Product Monograph

Including Patient Medication Information

ITULATEK®

Standardized Allergen Extract, White Birch (*Betula verrucosa*)

Sublingual Tablet For sublingual use

12 SQ-Bet

Allergy Immunotherapy

Therapeutic classification: Allergen extracts, White Birch

ATC code: V01AA05

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Pediatric indication: 1 Indications, 1.1 Pediatrics, 4.1 Dosing Considerations, 4.2 Recommended Dose and Dose Adjustments, 5 Overdose, 7 Warnings and precautions, 7.1.3 Pediatrics (under 5 years of age), 8 Adverse reactions, 8.1 Adverse Reaction Overview, 8.2.1 Clinical Trial Adverse Reactions Pediatrics, 8.3 Less common Clinical Trial Adverse Reactions, 8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics, 10.2 Pharmacodynamics, 14 Clinical trials, 14.1 Clinical Trials by indication..	2025-05

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

ITULATEK® (Standardized Allergen Extract, White Birch (Betula Verrucosa) Sublingual Tablet) is indicated as an allergy immunotherapy for the treatment of moderate to severe seasonal allergic rhinitis, with or without conjunctivitis, induced by pollen from birch, alder, hazel, and/or oak, in children and adults 5 to 65 years of age who have a clinical history of symptoms of allergic rhinitis, despite use of symptom-relieving medication, and a positive test of sensitization to one or more of the pollen of birch, alder, hazel or oak (skin prick test and/or specific IgE).

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

1.1. Pediatrics (5-17 years of age)

The safety and efficacy of immunotherapy with ITULATEK® have been established in pediatric patients 5-17 years of age. Therefore, Health Canada has authorized an indication for pediatric use (See 14 CLINICAL TRIALS). The safety and efficacy of ITULATEK® has not been studied in patients under 5 years of age (see 7 WARNINGS AND PRECAUTIONS / 7.1.3 Pediatrics).

1.2. Geriatrics

The safety and efficacy of immunotherapy with ITULATEK® in patients over 65 years of age have not been established (see 7 WARNINGS AND PRECAUTIONS / 7.1.4 Geriatrics).

2. Contraindications

ITULATEK® is contraindicated in patients who:

- Are hypersensitive to any of the non-medicinal ingredients in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Have previously had a severe systemic allergic reaction to birch or related tree pollen immunotherapy.
- Have unstable, severe or uncontrolled chronic or seasonal asthma (FEV1 <70% of predicted value after adequate pharmacologic treatment).
- Are taking β-blockers, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction.
- Have active inflammatory conditions in the oral cavity, e.g., oral lichen planus with ulcerations, severe oral candidiasis, dental extraction (see also 7 WARNINGS AND PRECAUTIONS / Patients with Oral Conditions).
- Have a history of eosinophilic esophagitis.

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions
• Treatment with ITULATEK® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. • Systemic allergic reactions, including severe local allergic reactions, are known risks in patients receiving allergy immunotherapy and may require emergency administration of epinephrine, antihistamines, bronchodilators or systemic corticosteroids (see 7 WARNINGS AND PRECAUTIONS / Immune). • Availability of an epinephrine device should be discussed with the recipient of ITULATEK® therapy (or their caregiver) (see 7 WARNINGS AND PRECAUTIONS/General). • The first tablet of ITULATEK® must be taken at the physician's office under medical supervision and the patient must be monitored for at least 30 minutes.

4. Dosage and Administration

4.1. Dosing Considerations

- The first dose of ITULATEK® should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of respiratory allergic diseases.
- After receiving the first dose, the patient should be kept under observation for at least 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 without medical supervision.
- Subsequent dose administration in children <12 years must be done under adult supervision and the child must be monitored for any signs of allergic reaction, including breathing difficulties. Observation should be for a minimum of 15 minutes.
- Initiate treatment with ITULATEK® at least 16 weeks prior to the tree pollen season and maintain dosing throughout the season.
- Methods of determining the presence of sensitization to tree pollen should include skin prick testing and/or serum testing for specific IgE against pollen extract of one or more of the pollen of birch, alder, hazel, or oak.

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of ITULATEK® is 1 sublingual tablet (12 SQ-Bet) daily.

If no improvement is observed during the first year of treatment with ITULATEK® there is no indication for continuing treatment.

Health Canada has not authorized an indication for patients under 5 years of age (see 7 WARNINGS AND PRECAUTIONS / 7.1.3 Pediatrics).

4.3. Administration

- ITULATEK® 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 within seconds.
- Do not take the tablet with food or beverage. Swallowing should be avoided for about 1 minute. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after handling the tablet.

4.4. Missed Dose

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

If a treatment interruption is more than 15 days, advise patients to consult a physician before restarting treatment with ITULATEK® (see 7 WARNINGS AND PRECAUTIONS / Immune).

5. Overdose

The risk of side effects may increase with intake of more than one sublingual tablet daily. In the event of an overdose, immediate medical evaluation is needed and any adverse effects should be treated symptomatically.

In a safety and tolerability trial in adults, no safety concerns were identified with intake of 2 ITULATEK® tablets daily for 28 days.

For management of a suspected drug overdose, contact your regional poison control centre.

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 - Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Sublingual	Sublingual tablet 12 SQ-Bet*	Gelatin (fish source) Mannitol Sodium hydroxide (for pH adjustment)

* SQ-Bet is the dose unit for ITULATEK®. SQ is a method for standardization on biological potency, major allergen content and complexity of the allergen extract. Bet is an abbreviation for Betula.

Description

ITULATEK® is a white to off-white circular sublingual tablet with an oval deboss on one side. ITULATEK® is designed to dissolve rapidly within seconds under the tongue.

Each ITULATEK® tablet contains 12 SQ-Bet of standardized natural birch pollen extract of White Birch (Betula verrucosa). ITULATEK® is free of lactose.

The active substance is a standardized allergen extract derived from White Birch.

ITULATEK® sublingual tablets are packaged in aluminum blister packs composed of a blister film and a lidding foil. The lidding foil is designed to be peeled back from the blister film to allow the removal of the tablets.

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

ITULATEK® is formulated as an orally disintegrating tablet designed to rapidly dissolve within seconds under the tongue. The active substance is a purified and standardized natural birch pollen extract. Each sublingual tablet has a strength of 12 SQ-Bet, which is determined based on major allergen content and total allergenic activity.

7. Warnings and Precautions

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with other immunotherapy treatments, patients treated with ITULATEK® 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 ITULATEK® should be discontinued in these patients (see Clinical Trial Experience in 8 ADVERSE REACTIONS).

Availability of an epinephrine device should be discussed with the recipient of ITULATEK® therapy (or their caregiver).

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

ITULATEK® should not be initiated in pregnant women.

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

Caution should be exercised in prescribing ITULATEK® to patients with active systemic autoimmune disorders and patients with immune defects, immunodeficiencies or immunosuppression or malignant neoplasia since the effect of allergy immunotherapy (AIT) in these conditions is not known. The physician should weigh the risk and benefit on an individual basis.

Carcinogenesis and Genotoxicity

The birch pollen allergen extract was not mutagenic under the testing conditions of 2 in vitro mutagenicity assay systems (see 16 NON-CLINICAL TOXICOLOGY). No carcinogenicity studies were conducted in animals with birch pollen allergen extract.

Gastrointestinal

Eosinophilic Esophagitis

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

Immune

Systemic Allergic Reactions

As with other immunotherapy treatments, potentially life-threatening systemic allergic reactions may occur. In addition, ITULATEK® may cause severe local reactions, including laryngopharyngeal swelling which may compromise breathing and be life-threatening. Signs and symptoms associated with a systemic allergic reaction may include syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, wheezing, bronchospasm, chest discomfort, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing and urticaria.

