were reported by 3.1% of GRASTEK® treated patients and 1.1% of patients treated with placebo. Local swelling assessed as severe occurred in 7 patients treated with GRASTEK®. The events self-resolved in 5 patients, and two patients were treated with an antihistamine.

In this trial, two adult patients treated with GRASTEK® had a treatment-related systemic allergic reaction, both of which self-resolved.

Pediatrics

Safety data are based on 3 clinical trials which randomized 881 patients between 5 and 17 years of age with grass pollen induced rhinoconjunctivitis. Overall, 445 patients received at least one dose of GRASTEK®. Of the patients treated with GRASTEK®, 31% had asthma and 86% were sensitized to other allergens in addition to grass. The patient population was 86% white and the majority (66%) of patients were male. The mean age of patients was 11.7 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.

The most common adverse reactions in pediatric patients treated with GRASTEK® in all clinical trials 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 most common adverse reactions in pediatric patients treated with GRASTEK® in North American clinical trial P05239 were oral pruritus (38.9% vs. 3.6% placebo), throat irritation (37.1% vs. 3.0%) and stomatitis (14.9% vs. 1.2%) (see Table 2).

Table 2 - Treatment-related Adverse Reactions Reported in ≥1% of Pediatric Patients in North America with Grass Pollen Induced Rhinoconjunctivitis with or without Asthma Treated with GRASTEK® and Occurring More Commonly than Placebo (P05239)

	GRASTEK® N= 175 n (%)	**PLACEBO N= 169 n (%)**
Cardiac Disorders	**2 (1.1)**	**0**
Palpitations	2 (1.1)	0
Ear and Labyrinth Disorders	**22 (12.6)**	**1 (0.6)**
Ear pruritus	20 (11.4)	1 (0.6)
Nervous System Disorders	**12 (6.9)**	**7 (4.1)**
Headache	7 (4.0)	4 (2.4)
Paraesthesia	2 (1.1)	0
Dizziness	2 (1.1)	0
Eye Disorders	**14 (8.0)**	**3 (1.8)**
Eye pruritus	11 (6.3)	3 (1.8)
Lacrimation increased	3 (1.7)	0
Eye irritation	2 (1.1)	0
Respiratory, Thoracic and Mediastinal Disorders	**84 (48.0)**	**14 (8.3)**
Throat irritation	65 (37.1)	5 (3.0)
Oropharyngeal pain	14 (8.0)	4 (2.4)
Pharyngeal erythema	13 (7.4)	3 (1.8)
Dry throat	7 (4.0)	2 (1.2)
Nasal Congestion	7 (4.0)	1 (0.6)
Pharyngeal edema	7 (4.0)	0
Cough	6 (3.4)	0
Sneezing	6 (3.4)	1 (0.6)
Nasal Discomfort	5 (2.9)	0
Dyspnea	3 (1.7)	0

Rhinorrhea	3 (1.7)	0
Throat tightness	3 (1.7)	0
Dysphonia	2 (1.1)	0
Oropharyngeal blistering	2 (1.1)	1 (0.6)
Gastrointestinal Disorders	**96 (54.9)**	**22 (13.0)**
Oral pruritus	68 (38.9)	6 (3.6)
Stomatitis	26 (14.9)	2 (1.2)
Mouth edema	18 (10.3)	1 (0.6)
Lip swelling	13 (7.4)	0
Paraesthesia oral	7 (4.0)	2 (1.2)
Dysphagia	5 (2.9)	0
Swollen tongue	5 (2.9)	0
Nausea	4 (2.3)	2 (1.2)
Oral pain	4 (2.3)	0
Dyspepsia	3 (1.7)	1 (0.6)
Hypoesthesia oral	3 (1.7)	0
Oral mucosal erythema	3 (1.7)	2 (1.2)
Tongue eruption	3 (1.7)	2 (1.2)
Lip edema	2 (1.1)	0
Tongue edema	2 (1.1)	0
Glossodynia	2 (1.1)	0
Gingival Pain	2 (1.1)	0
Dry Mouth	2 (1.1)	0
Salivary Gland Enlargement	2 (1.1)	0
Immune System Disorders	**2 (1.1)**	**0**
Hypersensitivity	2 (1.1)	0
Infections and Infestations	**6 (3.4)**	**0**
Rhinitis	2 (1.1)	0
Skin and Subcutaneous Tissue Disorders	**14 (8.0)**	**9 (5.3)**
Urticaria	3 (1.7)	0
Rash Pruritic	2 (1.1)	1 (0.6)
Vascular Disorders	**3 (1.7)**	**2 (1.2)**
Flushing	3 (1.7)	2 (1.2)
General Disorders and Administration Site Conditions	**9 (5.1)**	**2 (1.2)**
Chest discomfort	3 (1.7)	2 (1.2)
Chest Pain	2 (1.1)	0
Sensation of foreign body	2 (1.1)	0

Treatment-related severe adverse reactions were reported in 1.7% (8/447) of pediatric patients treated with GRASTEK® and no patients treated with placebo. These events (e.g. pruritus of the ear and mouth, throat irritation) were similar to the adverse reaction profile described in Table 2.