Treatment of severe allergic reactions may require the administration of epinephrine, antihistamines, inhaled bronchodilators and/or systemic corticosteroids. The effects of epinephrine may be potentiated in patients treated with tricyclic antidepressants, monoamino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of epinephrine may be reduced in patients treated with beta-blockers.

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

Patients may also need to be adequately monitored when taking the first reinitiated dose after a pause of ITULATEK® treatment of more than 15 days (see 8 ADVERSE REACTIONS / 8.4 Post-Market Adverse Drug Reactions).

Subsequent dose administration in children <12 years must be done under adult supervision and the child must be monitored for any signs of allergic reaction, including breathing difficulties. Observation should be for a minimum of 15 minutes.

Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the procedure of emergency self-administration of epinephrine (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). Instruct patients to seek immediate medical care upon use of self-administered epinephrine and to stop treatment with ITULATEK®.

Patients with cardiac disease such as unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension may be at increased risk in case of severe systemic allergic reactions. Clinical experience in treatment with ITULATEK® of patients with cardiac disease is limited and allergy immunotherapy should be prescribed with caution in patients with severe cardiovascular disease.

Patients with pre-existing oral allergy syndrome

Patients with a pre-existing condition of oral allergy syndrome may be more prone to experiencing local

adverse reactions and with increased severity. If significant local adverse reactions occur during treatment, the use of allergy pharmacotherapy (e.g. antihistamines) should be considered.

Patients with Oral Conditions

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

Respiratory

Patients with Asthma

Immunotherapy with ITULATEK® is contraindicated in patients who have unstable severe or uncontrolled asthma (chronic or seasonal). During treatment with ITULATEK®, instruct patients to stop treatment with ITULATEK® and contact their physician immediately if they have difficulty breathing or if asthma becomes inadequately controlled (see 2 CONTRAINDICATIONS).

Initiation of treatment with ITULATEK® should be postponed in patients with controlled asthma who are experiencing an acute respiratory tract infection until the infection has resolved.

7.1. Special Populations

7.1.1. Pregnancy

Immunotherapy with ITULATEK® should not be initiated during pregnancy because severe systemic reactions may be detrimental to the mother or fetus. No clinical data are available for the use of ITULATEK® during pregnancy. For animal studies refer to 16 NON-CLINICAL TOXICOLOGY.

7.1.2. Breastfeeding

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

7.1.3. Pediatrics (under 5 years of age)

The safety and efficacy of immunotherapy with ITULATEK® have not been studied in patients under 5 years of age.

7.1.4. Geriatrics

The safety and efficacy of immunotherapy with ITULATEK® in patients over 65 years of age have not been established.

8. Adverse Reactions

8.1. Adverse Reaction Overview

As with other immunotherapy treatments, potentially life-threatening systemic allergic reactions may occur. In addition, ITULATEK® may cause severe local reactions, including laryngopharyngeal swelling which may compromise breathing and be life-threatening. Signs and symptoms associated with a systemic allergic reaction may include syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, wheezing, bronchospasm, chest discomfort, abdominal pain, vomiting, diarrhea, rash, pruritus,

flushing and urticaria (see 7 WARNINGS AND PRECAUTIONS / Immune and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

The percentage of adult patients who discontinued from the clinical trials because of a treatment-related adverse reaction while exposed to ITULATEK® or placebo was 7% (32/436) and 2% (8/421), respectively. The most common treatment-related adverse reactions that led to trial discontinuation in adult patients who were exposed to ITULATEK® were throat irritation (10/436 patients), oral pruritus (8/436 patients), mouth swelling (8/436 patients), swollen tongue (5/436 patients), pharyngeal oedema (5/436 patients) and ear pruritus (5/436 patients). The percentage of pediatric patients (5-17 years of age) who discontinued ITULATEK® or placebo because of a treatment-related adverse reaction was 3% (17/508) and 1% (5/516), respectively.

Cumulatively in all clinical trials, one adolescent patient experienced a serious anaphylactic reaction related to the first administration of ITULATEK® and resulted in treatment with epinephrine (See 8.2.1 Clinical Trial Adverse Reactions - Pediatrics). None of the trials included co-prescription of epinephrine.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trial Experience

The safety data described below are based on a pooled analysis of 3 clinical phase II/III trials (TT-02, TT-03 and TT-04) with average durations ranging from 23 to 32 weeks. In total, these trials randomized 857 adult patients (18 years of age and older) with birch pollen-induced allergic rhinitis with or without conjunctivitis. Out of these there were 436 adult patients who were exposed to at least one dose of ITULATEK® (12 SQ-Bet). Patient demographics were similar between active and placebo. (See 14 CLINICAL TRIALS / 14.1 Clinical Trials by Indication for detailed demographics).

Majority of reported adverse reactions were mild to moderate. The most frequently reported adverse reactions were local allergic reactions that typically occurred within the first few days of treatment and disappeared within 1-3 months. For the majority, the reactions started within 10 minutes after intake of ITULATEK® on each day of occurrence and abated within an hour. For a minority of patients, local reactions persisted past the first 1-3 months.

Treatment-related adverse reactions reported in ≥1% of adult patients in the pooled analysis treated with ITULATEK® that occurred more commonly than in placebo-treated patients are shown in **Table 2**.

Table 2 Treatment-Related Adverse Reactions Reported in ≥1% of Adult Patients with Birch Pollen-Induced Rhinoconjunctivitis Treated with ITULATEK® and Occurring More Commonly than Placebo in the Pooled Phase II/III Clinical Trials

	ITULATEK® **n = 436** **n (%)**	**Placebo** **n = 421** **n (%)**
Ear and labyrinth disorders	56 (13%)	4 (<1%)
Ear pruritus	56 (13%)	4 (<1%)
Eye disorders	24 (6%)	15 (4%)

	ITULATEK® **n = 436** **n (%)**	**Placebo** **n = 421** **n (%)**
Eye pruritus	13 (3%)	12 (3%)
Lacrimation increased	7 (2%)	1 (<1%)
Conjunctivitis allergic	5 (1%)	3 (<1%)
Gastrointestinal disorders	295 (68%)	61 (14%)
Oral pruritus	167 (38%)	24 (6%)
Tongue pruritus	57 (13%)	7 (2%)
Paraesthesia oral	49 (11%)	15 (4%)
Mouth swelling	41 (9%)	1 (<1%)
Lip swelling	31 (7%)	1 (<1%)
Oral discomfort	24 (6%)	2 (<1%)
Swollen tongue	24 (6%)	2 (<1%)
Hypoaesthesia oral	20 (5%)	5 (1%)
Lip pruritus	20 (5%)	2 (<1%)
Oedema mouth	14 (3%)	-
Dysphagia	12 (3%)	-
Stomatitis	8 (2%)	1 (<1%)
Dyspepsia	7 (2%)	-
Oral pain	7 (2%)	5 (1%)
Tongue discomfort	7 (2%)	2 (<1%)
Glossodynia	6 (1%)	1 (<1%)
Lip oedema	5 (1%)	-
General disorders and administration site conditions	9 (2%)	1 (<1%)
Sensation of foreign body	9 (2%)	1 (<1%)
Immune system disorders	7 (2%)	1 (<1%)
Oral allergy syndrome	7 (2%)	1 (<1%)
Infections and infestations	7 (2%)	1 (<1%)
Rhinitis	7 (2%)	1 (<1%)
Nervous system disorders	6 (1%)	1 (<1%)
Dysgeusia	6 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders	181 (42%)	31 (7%)
Throat irritation	126 (29%)	13 (3%)
Oropharyngeal pain	24 (6%)	4 (<1%)
Pharyngeal swelling	24 (6%)	1 (<1%)
Cough	22 (5%)	3 (<1%)
Dry throat	10 (2%)	2 (<1%)
Pharyngeal oedema	10 (2%)	-
Dysphonia	9 (2%)	1 (<1%)
Rhinorrhoea	9 (2%)	5 (1%)
Pharyngeal paraesthesia	7 (2%)	1 (<1%)
Dyspnoea	5 (1%)	3 (<1%)

	ITULATEK® **n = 436** **n (%)**	**Placebo** **n = 421** **n (%)**
Nasal pruritus	5 (1%)	4 (<1%)
Skin and subcutaneous tissue disorders	6 (1%)	3 (<1%)
Urticaria	6 (1%)	3 (<1%)

n=number of subjects, age is based on collected age at screening

Treatment-related adverse reactions were reported by 345 (79%) of ITULATEK® treated patients and 134 (32%) of patients treated with placebo.

The most common treatment-related adverse reactions reported in the trials in patients treated with ITULATEK® were local administration site reactions of itching, irritation, sensation changes, discomfort, swellings, and pain involving the mouth, throat and ears. Oral pruritus was reported in 38% of ITULATEK® treated patients vs. 6% of placebo-treated patients. Throat irritation was reported in 29% of ITULATEK® treated patients vs. 3% of placebo-treated patients.

Oral allergy syndrome may worsen during treatment initiation, symptoms may resolve during continued treatment. Treatment-related oral allergy syndrome or worsening of oral allergy syndrome were reported by 7 (2%) patients treated with ITULATEK® and 1 patient (<1%) treated with placebo.

A total of 74% (323/436) of adult patients treated with ITULATEK® reported at least one local administration site reaction vs 19% (79/421) of subjects treated with placebo.

Treatment-related severe adverse reactions were reported by 21 of 436 (5%) of ITULATEK® treated patients and 1 of 421 (<1%) of patients treated with placebo. These events were local administration site reactions and included throat irritation and oral pruritus. Local swellings assessed as severe occurred in 6 of 436 (1%) patients treated with ITULATEK®. All patients were treated with symptom-relieving medication such as antihistamines and oral steroids.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Children (5-11 years of age)

Safety data for children (5-11 years of age) are based on 1 clinical phase III trial (TT-06) with approximately duration of 12 months. In total, the trial randomized 597 children with birch pollen-induced allergic rhinitis with or without conjunctivitis. Out of these, 297 were exposed to at least 1 dose of ITULATEK® (12 SQ-Bet). Patient demographics were similar between active and placebo. (See 14 CLINICAL TRIALS / 14.1 Clinical Trials by Indication for detailed demographics).

Overall, the safety profile of children treated with ITULATEK® was similar to that observed in adult patients. The majority of adverse reactions were mild to moderate in severity and seen with a similar frequency category for children compared to adults. However, the following treatment-related adverse reactions reported in ≥1% of children were observed more frequently in children compared to adult patients: abdominal pain (3% vs. <1%), nausea (2% vs. <1%), oral mucosal erythema (1% vs. 0%), vomiting (1% vs. <1%), rhinitis allergic (1% vs. <1%).

Treatment-related oral allergy syndrome or worsening of oral allergy syndrome was reported by 5 (2%) children treated with ITULATEK® and not reported for children treated with placebo.

The safety profile of children with reported asthma was similar to children without asthma.

Treatment-related adverse reactions reported in ≥1% of children treated with ITULATEK® that occurred more commonly than in placebo-treated patients are shown in **Table 3.**

Table 3 Treatment-Related Adverse Reactions Reported in ≥1% of Children with Birch Pollen-Induced Rhinoconjunctivitis Treated with ITULATEK® and Occurring More Commonly than in Children Treated with Placebo in the Pooled Phase II/III Clinical Trials

	ITULATEK® **n = 297** **n (%)**	**Placebo** **n = 300** **n (%)**
Ear and labyrinth disorders	13 (4%)	3 (1%)
Ear pruritus	13 (4%)	3 (1%)
Eye disorders	**8 (3%)**	**2 (1%)**
Eye pruritus	5 (2%)	1 (<1%)
Conjunctivitis allergic	3 (1%)	1 (<1%)
Gastrointestinal disorders	**136 (46%)**	**21 (7%)**
Oral pruritus	69 (23%)	8 (3%)
Tongue pruritus	40 (13%)	5 (2%)
Paraesthesia oral	13 (4%)	3 (1%)
Oral discomfort	12 (4%)	2 (1%)
Mouth swelling	11 (4%)	2 (1%)
Lip swelling	10 (3%)	-
Abdominal pain	8 (3%)	2 (1%)
Lip pruritus	7 (2%)	3 (1%)
Nausea	7 (2%)	-
Dysphagia	5 (2%)	-
Lip oedema	3 (1%)	-
Oral mucosal erythema	3 (1%)	-
Vomiting	3 (1%)	-
General disorders and administration site conditions	**6 (2%)**	**-**
Sensation of foreign body	6 (2%)	-
Immune system disorders	**5 (2%)**	**-**
Oral allergy syndrome	5 (2%)	-
Respiratory, thoracic and mediastinal disorders	**72 (24%)**	**16 (5%)**
Throat irritation	57 (19%)	13 (4%)
Cough	7 (2%)	3 (1%)
Pharyngeal paraesthesia	6 (2%)	-
Oropharyngeal pain	5 (2%)	1 (<1%)
Nasal pruritus	3 (1%)	1 (<1%)
Rhinitis allergic	3 (1%)	-
Skin and subcutaneous tissue disorders	**3 (1%)**	**-**

	ITULATEK® n = 297 n (%)	Placebo n = 300 n (%)
Urticaria	3 (1%)	-

n = number of participants with event, % = participants with event in percent of total number of participants in treatment group. Age is based on collected age at screening. Children (5-11 years of age) were only included in TT-06.

Adolescents (12-17 years of age)

Safety data for adolescent patients are based on a pooled analysis of 3 clinical phase II/III trials (TT-02, TT-04 and TT-06) with average durations ranging from 28 weeks to 12 months. In total, these trials randomized 427 adolescent patients (11-17 years of age) with birch pollen-induced allergic rhinitis with or without conjunctivitis. Out of these, there were 211 who were exposed to at least 1 dose of ITULATEK® (12 SQ-Bet). Patient demographics were similar between active and placebo. (See 14 CLINICAL TRIALS / 14.1 Clinical Trials by Indication for detailed demographics).

Overall, the safety profile in adolescent patients treated with ITULATEK® was similar to that observed in adult patients. The majority of adverse reactions were mild to moderate in severity and seen with a similar frequency category for adolescent patients compared to adults. However, the following treatment-related adverse reactions reported in ≥1% of adolescent patients were observed more frequently in adolescents compared to adult patients: glossitis (1% vs. <1%), throat irritation (31% vs. 29%), rash (1% vs. <1%).

1 adolescent patient experienced a treatment-related serious anaphylactic reaction after first administration of ITULATEK®. The patient was treated with epinephrine and discontinued treatment.

Treatment-related oral allergy syndrome or worsening of oral allergy syndrome was reported by 1 (<1%) adolescent patient treated with ITULATEK® and 1 (<1%) adolescent treated with placebo.

The safety profile of adolescent patients with reported asthma was similar to adolescents without asthma.