There was one [(1/447), 0.2%] treatment-related systemic allergic reaction reported in pediatric patients treated with GRASTEK® and one [(1/434), 0.2%] treatment-related systemic allergic reaction in patient treated with placebo.

The safety profile of GRASTEK® was generally similar in pediatric and adult patients.

Less Common Clinical Trial Adverse Reactions (< 1%)

Ear and Labyrinth disorders: ear congestion, ear discomfort, ear pain
Eye Disorders: conjunctivitis, eye pain, eye swelling, eyelid irritation, eyelid edema, ocular hyperaemia
Gastrointestinal disorders: oral pain, salivary gland enlargement, abdominal discomfort, abdominal pain, abdominal pain upper, diarrhea, gastrointestinal pain, gastroesophageal reflux disease gingival bleeding, glossitis, lip blister, lip disorder, odynophagia, oral discomfort, oral mucosal blistering, palatal edema, retching, salivary hypersecretions, sensitivity of teeth, tongue disorder, vomiting
General disorders and administration site conditions: application site swelling, fatigue, non-cardiac chest pain, pain, paresthesia mucosal, sensation of foreign body
Infections and Infestations: abscess oral, carbuncle, gastroenteritis viral, upper respiratory tract infection, viral infection
Immune System Disorders: hypersensitivity
Metabolism and Nutrition Disorders: decreased appetite
Nervous System disorders: burning sensation, dysgeusia, somnolence, paraesthesia, sinus headache and dizziness
Respiratory, thoracic and mediastinal disorders: asthma, asthma exercise induced, pharyngeal erythema, dysphonia, epistaxis, nasal congestion and nasal obstruction, oropharyngeal discomfort, tonsillar hypertrophy, wheezing
Skin and subcutaneous tissue disorders: dermatitis atopic, erythema, hyperhidrosis, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash papular, skin burning sensation

Adverse Drug Reactions of Special Interest in Controlled Clinical Trials

- Hypersensitivity Reactions (systemic reactions): There were 8 subjects (7 adult, 1 pediatric) with systemic allergic reactions who were exposed to GRASTEK®.
- Severe Local Reactions and progression of oral reactions to the throat: There were no subjects exposed to GRASTEK® who developed serious local allergic swellings or airway compromise.
- Acute Asthma: There were no serious treatment-related asthma exacerbations in the clinical development program.

Post-marketing Adverse Drug Reactions

In post-marketing experience with Timothy Grass (*Phleum pratense)* tablets, rare cases of serious systemic allergic reactions, including anaphylactic reactions, have been reported. The majority of these events occurred with the first dose. In cases for which timing was reported, symptoms and signs of a serious systemic allergic reaction generally occurred within 30 minutes.

Most of these events were characterized by asthma symptoms, such as dyspnea, cough and shortness of breath, and local allergic reactions of the mouth and throat.

Other post-marketing adverse reactions include:
Gastrointestinal disorders: enlarged uvula; eosinophilic esophagitis (see **WARNINGS AND PRECAUTIONS / Gastrointestinal**)
Respiratory, thoracic and mediastinal disorders: stridor

DRUG INTERACTIONS

Overview
Interactions with other drugs have not been established.

Co-administration of GRASTEK® 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 established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

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 GRASTEK® 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.
- GRASTEK® should only be administered to children under adult supervision.

- Initiate dosing at least 8 weeks before the grass pollen season and maintain dosing throughout the season.
- Treatment with GRASTEK® can be initiated at any time during the year.
- In patients with history of grass allergy, methods of determining the presence of Timothy and related grasses should also include skin prick testing or IgE testing for specific IgE against *Phleum pratense.*

Recommended Dose
The recommended dose of GRASTEK® for adults and children 5 years of age and older is one (1) sublingual tablet (2800 Bioequivalent Allergy Units) daily.

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

Interruption of Treatment
A review of subjects who experienced treatment interruptions from the controlled clinical studies does not reveal a risk to interrupting and restarting treatment with GRASTEK®.