Treatment-related adverse reactions reported in ≥1% of adolescent patients treated with ITULATEK® that occurred more commonly than in placebo-treated patients are shown in **Table 4.**

Table 4 Treatment-Related Adverse Reactions Reported in ≥1% of Adolescent Patients with Birch Pollen-Induced Rhinoconjunctivitis Treated with ITULATEK® and Occurring More Commonly than in Adolescent Patients Treated with Placebo in the Pooled Phase II/III Clinical Trials

	ITULATEK® n = 211 n (%)	Placebo n = 216 n (%)
Ear and labyrinth disorders	**13 (6%)**	**-**
Ear pruritus	13 (6%)	-
Gastrointestinal disorders	**115 (55%)**	**24 (11%)**
Oral pruritus	60 (28%)	13 (6%)
Tongue pruritus	26 (12%)	4 (2%)
Paraesthesia oral	16 (8%)	5 (2%)

	ITULATEK® **n = 211** **n (%)**	**Placebo** **n = 216** **n (%)**
Mouth swelling	14 (7%)	4 (2%)
Lip pruritus	7 (3%)	-
Lip swelling	7 (3%)	1 (<1%)
Oral discomfort	7 (3%)	1 (<1%)
Swollen tongue	7 (3%)	-
Hypoaesthesia oral	4 (2%)	1 (<1%)
Glossitis	3 (1%)	-
Oral pain	3 (1%)	1 (<1%)
Stomatitis	3 (1%)	1 (<1%)
Tongue discomfort	3 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders	**77 (36%)**	**11 (5%)**
Throat irritation	65 (31%)	9 (4%)
Cough	7 (3%)	2 (1%)
Pharyngeal swelling	6 (3%)	1 (<1%)
Oropharyngeal pain	5 (2%)	-
Pharyngeal oedema	3 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders	**3 (1%)**	**-**
Rash	3 (1%)	-

n = number of participants with event, % = participants with event in percent of total number of participants in treatment group. Age is based on collected age at screening.

8.3. Less Common Clinical Trial Adverse Reactions

The following adverse reactions occurred less common (<1%):

- **Cardiac disorders**: tachycardia
- **Ear and labyrinth disorders**: ear discomfort, tinnitus
- **Eye disorders**: Eye irritation, eyelid oedema, foreign body sensation in eyes
- **Gastrointestinal disorders**: abdominal pain upper, aptyalism, diarrhoea, enlarged uvula, flatulence, gastritis, gastrointestinal pain, gastrooesophageal reflux disease, gingival erythema, gingival swelling, glossitis, lip blister, mouth ulceration, oesophageal discomfort, oesophageal irritation, oesophageal pain, oral mucosal blistering, palatal oedema, palatal swelling, regurgitation, tongue blistering, tongue oedema, tongue ulceration, vomiting
- **General disorders and administration site conditions**: chest discomfort, fatigue, feeling hot, malaise, mucosal haemorrhage, non-cardiac chest pain, swelling
- **Immune system disorders**: seasonal allergy
- **Infections and infestations**: conjunctivitis, oral herpes, sinusitis
- **Injury, poisoning and procedural complications:** intentional overdose, overdose, mouth injury

- **Investigations**: aspartate aminotransferase abnormal, blood lactate dehydrogenase abnormal, blood bilirubin abnormal, electrocardiogram abnormal, gastric pH decreased, transaminases abnormal
- **Metabolism and nutrition disorders**: appetite disorders
- **Musculoskeletal and connective tissue disorders:** arthralgia, joint swelling, myalgia
- **Nervous system disorders**: burning sensation, dysarthria
- **Psychiatric disorders**: restlessness
- **Respiratory, thoracic and mediastinal disorders**: asthma, catarrh, choking sensation, throat clearing, dyspnoea at rest, epistaxis, grunting, increased upper airway secretion, laryngeal oedema, larynx irritation, nasal discomfort, oropharyngeal discomfort, oropharyngeal swelling, pharyngeal hypoaesthesia
- **Skin and subcutaneous tissue disorders**: angioedema, dermatitis atopic, dry skin, erythema, rash
- **Vascular disorders**: hot flush

Adverse Drug Reactions of Special Interest in Controlled Clinical Trials

- Systemic Allergic Reactions: No subjects exposed to ITULATEK® developed systemic allergic reactions.
- Serious and Severe Local Reactions and Progression of Oral Reactions to the Throat: No subjects exposed to ITULATEK® developed serious local allergic swellings or airway compromise. Severe reactions that affected the throat included throat tightness (n=1), pharyngeal edema (n=1) and dysphagia (n=1).
- Acute Asthma: There were no serious treatment-related asthma exacerbations in subjects exposed to ITULATEK®.

8.3.1. Less Common Clinical Trial Adverse Reactions – Pediatrics

Children (5-11 years of age)

The following adverse reactions occurred less common (<1%) in children:

- **Eye disorders:** eye irritation, swelling of eyelid
- **Gastrointestinal disorders:** abdominal pain upper, diarrhoea, dry mouth, dyspepsia, gastrooesophageal reflux disease, glossitis, glossodynia, hypoaesthesia oral, lip blister, mouth ulceration, odynophagia, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue oedema
- **General disorders and administration site conditions:** chest pain, swelling face
- **Infections and infestations:** molluscum contagiosum, otitis media
- **Investigations:** weight decreased
- **Nervous system disorders:** headache, taste disorder
- **Respiratory, thoracic and mediastinal disorders:** asthma, choking sensation, dry throat, dysphonia, nasal congestion, nasal obstruction, pharyngeal swelling, rhinorrhoea, sneezing, suffocation feeling, throat clearing, throat tightness
- **Skin and subcutaneous tissue disorders:** dermatitis, eczema, pruritus, rash, rash macular, rash pruritic

Adolescents (12-17 years of age)

The following adverse reactions occurred less common (<1%) in adolescent patients:

- **Ear and labyrinth disorders:** ear discomfort
- **Eye disorders:** blepharitis, conjunctival hyperaemia, eye irritation, ocular hyperaemia
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, aerophagia, dyspepsia, dysphagia, lip erythema, oedema mouth, oesophageal irritation, oesophageal pain, oral mucosal erythema, salivary hypersecretion, tongue ulceration
- **General disorders and administration site conditions:** asthenia, chest pain, malaise, pyrexia, sensation of foreign body
- **Immune system disorders:** anaphylactic reaction, hypersensitivity, oral allergy syndrome
- **Infections and infestations:** nasopharyngitis, sinusitis
- **Musculoskeletal and connective tissue disorders:** pain in extremity
- **Nervous system disorders:** disturbance in attention, headache, poor quality sleep, speech disorder, taste disorder
- **Psychiatric disorders:** mental disorder, panic attack
- **Respiratory, thoracic and mediastinal disorders:** bronchospasm, catarrh, dry throat, dyspnoea, nasal congestion, nasal pruritus, oropharyngeal discomfort, pharyngeal erythema, pharyngeal hypoaesthesia, pharyngeal paraesthesia, rhinorrhoea, throat tightness, upper respiratory tract congestion
- **Skin and subcutaneous tissue disorders:** dermatitis atopic, eczema, pruritus

8.4. Post-Market Adverse Reactions

The following adverse reactions have been identified during post-market use of ITULATEK®.

Gastrointestinal disorders: eosinophilic esophagitis (see 7 WARNINGS AND PRECAUTIONS / Gastrointestinal)

9. Drug Interactions

9.1. Drug Interactions Overview

No potential drug interactions have been identified, and no drug interaction studies have been conducted in humans.

Co-administration with other immunotherapy has not been studied.

9.2. Drug-Behaviour 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.

The interaction of ITULATEK with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.3. Drug-Drug Interactions

Interactions with other drugs have not been established.

- See 2 CONTRAINDICATIONS for potential drug-drug interactions with beta-blockers.

- See 7 WARNINGS AND PRECAUTIONS / General for potential drug-drug interactions with MAOIs or tricyclic antidepressants.