Administration
- GRASTEK® 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.
- 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 2800 BAU. In the event of an overdose, any adverse effects should be treated symptomatically. In clinical trials, local reactions, such as oral pruritus and mouth edema were observed with daily doses of up to 37,592 BAU of *Phleum pratense*. These events were of short duration, of mild or moderate intensity, and did not lead to study discontinuation

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. Based on the results of a 5 year European study in which immunologic parameters were assessed, physicians can expect to see a significant increase in *Phleum pratense* specific IgG_4 (blocking antibody) as early as 2 months after initiation of treatment with GRASTEK®. In addition, increased levels of IgG_4 were seen during 3 years of treatment as well as for two years after treatment cessation. Based on the same study, physicians can also expect to see a marked rise in *Phleum pratense* specific IgE shortly after initiation of treatment with GRASTEK®. The increase in IgE levels abated over time. The clinical significance of these finding has not been established.

Pharmacokinetics

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

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

GRASTEK® is a white to off-white circular sublingual tablet with a debossed, round detail on one side. GRASTEK® is a sublingual tablet designed to rapidly dissolve under the tongue.

Composition

Each GRASTEK® tablet contains 2800 BAU of standardized natural grass pollen extract of Timothy Grass *(Phleum pratense)*.

The active substance is a purified, standardized allergenic extract derived from Timothy grass pollen. GRASTEK® contains the following inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF. GRASTEK® is free of lactose.

Packaging
GRASTEK® 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 with 10 tablets each).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance
The potency (in Bioequivalent Allergy Units) of GRASTEK® is determined by standardization against reference extracts and reference serum pools distributed by the Center for Biologics Evaluation and Research (CBER), U S Food and Drug Administration. The potency of the standard is based on quantitative skin testing**.**

Proper name: Standardized Allergenic Extract, Timothy Grass (*Phleum pratense*)

Molecular formula and molecular mass: A complex mixture of proteins and other biologically derived substances extracted from natural grass pollen that is partially purified; therefore, there is no molecular formula and detailed structural information.

Physicochemical properties: Light to dark yellow/brown non-adhesive frozen droplets that are soluble in a range of buffers and water.

Product Characteristics:
The drug substance is prepared by extraction of Timothy grass 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 relevant allergens.

CLINICAL TRIALS

The safety and efficacy of GRASTEK® in the treatment of allergic rhinoconjunctivitis in grass pollen allergic patients 5 years of age and older, with or without asthma, were assessed in 6 double-blind, parallel group, multicenter clinical trials; four were conducted in North America and two in Europe (see Table 3). Patients had a history of grass induced rhinoconjunctivitis and sensitivity to grass as determined by specific testing (IgE). In these studies, patients initiated GRASTEK® or placebo approximately 12 weeks prior to the season. In the long-term study, patients received GRASTEK® or placebo daily for 3 years and were followed for 2 years without treatment.

Efficacy was assessed by self-reporting 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 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.

In 3 out of the 4 North American clinical trials (P05238, P05239, P08067 and GT-14) all subjects were co-prescribed self-injectable epinephrine. There were two subjects who self-administered epinephrine for treatment-related adverse events; one subject was treated with GRASTEK®, one subject was treated with placebo.

Study demographics and trial design

Table 3: Summary of patient demographics for GRASTEK® clinical trials

Study#/ Sites	**Trial design** ***Primary Endpoint(s)***	**Dosage and Duration**	**No. of subjects**	**Age Range (mean)** ***Male/Female***
P08067 [a] North America	Phase 3: Efficacy & Safety R, MC, DB, PG, PC *Average combined rhinoconjunctivitis DSS and DMS during the entire GPS.*	2800 BAU Placebo Approx. 24 weeks	752 749	5-65 (33.2) *787 / 714*
GT-14 North America	Phase 3: Efficacy & Safety R, DB, MC, PC, PG *Average rhinoconjunctivitis DSS during the entire GPS.*	2800 BAU Placebo Approx. 24 weeks	163 166	18-65 (35.9) *153 /176*
P05238 [a] North America	Phase 3 Efficacy & Safety R, MC, DB, PG, PC *Average combined rhinoconjunctivitis DSS and DMS during the entire GPS.*	2800 BAU Placebo Approx. 24 weeks	213 225	18-63 (35.9) *217 / 221*
P05239[a] North America	Phase 3: Efficacy & Safety R, MC, DB, PG, PC *Average combined rhinoconjunctivitis DSS and DMS during the entire GPS.*	2800 BAU Placebo Approx. 24 weeks	175 169	5-18 *(*12.3) *223 / 121*
GT-08 Europe	Phase 3:Efficacy & Safety R, DB, MC, PC, PG *Average rhinoconjunctivitis DSS and DMS during the entire GPS.*	2800 BAU Placebo 5 years	316 318	18-65[b] (34.0) *372 / 262*
GT-12 Europe	Phase 3:Efficacy & Safety R, DB, MC, PC, PG *Average rhinoconjunctivitis DSS and DMS during the entire GPS.*	2800 BAU Placebo Approx. 24 weeks	126 127	5-16 (10.1) *166 / 87*