9.4. Drug-Food Interactions

Tree pollen allergic patients may experience oral allergy symptoms from intake of tree pollen cross reacting foods. Symptoms include oropharyngeal pruritus and swellings. ITULATEK® treated patients with related food allergy may more often experience local reactions and temporary treatment interruptions compared to patients without tree pollen-related food allergy.

9.5. Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.6. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10. Clinical Pharmacology

10.1. 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.

10.2. Pharmacodynamics

Immunological changes in response to ITULATEK®:

Clinical trials (TT-02, TT-03 TT-04 and TT-06) showed that ITULATEK® treatment induced a time and dose-dependent increase in serum levels of birch-specific IgE and birch-specific IgG_4 and IgE-BF compared to placebo during the treatment course. The level of birch-specific IgE peaked at about 1 month after treatment initiation and then gradually declined throughout off-season and the tree pollen season while the level of birch-specific IgG_4 gradually increased with time during the entire treatment course. Across trials the same trend of time- and dose-dependent increase in serum levels of antibodies during the treatment period was observed in IgE and IgG_4 that effectively binds to alder, hazel, or oak extract but at a lower magnitude compared to that of corresponding birch-specific IgE and especially, birch-specific IgG_4.

10.3. Pharmacokinetics

No pharmacokinetic studies in animals or clinical studies investigating the pharmacokinetic profile and metabolism of birch pollen allergen extract have been conducted.

11. Storage, Stability, and Disposal

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

12. Special Handling Instructions

There are no special handling instructions for ITULATEK®.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

The biological potency of the drug substance is expressed in SQ-Bet units. Each batch of drug substance is standardized against the in-house reference preparation. During the standardization, the SQ-Bet potency is assigned to the drug substance based on the total allergenic activity and the major allergen content.

Non-proprietary name of the drug substance: Standardized Allergen Extract, White Birch (*Betula verrucosa*).

Molecular formula and molecular mass: A complex mixture of proteins and other biologically derived substances extracted from birch pollen that is partially purified. Detailed structural information is unknown.

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 birch pollen, which is then purified by filtration and stabilized into frozen droplets before incorporation in the final dosage form. The characterization of the major allergenic components includes identification of the relevant allergens.

14. Clinical Trials

14.1. Clinical Trials by Indication

Allergic Rhinitis

The safety and efficacy of ITULATEK® (12 SQ-Bet) for the treatment of subjects with birch pollen-induced allergic rhinitis and/or conjunctivitis was investigated in 2 pivotal phase III double-blind, placebo-controlled, randomized clinical field efficacy trial (Trial TT-04 and TT-06).

Table 5 Summary of trial design and patient demographics for ITULATEK® allergic rhinitis clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age range (mean)	Sex Male(%)/ Female(%)
TT-04	Phase III: Efficacy and Safety R, MC, DB, PG, PC	12 SQ-Bet QD placebo between 6.5 months and 9.5 months	320 314 (Total = 634)	12 - 65 years (36)	298 (47) / 336 (53)
TT-06	Phase III: Efficacy and Safety R, MC, DB, PG, PC	12 SQ-Bet QD Placebo QD Approximately 12 months	473 479 (Total = 952)	5 - 17 years (10.2)	*573 (60) / 379 (40)*

R=randomized; MC=multi-center; DB=double-blind; PG=parallel-group, PC=placebo-controlled; QD=once a day

Study TT-04

TT-04 was a phase III randomized, parallel-group, double-blind, placebo-controlled, multi-site field trial conducted in Europe (Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, and France) and Russia that compared the efficacy of ITULATEK® (N=320) with that of placebo (N=314) in the treatment of subjects with birch pollen-induced allergic rhinitis with or without conjunctivitis. Subjects 12 through 65 years of age were enrolled if they had a history of symptomatic allergic rhinoconjunctivitis and were sensitized to birch as determined by specific IgE and skin prick test.

A total of 60 adolescent subjects (9.5%) were included in the trial.

Subjects were asked to fill in a daily diary for 7 days in the evening during the previous birch pollen season to capture information on rhinitis and/or conjunctivitis symptoms, use of symptom-relieving medications and impact of rhinitis and/or conjunctivitis on daily life and quality of life. The information collected in the diary was used to select patients with a documented clinically relevant history of moderate to severe allergic rhinitis and/or conjunctivitis induced by birch pollen with or without asthma (controlled / partly controlled) despite having received treatment with symptom-relieving medication. An appropriate minimum level of allergic rhinoconjunctivitis symptoms induced by birch pollen during the previous birch pollen season and a minimum use of antihistamines and/or nasal steroids during the screening period were required (i.e. an average daily symptom score ≥6 (on a scale of 0 to 18) with at least 2 moderate or 1 severe symptom and use of antihistamines and/or nasal steroids on at least 4 of the 7 days of the screening period). Patients with severe or uncontrolled asthma were excluded from the trial.

The majority of subjects were IgE-sensitized to additional birch related species including alder (98%), hazel (95%), hornbeam (95%), beech (93%) and oak (86%). Furthermore, 76% of subjects were polysensitized to other non-tree related allergens such as grass or house dust mites. The patient

population was 97% White and the mean age was 36 years. 66% of subjects reported pollen food syndrome and 44% reported asthma. Patient demographics were similar between active and placebo.

Efficacy was evaluated by self-reporting of symptoms and medication use in an eDiary. Based on these self-assessments, the total combined score (TCS), daily symptom score (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and 2 ocular symptoms (gritty/itchy eyes and watery eyes). Each of these symptoms were individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summarized to achieve the DSS. Subjects in active and placebo arms of this trial were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid. The daily TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS.

The primary endpoint was the average TCS during the birch pollen season (BPS). Key secondary endpoints in this trial included the average rhinoconjunctivitis DSS during the BPS and the average TCS and DSS during the tree pollen season (TPS). Other secondary endpoints included the average rhinoconjunctivitis DMS during both the BPS and the TPS.

Trial sites were assigned to 30 pollen regions, and the start date of the BPS for each pollen region was defined as the first day of 3 consecutive days with birch pollen counts ≥ 30 grains/m3. The stop date was defined as the last day in the last occurrence of 3 consecutive days with birch pollen count ≥ 30 grains/m3. For the alder and hazel seasons, the start date was defined as the first day of 3 consecutive days with pollen counts ≥10 grains/m3, and the stop date was defined as the last day in the last occurrence of 3 consecutive days with pollen counts ≥10 grains/m3. TPS was defined as days included in any of the hazel, alder and birch pollen seasons.

Study TT-06

TT-06 was a phase III randomized, parallel-group, double-blind, placebo-controlled, multi-regional trial conducted in Europe (Poland, Lithuania, Germany, Slovakia, Hungary, Denmark, Austria, Belgium and the Netherlands), Canada and Russia. The trial compared ITULATEK® (N=473) to placebo (N=479) in the treatment of children (5 through 17 years of age) with birch pollen-induced moderate to severe allergic rhinitis and/or conjunctivitis. The trial included 2 cohorts initiated in 2 consecutive years.

Subjects were enrolled if they had a history of moderate to severe allergic rhinitis and/or conjunctivitis and were sensitized to birch as determined by specific IgE and skin prick test.

The majority of subjects were polysensitized (73%) i.e. had a positive SPT towards allergen(s) in addition to birch. Of the tested allergens, the most common co-sensitizations included grass (49%), cat (35%), dog (28%) and house dust mite (25%). The vast majority of the patient population was White (98.8%) with a mean age of 10.2 years. 13% of subjects reported oral allergy syndrome and 32% had a history of asthma at baseline. Patient demographics were similar between active and placebo.