BAU = Bioequivalent Allergy Units; DB = double blind; DR = dose ranging; MC = Multicenter;
PC = placebo-controlled; PD = pharmacodynamic; PG = parallel-group; R= randomized
DSS = daily symptom score; DMS = daily medication score; GPS = grass pollen season
[a] Includes Canadian population
[b] Age range represents age at screening

Study Results

Study P08067: Adults and Children

This double-blind placebo controlled trial, conducted in North America, evaluated 1501 patients 5 years of age and older comparing GRASTEK® (N=752) and placebo (N=749) administered as a sublingual tablet daily for approximately 24 weeks. This trial included patients 5 to 65 years of age (approximately 80% were 18 years and older) with a history of grass pollen induced rhinoconjunctivitis. The patient population was 84% White and 52% male. In this study, approximately 25% of patients had mild to moderate asthma and 85% were sensitized to other allergens in addition to grass. Patients with severe asthma were excluded from the trial. All treatment groups were balanced with regard to baseline characteristics.

The primary efficacy endpoint was the total combined score (TCS), which is the sum of the rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) during the entire grass pollen season. The impact of grass pollen allergic rhinoconjunctivitis on patients' quality of life was evaluated using the age adjusted Rhinitis Quality of Life Questionnaire.

Based on an analysis using the longitudinal data analysis model on the repeated measurement of daily scores, patients treated with GRASTEK® had significant relief of nasal and ocular symptoms and reduction in standard allergy medication use as measured by improvement in TCS from the start of and throughout the entire grass season compared to placebo treated patients. Similarly, GRASTEK® improved the individual DSS and DMS compared to placebo for the entire season (see Table 4).

Table 4: Study P08067
Longitudinal Data Analysis Results for TCS, DSS, and DMS during the entire GPS (FAS)

P08067 **Average GPS duration: 53 days** **Average Entire GPS pollen count: 23 grains/m^3**					
Endpoint	**GRASTEK® n=629 (Mean)**	**Placebo n=672 (Mean)**	**Treatment Difference (GRASTEK® - PBO)**	**Between Treatment Comparison**	**Percent reduction in GRASTEK® group (95% CI)†**
Entire GPS			**Estimate (95% *CI*)**	**p-Value**	**Estimate (95% CI)**
TCS	(3.96)	(4.82)	-0.85 (-1.30, -0.41)	<0.001	-18% (-26, -9)
DSS	(3.10)	(3.56)	-0.46 (-0.78, -0.15)	0.004	-13% (-21, -4)
DMS	(0.86)	(1.26)	-0.40 (-0.64, -0.15)	0.002	-31% (-47, -13)

n = Number of subjects included in the analysis; CI= Confidence Interval
GPS = Grass Pollen Season; FAS = full analysis set
† Percent reduction in the GRASTEK® group compared to Placebo: 100*(GRASTEK®-Placebo)/Placebo. The 95% CI based on the 2.5th and 97.5th percentiles of the 5,000 bootstrap sample.
Note: The longitudinal data analysis was performed post-hoc. Analysis model on daily score included treatment, age category, asthma status, and pollen region as covariates; the model was adjusted for different variances for different treatment groups, a subject-level random intercept plus an AR(1) correlation structure.
Range for GPS duration: 7-131 days; Range for average entire GPS pollen count: 3-102 grains/m^3.

During the peak grass pollen season and based on a longitudinal data analysis model, the difference in TCS for patients who received GRASTEK® compared to placebo was -1.16, which corresponds to a relative difference of -22% . The peak season was defined as maximum 15 days with the highest moving average pollen counts during the entire pollen season.

Study GT-08: Adult Patients 18 Years and Older

This double-blind study, conducted in Europe, of approximately 5 years duration, included 634 randomized patients between 18 and 65 years of age. The patient population was 96% White and the majority (59%) of patients were male; the mean age of patients was 34 years. Patients received either GRASTEK® or placebo for three consecutive years and were then observed for two years during which they did not receive study drug. The co-primary endpoints were rhinoconjunctivitis daily symptom score and daily medication score.

At year 1, the clinical results showed that treatment with GRASTEK® 2800 BAU was more effective than placebo (see Table 5).