Efficacy was evaluated by self-reporting of symptoms and medication use in an eDiary. Based on these self-assessments, the TCS, DSS and DMS for rhinoconjunctivitis were calculated. DSS was the sum of 4

rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes). Each of these symptoms were individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summarized to achieve the DSS (range 0-18). Subjects in active and placebo arms of this trial were provided with open-label rhinoconjunctivitis rescue medication (including oral and ocular antihistamines and nasal corticosteroids) as needed. The DMS measured the use of these symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid (range 0-20).

The primary endpoint was the average TCS during the BPS. The TCS is the sum of the DSS and the DMS. The key secondary endpoints were the average TCS during the TPS, the average DSS during the BPS and TPS, and the average DMS during the BPS and TPS. TPS was defined as the combined alder, hazel, birch and, oak pollen season.

Trial sites were assigned to 39 pollen regions, and the start date of BPS for each pollen region was defined as the first day of 3 consecutive days with birch pollen counts ≥ 30 grains/m3. The stop date was defined as the last day in the last occurrence of 3 consecutive days with birch pollen counts ≥ 30 grains/m3. For the hazel, alder, and oak seasons, the start date was defined as the first day of 3 consecutive days with pollen counts ≥10 grains/m3, and the stop date was defined as the last day in the last occurrence of 3 consecutive days with pollen counts ≥10 grains/m3. TPS was defined as all days included in any of the hazel, alder, birch and oak pollen seasons.

Study results

Study TT-04

The mean duration of the BPS was 24 days (range 10 - 42 days), the mean duration of the TPS was 50 days (range 14 - 68 days), and the mean duration of treatment was 224 days (range 1 – 282 days). The rate of discontinuation was higher in the ITULATEK® group (12.5%) compared to the placebo group (7%), and the difference was mainly driven by a higher number of discontinuations due to adverse events in the ITULATEK® group (8.1%) compared to the placebo group (2.5%).

Patients treated with ITULATEK® had a statistically significant reduction of rhinoconjunctivitis symptoms as measured by a decrease in TCS during the BPS compared to placebo-treated subjects. Statistically significant reductions were also observed for the key secondary endpoints of DSS during the BPS, TCS during the TPS, and DSS during the TPS. Improvements were also observed in patients treated with ITULATEK® for DMS during both BPS and TPS. The results of this trial are shown in **Table 6**

Table 6 Total Combined Score, Daily Symptom Score, and Daily Medication Score during the BPS and TPS (TT-04)

Endpoint	ITULATEK® N=320 Adjusted Mean	Placebo N=314 Adjusted Mean	Treatment Difference in Adjusted Means (Placebo-ITULATEK®)			Difference Relative to Placebo[#]	
			Estimate	95% CI	p-value	Estimate	95% CI
Primary Endpoint							
TCS BPS	4.93	7.67	2.74	(1.69 ; 3.78)	<0.0001	35.7%	(24.3 ; 46.2)
Secondary Endpoints							
TCS TPS	4.16	6.21	2.05	(1.21 ; 2.89)	<0.0001	33.0%	(21.4 ; 43.7)
DSS BPS	2.42	3.62	1.20	(0.71 ; 1.69)	<0.0001	33.1%	(21.5 ; 43.7)
DSS TPS	2.13	3.00	0.87	(0.47 ; 1.26)	<0.0001	28.9%	(17.5 ; 39.5)
DMS BPS	1.80	3.24	1.44	(0.79 ; 2.09)	<0.0001	44.4%	(28.3 ; 58.5)
DMS TPS	1.47	2.58	1.11	(0.59 ; 1.63)	<0.0001	43.1%	(26.8 ; 57.3)

N = Number of subjects in analysis set (FAS with observations).
N = Number of randomized subjects.
CI= confidence interval, TCS = total combined score (sum of the DSS and DMS), DSS = daily symptom score, DMS = daily medication score, BPS = birch pollen season, TPS = tree pollen season.
[#]Difference Relative to Placebo is calculated as (Placebo-Active 12 SQ-Bet) / Placebo*100%.
The analysis is based on a linear mixed effect model with treatment as fixed class effect and pollen region as a random class variable. Rubin's multiple imputation strategy is used and missing values in both treatment groups are sampled from the observed data of the endpoint in the placebo group.
The control for multiplicity of the type I error rate is done by hierarchical testing, pre-specifying the order of the hypothesis to be tested. The sequence of testing is included in this order TCS during BPS, DSS during BPS, TCS during TPS and DSS during TPS. The analysis of the DMS during the BPS as well as the TPS in not included in the hierarchical testing.

Study TT-06

The mean duration of the BPS was 28 days (range 4 - 47 days) in cohort 1 and 23 days (range 10 - 45 days) in cohort 2. The mean duration of the TPS was 76 days (range 12 - 139 days) in cohort 1 and 77 days (range 36-142) in cohort 2. The mean duration of treatment was 253 days (range 1 – 385 days) in the ITULATEK® group and 258 days (range 1 – 384 days) in the placebo group). The trial and treatment discontinuation rate were low in both treatment groups with more treatment discontinuations due to adverse event in the ITULATEK® group (2.7%) compared to the placebo group (0.8%).

The efficacy of ITULATEK® in children (5-17 years) with birch pollen-induced allergic rhinitis and/or conjunctivitis was investigated in TT-06 (see **Table 7**, **Table 8**, and **Table 9** for results)

Table 7 Total Combined Score, Daily Symptom Score, and Daily Medication Score during the BPS and TPS in children aged 5-17 (treatment policy estimand[a]) (FAS) (TT-06)

Endpoint	ITULATEK® N=473 Adjusted Mean	Placebo N=479 Adjusted Mean	Treatment Difference in Adjusted Means (Placebo-ITULATEK®)			Difference Relative to Placebo[b]	
			Estimate	95% CI	p-value	Estimate	95% CI
Primary Endpoint							
TCS BPS	4.74	5.87	1.13	(0.42; 1.84)	0.0019[c]	19.2%	(7.6; 29.5)
Key Secondary Endpoints							
TCS TPS	3.75	4.51	0.76	(0.26; 1.26)	0.0031[c]	16.8%	(6.1; 26.4)
DSS BPS	2.48	2.76	0.28	(-0.06; 0.63)	0.1115	10.2%	(-2.5; 21.4)
DSS TPS	2.10	2.30	0.20	(-0.07; 0.46)	0.1421[d]	8.7%	(-3.0; 19.1)
DMS BPS	1.59	2.40	0.80	(0.39; 1.22)	0.0001[d]	33.5%	(18.1; 46.5)
DMS TPS	1.21	1.71	0.50	(0.22; 0.78)	0.0005[d]	29.2%	(14.1; 42.0)

N = Number of subjects in full analysis set, CI = confidence interval, TCS = total combined score (sum of the DSS and DMS), BPS = birch pollen season, TPS = tree pollen season, DSS = daily symptom score, DMS = daily medication score.

[a]The treatment policy estimand assesses the treatment effect of ITULATEK® regardless of adherence to treatment and provides a broad perspective of the treatment effect in clinical practice in the selected patient population.

[b]Difference relative to placebo: (placebo-ITULATEK®)/placebo*100%

[c]Statistically significant as it is controlled for multiplicity with a pre-specified hierarchical testing strategy.

[d] Not statistically significant as it is not controlled for multiplicity.