Table 5: Study GT-08
Longitudinal Data Analysis Results for TCS, DSS and DMS during the entire GPS (FAS)

GT-08 / Year 1 **Average GPS duration: 58 days** **Average Entire GPS pollen count: 45 grains/m^3**				
Efficacy Endpoint	**GRASTEK® Score (Mean) n=282**	**Placebo Score (Mean) n=286**	**Treatment Difference (GRASTEK®-PBO) [Estimate (95% CI)]**	**Percent Reduction in GRASTEK® Group**
TCS	5.02	7.23	-2.21 (-2.84, -1.58)	-31%
DSS	2.98	4.21	-1.24 (-1.61, -0.86)	-29%
DMS	2.05	3.02	-0.97 (-1.35, -0.59)	-32%

n = Number of Subjects included in the analysis; CI= Confidence Interval;
GPS = Grass Pollen Season; FAS = full analysis set
Note: Percent reduction in the GRASTEK® group compared to Placebo: 100*(GRASTEK®-Placebo)/Placebo.
Note: The longitudinal data analysis was performed post-hoc. Analysis model on daily score included treatment, site and asthma as covariates and adjusted for different variances for different treatment groups, a subject-level random intercept plus an AR(1) correlation structure.
Range for GPS duration: 16-86 days.
Range for average entire GPS pollen count: 10 - 151.4 grains/m^3.

Of the 634 patients randomized in the study, 351 (55%) and 308 (49%), respectively, remained at years 2 and 3. The differences in TCS for patients who received GRASTEK *versus* placebo were approximately -35% and -27% respectively.

For the last 2 years without treatment (continued in Year 4: n =283 of 634 = 45%; Year 5: n=258 of 634 = 41%), the difference in TCS for patients who received GRASTEK® *versus* placebo was -21% for Year 4 and -17% for Year 5 respectively.

Given that a large proportion of subjects that were originally randomized are not included in the analyses at year 2, year 3 and for the last 2 years without treatment, these results should be interpreted with some caution.

Other Clinical Trials: Adults

Table 6: Studies GT-14 and P05238
Longitudinal Data Analysis Results for TCS, DSS and DMS during the entire GPS (FAS)

Study number (Average GPS Duration); (Mean Entire GPS pollen count)				
Efficacy Endpoint	**GRASTEK® Score (Mean)**	**Placebo Score (Mean)**	**Treatment Difference (GRASTEK®-PBO) [Estimate (95% CI)]**	**Percent Reduction in GRASTEK® Group**
GT-14 (43 days); (44 grains/m^3)				
N	139	150		
TCS	6.75	7.44	-0.69 (-1.76, 0.38)	-9%
DSS	5.73	6.02	-0.30 (-1.10, 0.51)	-5%
DMS	1.02	1.42	-0.39 (-0.85, 0.07)	-27%
P05238 (52 days); (27 grains/m^3)				
N	184	207	-	-
TCS	5.08	6.31	-1.23 (-2.12, -0.35)	-19%
DSS	3.84	4.65	-0.81 (-1.41, -0.22)	-18%
DMS	1.25	1.67	-0.42 (-0.91, +0.07)	-25%

n = Number of Subjects included in the analysis; CI= Confidence Interval;
GPS = Grass Pollen Season; FAS = full analysis set
Percent reduction in the GRASTEK® group compared to Placebo: 100*(GRASTEK®-Placebo)/Placebo.
Note: The longitudinal data analysis was performed post-hoc. Analysis model on daily score included treatment, site and asthma as covariates and adjusted for different variances for different treatment groups, a subject-level random intercept plus an AR(1) correlation structure.
Range for GPS duration: 24 - 120 days for GT-14 and 7-162 days for P05238.
Range for average entire GPS pollen count: 8 - 180 grains/m^3 for GT-14 and 2-108 grains/m^3 for P05238.

Overall, the clinical results show that treatment with GRASTEK® 2800 BAU was more effective than placebo across multiple studies covering a long range of seasons with variable pollen exposure. The North American study, GT-14, did not demonstrate a statistically significant advantage over placebo due to inclusion of patients who had high pre-seasonal symptoms resulting in lack of study sensitivity.

Study P05239: Children

This double-blind clinical trial, conducted in North America, of approximately 24 weeks duration evaluated 344 pediatric patients 5 to 17 years of age who were treated with either GRASTEK® or placebo once daily. The patient population was 88% White and the majority (65%) of patients were male. The mean age of patients was 12.3 years. In this study, 26% of patients had mild to moderate asthma and most patients (89%) were sensitized to other allergens in addition to grass. Patients with severe asthma were excluded from the trial. All treatment groups were balanced with regard to baseline characteristics.

The primary endpoint was the total combined score (TCS), which is the sum of the rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) during the entire grass pollen season. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was also assessed to evaluate the effect of GRASTEK®.

Pediatric patients treated with GRASTEK® had significant relief of nasal and ocular symptoms and reduction in standard allergy medication use, as measured by improvement in TCS from the start of and throughout the entire grass pollen season compared to placebo treated patients (see Table 7). Similarly, GRASTEK® improved the individual DSS and DMS compared to placebo for the entire season.

Table 7: Study P05239
Longitudinal Data Analysis Results for TCS, DSS and DMS during the entire GPS (FAS)

P05239 **Average GPS duration: 58 days** **Average Entire GPS pollen count: 28 grains/m^3**				
Efficacy Endpoint	**GRASTEK® Score (Mean) n=149**	**Placebo Score (Mean)** n=158	**Treatment Difference (GRASTEK®-PBO) [Estimate (95% CI)]**	**Percent Reduction in GRASTEK® Group**
TCS	4.61	6.26	-1.65 (-2.61, -0.70)	-26%
DSS	3.71	4.93	-1.22 (-1.97, -0.48)	-25%
DMS	0.90	1.33	-0.43 (-0.87, 0.02)	-32%

n = Number of Subjects included in the analysis; CI= Confidence Interval;
GPS = Grass Pollen Season; FAS = full analysis set
Percent reduction in the GRASTEK® group compared to Placebo: 100*(GRASTEK®-Placebo)/Placebo.
Note: The longitudinal data analysis was performed post-hoc. Analysis model on daily score included treatment, site and asthma as covariates and adjusted for different variances for different treatment groups, a subject-level random intercept plus an AR(1) correlation structure.
Range for GPS duration: 7-162 days.
Range for average entire GPS pollen count: 1-99 grains/m^3.

Similar to P05239, European study GT-12 yielded statistically significant results in favour of GRASTEK® for TCS (p-Value = 0.022), DSS (p-Value = 0.022) and DMS (p-Value = 0.016).

DETAILED PHARMACOLOGY

No dedicated animal safety pharmacology studies were conducted with GRASTEK® (*Phleum pratense*). However, there were no overt central nervous system or respiratory effects noted for up to 6-months of dosing in the mouse and 12-months of dosing in the dog based on routine clinical observations.

For Human data, see **PART I: ACTION AND CLINICAL PHARMACOLOGY**.

TOXICOLOGY

Animal Toxicology

General toxicity studies in mice dosing up to 6 months and dogs dosing up to 12-month at doses up to 500,000 SQU (6.7-fold greater than the human recommended dose) have not revealed any effects of toxicological concern. The most frequent finding in the mouse was a decrease in body weight which was related to a reduction of food intake. In toxicological studies in dogs, daily dosing for one year was associated with an increase of arteritis/periarteritis in male dogs, but not in females at 500,000 SQU.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long term studies have been performed in animals to evaluate the carcinogenic potential of *Phleum pratense*.

Based on in vitro assays for mutagenicity, *Phleum pratense* does not pose a genotoxic risk for humans.

Reproduction studies have been performed in mice at doses up to 500,000 SQU (Standardized Quality Unit), which is 6.7-fold greater than the human dose of 2800 BAU (equivalent to 75,000 SQU). There was an increase in total major fetal abnormalities in the low and medium doses in the combined fertility and teratology study. At high doses (500000 SQ-U/day), the incidence of embryo-fetal resorption, incomplete ossification of the hyoid, and reduction of body weight in females were also higher compared to the control.

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7. GT-14, Data on File

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PART III: CONSUMER INFORMATION

GRASTEK®

(Standardized Allergen Extract, Timothy Grass *(Phleum pratense)* Sublingual Tablets 2800 BAU)

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

ABOUT THIS MEDICATION

What the medication is used for:
GRASTEK® is used for the treatment of adults and children 5 years of age and older with a history of allergy to specific grass pollen. Grass pollen allergy is characterized by rhinitis (sneezing, runny or itchy nose, nasal congestion) with or without conjunctivitis (itch and/or watery eyes).

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

GRASTEK® has not been tested in patients younger than 5 year or older than 65 years of age.

What it does:
GRASTEK® is an allergy tablet that reduces symptoms due to specific grass allergens. It contains an allergen extract that helps to make you less sensitive to the grass pollens you are allergic to.

When it should not be used:
Do not take GRASTEK® if you or your child:

- Have severe or difficult-to-control asthma;
- Are allergic (hypersensitive) to any of the other ingredients of GRASTEK® (see What the non- medicinal ingredients are);
- Have had a serious allergic reaction to grass pollen allergy shots, tablets or drops;
- Are taking beta-blockers (a medicine prescribed for heart conditions, such as high blood pressure);
- Have any swelling or sores in your mouth

What the medicinal ingredient is:
The active substance is Standardized Allergen Extract of Timothy Grass *(Phleum pratense)*

What the non-medicinal ingredients are:
fish gelatin, mannitol, sodium hydroxide. GRASTEK® does not contain lactose.

What dosage forms it comes in:
GRASTEK® is a prescription tablet that you place under your tongue once daily.