Multiple imputations were used to impute missing data under the treatment policy strategy. The square root transformed endpoint was analysed in a linear mixed effect model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Table 8 Total Combined Score, Daily Symptom Score, and Daily Medication Score during the BPS and TPS in children aged 5-11 (treatment policy estimand[a]) (FAS) (TT-06)

Endpoint	ITULATEK® N=297 Adjusted Mean	Placebo N=300 Adjusted Mean	Treatment Difference in Adjusted Means (Placebo-ITULATEK®)		Difference Relative to Placebo[b]	
			Estimate	95% CI	Estimate	95% CI
Primary Endpoint						
TCS BPS	5.09	6.88	1.79	(0.84; 2.75)	26.0%	(13.2; 37.1)
Key Secondary Endpoints						
TCS TPS	3.91	5.24	1.34	(0.67; 2.01)	25.5%	(13.8; 35.8)
DSS BPS	2.25	2.67	0.42	(-0.00; 0.84)	15.7%	(-0.1; 29.2)
DSS TPS	1.84	2.21	0.36	(0.04; 0.68)	16.4%	(2.1; 28.9)
DMS BPS	2.16	3.50	1.34	(0.72; 1.96)	38.3%	(23.0; 51.0)
DMS TPS	1.64	2.55	0.91	(0.48; 1.34)	35.8%	(21.2; 48.0)

N = Number of subjects in full analysis set, CI = confidence interval, TCS = total combined score (sum of the DSS and DMS), BPS = birch pollen season, TPS = tree pollen season, DSS = daily symptom score, DMS = daily medication score.

[a]The treatment policy estimand assesses the treatment effect of ITULATEK® regardless of adherence to treatment and provides a broad perspective of the treatment effect in clinical practice in the selected patient population.

[b]Difference relative to placebo: (placebo-ITULATEK®)/placebo*100%.

Multiple imputations were used to impute missing data under the treatment policy strategy. The square root transformed endpoint was analysed in a Linear mixed effect model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

Table 9 Total Combined Score, Daily Symptom Score, and Daily Medication Score during the BPS and TPS in children aged 12-17 (treatment policy estimand[a]) (FAS) (TT-06)

Endpoint	ITULATEK® N=176 Adjusted Mean	Placebo N=179 Adjusted Mean	Treatment Difference in Adjusted Means (Placebo-ITULATEK®)		Difference Relative to Placebo[b]	
			Estimate	95% CI	Estimate	95% CI
Primary Endpoint						

TCS BPS	4.56	4.74	0.18	(-0.91; 1.26)	3.7%	(-21.6; 23.8)
Key Secondary Endpoints						
TCS TPS	3.75	3.65	-0.09	(-0.86; 0.68)	-2.5%	(-26.5; 16.7)
DSS BPS	2.76	2.79	0.03	(-0.55; 0.61)	1.0%	(-22.0; 19.7)
DSS TPS	2.44	2.34	-0.10	(-0.55; 0.35)	-4.4%	(-26.1; 13.5)
DMS BPS	1.19	1.40	0.21	(-0.33; 0.75)	15.1%	(-28.8; 44.4)
DMS TPS	0.90	0.95	0.04	(-0.32; 0.41)	4.7%	(-41.6; 35.7)

N = Number of subjects in full analysis set, CI = confidence interval, TCS = total combined score (sum of the DSS and DMS), BPS = birch pollen season, TPS = tree pollen season, DSS = daily symptom score, DMS = daily medication score.

[a]The treatment policy estimand assesses the treatment effect of ITULATEK® regardless of adherence to treatment and provides a broad perspective of the treatment effect in clinical practice in the selected patient population.

[b]Difference relative to placebo: (placebo-ITULATEK®)/placebo*100%.

Multiple imputations were used to impute missing data under the treatment policy strategy. The square root transformed endpoint was analysed in a Linear mixed effect model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General toxicology The general toxicity studies with birch pollen extract were conducted in rats and mice. No safety concerns were revealed by any of the studies including the study of daily sublingual administration of the pollen extract up to 6.54 DU/mouse/day for 26 Weeks in CD-1 mice.

Genotoxicity The mutagenic potential of the birch pollen allergen extract was studied in 2 in vitro assay systems (modified Ames assay and mouse lymphoma assay). The allergen extract was not mutagenic under the testing conditions in these studies.

Carcinogenicity No studies have been performed to evaluate the carcinogenic potential of birch pollen allergen extract.

Reproductive and developmental toxicology A general toxicity study of sublingual administration of the allergen extract up to 6.54 DU/mouse/day for 26 Weeks in CD-1 mice did not detect abnormality in male and female reproductive organs.

A reproductive in vivo toxicity study has been performed with birch pollen allergen extract at doses up to 122.6 DU/animal/day which is 10-fold greater than the human dose of 12 SQ-Bet. No effect on maternal animals was detectable. Any embryo-fetal development observations were considered a background finding in the strain of mice investigated.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ITULATEK®

Standardized Allergen Extract, White Birch (Betula Verrucosa)

Sublingual Tablet, 12 SQ-Bet

This Patient Medication Information is written for the person who will be taking **ITULATEK®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ITULATEK®**, talk to a healthcare professional.

Serious warnings and precautions box

- ITULATEK® is intended for use only by doctors with adequate training and experienced in the treatment of allergic diseases.
- It is common for patients to experience mild or moderate local allergic reactions with ITULATEK® (for example, an itchy mouth or a sore throat). Serious life-threatening allergic reactions which require immediate medical attention may occur in patients treated with ITULATEK®. 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 need for an epinephrine device should be decided on a case-by-case basis and discussed with your doctor.
- The first tablet of ITULATEK® 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.

What ITULATEK® is used for:

ITULATEK® is for children and adults aged 5 to 65 who are allergic to tree pollen from birch, alder, hazel, and/or oak and have allergic rhinitis (with or without conjunctivitis). Symptoms of allergic rhinitis include sneezing, runny or itchy nose, stuffed up nose (with or without symptoms of conjunctivitis such as itchy, burning, red, or watery eyes).

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

ITULATEK® is NOT a medication that gives immediate relief for symptoms of tree pollen allergy.

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

How ITULATEK® works:

ITULATEK® is a tablet that treats your allergy caused by tree pollen from birch, alder, hazel and/or oak. It contains a birch pollen allergen extract that helps to make you less sensitive to the tree pollen you are allergic to.

The ingredients in ITULATEK® are:

Medicinal ingredients: Standardized Allergen Extract, White Birch (*Betula verrucosa*).

Non-medicinal ingredients: fish gelatin, mannitol and sodium hydroxide. ITULATEK® does not contain lactose.

ITULATEK® comes in the following dosage form(s):

ITULATEK® is a prescription tablet that you take once a day by placing it under your tongue.
Each tablet contains 12 SQ-Bet of a Standardized Allergen Extract, White Birch (*Betula verrucosa*).

Do not use ITULATEK® if:

- you are allergic (hypersensitive) to any of the non-medicinal ingredients of ITULATEK® (see **What are the ingredients in ITULATEK®?**)
- you have had a serious allergic reaction to tree pollen allergy shots, tablets or drops
  - you have severe or unstable asthma
  - you are taking beta-blockers (a medicine prescribed for heart conditions, such as high blood pressure)
  - you have any swelling or sores in your mouth or have recently had any mouth injury or mouth surgery (such as a tooth removal or tooth loss). Your doctor may delay the start of your treatment until you are better
  - you have a history of eosinophilic esophagitis

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ITULATEK®. Talk about any health conditions or problems you may have, including if you:

- have worsening asthma symptoms or breathing problems
  - have an airway infection, such as common cold, sore throat or pneumonia on the day you are to take the first dose of ITULATEK® - your doctor may delay the start of your treatment until you are better
  - are pregnant or plan to become pregnant
  - are breastfeeding or plan to breastfeed. It is not known if ITULATEK® will pass into breast milk
  - are being treated for depression with tricyclic antidepressants, monoamino oxidase inhibitors (MAOIs) or for Parkinson's disease with COMT inhibitors
  - have a heart disease and/or you are being treated with beta-blockers
  - are being vaccinated. Your doctor will decide if you can be vaccinated without interrupting treatment with ITULATEK®

- have an illness that affects the immune system, are taking medicine that suppress the immune system or have certain cancers

Other warnings you should know about:

There is limited experience with ITULATEK® in patients younger than 5 or older than 65. Therefore, the use of ITULATEK® is not recommended in these age groups.