Each tablet has a strength of 2800 Bioequivalent Allergy Units (BAU).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

- GRASTEK® is intended for use only by physicians with adequate training and experienced in the treatment of allergic diseases. With prescription for children, the doctor should also have relevant experience in treating children.
- It is common for patients to experience mild or moderate local allergic reactions with GRASTEK® (for example, an itchy mouth or a sore throat). Serious allergic reactions which can be life-threatening have happened in patients treated with GRASTEK®. If you experience stronger allergic reactions with a feeling of tightness or swelling in the throat, difficulty swallowing or breathing and voice changes, contact your physician immediately. The treatment has to be stopped immediately until your physician advises otherwise.
- The first tablet of GRASTEK® must be taken at the doctor's office. Your doctor will also tell you to stay on site for 30 minutes to check out for possible side effects to the treatment you may have.
- Children must be watched by an adult for at least 30 minutes after each dose.

Stop treatment with GRASTEK® and contact your doctor 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 GRASTEK®, tell your doctor if you or your child:

- 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 plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if GRASTEK® will pass into breast milk.

- have diseases affecting the immune system e.g. autoimmune diseases, immune complex diseases or (severe) immune deficiency diseases.
- have malignant diseases (e.g. cancer).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor 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 medicines while you are using GRASTEK®. **No drug interaction studies have been done in patients.**

PROPER USE OF THIS MEDICATION

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

- Your child should only be given each dose of GRASTEK® by an adult.
- Your doctor may prescribe medicines for you or your child to take should you have a serious allergic reaction.

After the first dose, you or your child may take GRASTEK® at home. GRASTEK® should only be given to your child under adult supervision.

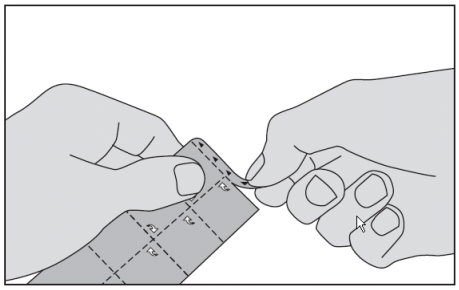
Usual dose:
GRASTEK® treatment can begin at any time during the year. For symptom improvement during the first grass pollen season, you should start taking GRASTEK® at least 8 to 12 weeks before the grass pollen season usually begins. Take GRASTEK® once daily for as long as your doctor tells you to take it, usually until at least the end of the yearly grass pollen season.

How should I take GRASTEK®?

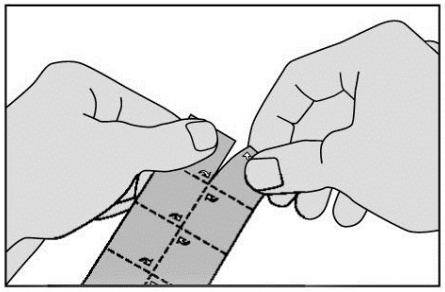
1. Do not use food or water to take the tablet.
2. Remove the tablet from the package with dry hands by carefully removing the foil.
3. Place the tablet under the tongue right away. It will dissolve.
4. Do not swallow for about 1 minute.
5. Do not drink or eat for 5 minutes after taking the tablet.
6. Wash your hands after handling the tablet.

Detailed Instructions

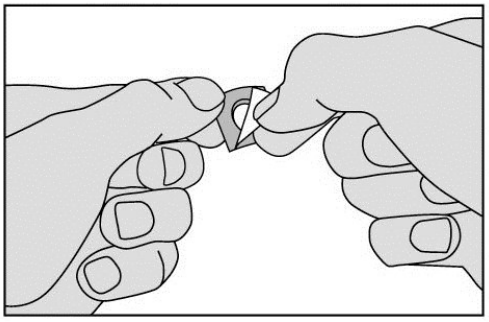
1. Tear off the strip marked with triangles.

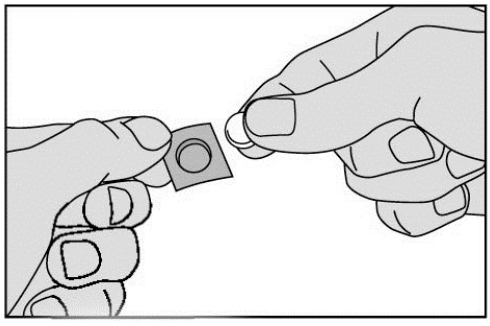


2. Tear a square off the blister pack along the perforated lines.

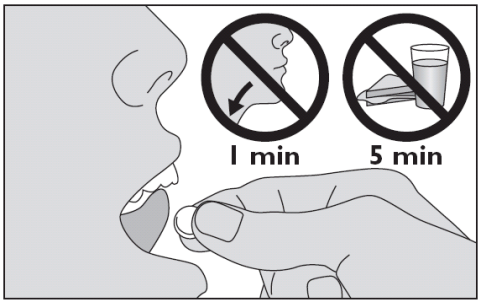


3. Remove the tablet carefully from the foil *(do not force the tablet through the foil. It may become damaged as it easily breaks. Instead, fold back the marked corner of the foil and then pull it off)*. Take it immediately.





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 GRASTEK®

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

If necessary, your physician may at the same time prescribe medications to treat the possible allergic reactions due to GRASTEK® treatment.

Missed Dose or Interruption of Treatment:

If you miss a dose, return to your normal schedule the next day. Do not take a double dose to make up for forgotten dose.

Overdose:

- Do not take more than one GRASTEK® tablet daily.
- Do not take a double dose to make up for forgotten dose.

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, GRASTEK® can cause side effects, although not everybody gets them. The side effects usually happen during the first days or weeks of treatment and go away on their own.

The most common side effects of GRASTEK® include:

- itching or swelling of the mouth
- throat irritation
- itching of eyes, nose and throat

Uncommonly, stronger allergic reactions to GRASTEK® can occur, such as swelling of the throat, difficulty swallowing or breathing, and voice changes. **If you experience these symptoms, contact your physician or pharmacist immediately, and do not take any more doses until being assessed by your doctor.**

The following side effects were reported by adults or by children and adolescents who were treated with GRASTEK® in clinical studies:

Very common (seen in at least 1 in 10 patients):
Mouth itching and/or swelling and/or inflammation, irritation in the throat, swelling in the mouth.

Common (seen in at least 1 in 100 patients, but in less than 1 in 10 patients):
Mouth: Mouth tingling and/or numbness and/or pain, and/or discomfort and/or redness, inflammation and/or burning, decreased sensation, dryness, blisters, itching of the tongue and/or lips, swelling in the lips and/or tongue and/or throat or the roof of the mouth, inflammation and/or burning sensation in the tongue, pain in the gums. **Throat:** tightness, difficulty swallowing, enlarged glands, pain and/or swelling and/or redness, blisters, dryness. **Nose:** sneezing, runny nose, dryness, irritation inside the nose, congestion, uncomfortable feeling in the nose. **Eyes:** itching and/or irritation, watery eyes. **Other:** headache, chest pain and/or discomfort, rapid heartbeat, shortness of breath, cough, dizziness, abnormal skin sensation, nausea, upset stomach, fatigue, itching, itch rash, hives, change in voice, sensation of a foreign body, sudden redness of the skin, excessive sensitivity.

Uncommon (seen in at least 1 in 1,000 patients, but in less than 1 in 100 patients:
A feeling that the ear is blocked, uncomfortable feeling in the ear, ear pain, eye pain, inflammation of the eye, swelling of the eye, irritation of the eyelid, redness of the eye, oral pain, salivary gland enlargement, stomach pain, diarrhea, acid stomach, bleeding of the gums, inflammation of the tongue, blistering of the lip and mouth, pain with swallowing, oral discomfort, sensitive teeth, excessive salivating, vomiting, pain, stomach virus, mouth abscess, skin infection around the eye, upper respiratory infection, loss of appetite, sleepiness, burning sensation, sinus headache, asthma, asthma caused by exercise, nose bleed, obstruction in the nose, wheezing, swelling of the tonsils, skin rashes, redness of the skin, excessive sweating.

The following side effect was reported with general use: Eosinophilic esophagitis (EoE) which may present as any of the following symptoms that do not go away or worsen: heartburn, difficulty swallowing, pain with swallowing, or chest pain.

The following additional side effects have been reported with GRASTEK®:

- high-pitched unusual breathing sound that may be a sign of trouble breathing

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 or pharmacist
		Only if severe	In all cases	
Very common	Swelling in the mouth	√		
Common	Swollen tongue	√		
	Swelling in the throat	√		
	Trouble swallowing			√
	Chest discomfort	√		
	Hives all over your body	√		
	Itching all over your body	√		
	Throat tightness			√
	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 GRASTEK®, contact your doctor or pharmacist.

HOW TO STORE IT

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

- Report online at MedEffect
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789, 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

Also, you can report any suspected adverse reactions associated with the use of health products to ALK-Abelló, Inc. by one of the following 2 ways:

- Call toll-free at 1-800-325-7354 (for English) or at 1-800-663-0972 (for French)
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to +1 866-255-2244, or
  - Mail to: ALK-Abelló, Inc.
    Pharmacovigilance
    Email: AdverseEvents@alk.net

This document plus the full product monograph, prepared for health professionals can be found at **http://www.alk.net** or by contacting the sponsor, **ALK-Abelló, Inc.** at 1-800-325-7354 (for English) or at 1-800-663-0972 (for French).

Although the information shown in this document is current as of the date shown below, more current consumer information may be available at the manufacturer's contact as given above.

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

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