Stop treatment and get emergency medical treatment right away if you have any of the following symptoms after taking ITULATEK®:

- dizziness, fainting, fast or weak heartbeat, feeling nervous or feeling of "impending doom"
- throat tightness or swelling of the tongue or throat that causes trouble speaking, breathing or swallowing
- wheezing, shortness of breath, cough, chest tightness or trouble breathing
- stomach cramps, vomiting or diarrhea
- skin rash, itching, flushing or hives

Children must be watched by an adult for any signs of allergic reactions, including breathing difficulties, for a minimum of 15 minutes after taking each tablet. The need for an epinephrine device should be decided on a case-by-case basis and discussed with your doctor.

Stop treatment with ITULATEK® 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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Your doctor will tell you if it is safe to take other medicines while you are using ITULATEK®**. No drug interaction studies have been done in patients taking ITULATEK®.**

How to take ITULATEK®:

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

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

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

Usual dose:

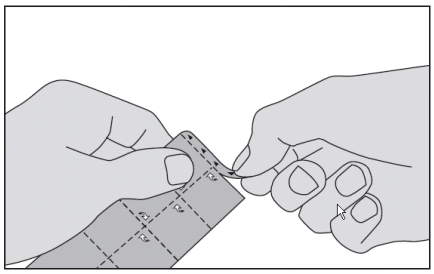
Take ITULATEK® once daily for as long as your doctor tells you to take it, usually until at least the end of the yearly tree pollen season. If no effect is seen during the first year of treatment with ITULATEK®, you should discuss with your doctor if you should continue the treatment. For symptom improvement during the first tree pollen season, you should start taking ITULATEK® at least 16 weeks before the tree pollen season usually begins.

How should I take ITULATEK®?

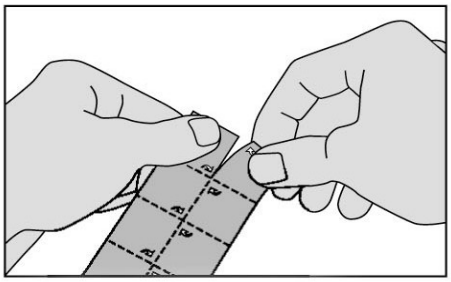
1. Do not use food or water to take the tablet
2. Remove the tablet from the package with dry hands by carefully removing the foil. (If your hands are wet or damp, the tablet will break or dissolve too soon)
3. Place the tablet under the tongue right away. It will rapidly dissolve
4. Do not swallow for 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

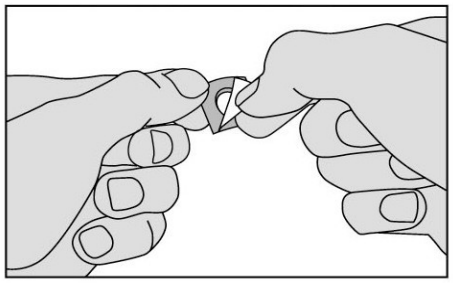
1. Tear off the strip marked with triangles at the top of the blister pack.

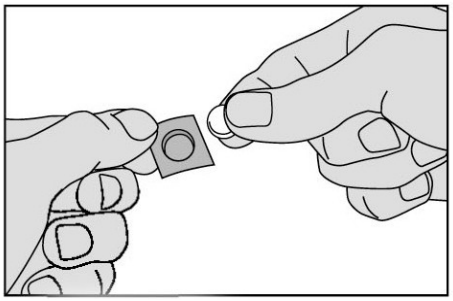


2. Tear a square off the blister pack along the perforated lines.

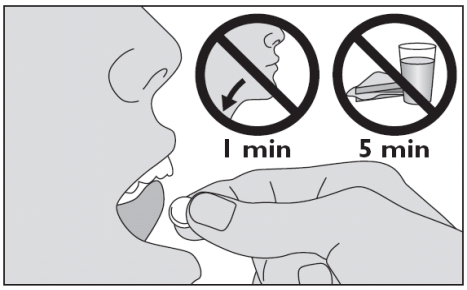


3. Remove the tablet carefully from the foil (*do not force the tablet through the foil. It may become damaged as it easily breaks. Instead, fold back the marked corner of the foil and then pull it off*). Take it immediately.





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 ITULATEK®

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

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

Overdose:

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

If you think you, or a person you are caring for, have taken too much ITULATEK®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

Do not take more than one ITULATEK® tablet daily. If you miss a dose, return to your normal schedule the next day. Do not take a double dose to make up for the forgotten dose.

Possible side effects from using ITULATEK®

These are not all the possible side effects you may have when taking ITULATEK®. If you experience any side effects not listed here, tell your healthcare professional.

Side effects caused by ITULATEK® usually happen early in treatment, but can happen even if you have been taking ITULATEK® for months.

The most common side effects of ITULATEK® include:

- itching of the ears, mouth, tongue
- swelling of the mouth, tongue and lips
- cough or swelling in the throat
- painful or irritated throat
- numb or prickling sensation in the mouth

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

- swelling of the throat, mouth or tongue
- difficulty swallowing or breathing
- asthma attack/wheezing
- hives/itchy rash
- voice changes (hoarse voice or trouble speaking)
- rapid heart rate
- low blood pressure
- fainting

Side effects reported by adults who were treated with ITULATEK® include:

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

Mouth: itching, swelling, prickling sensation

Tongue: itching

Throat: irritation

Ear: itching

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

Mouth: dryness, oral allergy syndrome (itching and/or swelling in the mouth and throat after eating certain raw foods), altered taste, pain, numbness, discomfort, blisters, inflammation

Tongue: swelling, pain or burning feeling

Lips: swelling, itching

Throat: dryness, pain, swelling, pain when swallowing or difficulty swallowing, prickling sensation

Eye: inflammation, tear flow, itching

Other: runny nose, cough, hoarseness, shortness of breath, heartburn, hives, sensation of something stuck, nausea

Uncommon [between 0.1% and 1% of patients (more than 1 in 1000 but less than 1 in 100)]:

Mouth: ulcers

Tongue: inflammation

Lips: blistering

Throat: swelling, tightness

Other: irritation of the oesophagus, rapid swelling of face, mouth and throat, abdominal pain upper

Not known (frequency cannot be estimated from available data):

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 side effects observed in children (5-17 years of age) are similar to those in adults. In clinical trials, anaphylactic reaction has been reported in adolescent patients with the frequency *uncommon [between 0.1% and 1% of patients (more than 1 in 1000 but less than 1 in 100)].*

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Swelling in the mouth	√		
COMMON Difficulty swallowing			√
Hives all over your body			√
Sensation of something stuck in the throat	√		
Swelling in the throat		√	
Swollen tongue	√		
Oral allergy syndrome	√		
UNCOMMON Chest discomfort	√		
Rapid swelling in the face, mouth or throat			√
Throat tightness			√
RARE Severe allergic reaction			Seek emergency help immediately

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store at room temperature (15 to 30°C)
- Store in the original blister to protect from moisture

- Do not use beyond the expiry date on the label
- Keep out of reach and sight of children

If you want more information about ITULATEK®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html)
- Contact regarding reporting of Side Effects to ALK Inc.:Telephone (toll-free): 1-800-325-7354 (for English) or 1-800-663-0972 (for French). Fax (toll-free): 1-866-255-2244

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

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