

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Itulazax 12SQ-Bet Oral Lyophilisate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Standardised allergen extract of pollen from white birch (*Betula verrucosa*) 12 SQ-Bet\* per oral lyophilisate.

For the full list of excipients, see section 6.1.

\* [SQ-Bet is the dose unit for ITULAZAX. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract. Bet is an abbreviation for Betula.]

## 3 PHARMACEUTICAL FORM

Oral lyophilisate

White to off-white freeze-dried debossed oral lyophilisate

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

ITULAZAX is indicated in adult patients for the treatment of moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group<sup>[1]</sup>. ITULAZAX is indicated in patients with a clinical history of symptoms despite use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE).

<sup>[1]</sup> Birch homologous group: (*Betula verrucosa* (birch), *Alnus glutinosa* (alder), *Carpinus betulus* (hornbeam), *Corylus avellana* (hazel), *Quercus alba* (oak), and *Fagus sylvatica* (beech)).

### 4.2 Posology and method of administration

#### Posology

The recommended dose for adult patients is one oral lyophilisate (12 SQ-Bet) daily.

It is recommended that treatment with ITULAZAX should be initiated outside the pollen season and continued during the tree pollen season. Clinical effect during the tree (birch homologous group) pollen season has been demonstrated when treatment is initiated at least 16 weeks prior to the expected start of the tree (birch homologous group) pollen season and continued throughout the season. There are no clinical data available for an in-season treatment start.

International treatment guidelines refer to a treatment period of 3 years for allergy immunotherapy to achieve disease modification. Long-term efficacy has not yet been established. If no improvement is observed during the first year of treatment with ITULAZAX there is no indication for continuing treatment.

#### *Elderly population*

Clinical experience in patients  $\geq 65$  years of age is limited.

#### *Paediatric population*

Clinical experience with ITULAZAX in children aged 12-17 years is limited and in children <12 years of age, safety and efficacy data have not been established. Therefore, ITULAZAX is not intended for use in patients <18 years of age. Currently available adolescent data are described in section 5.1, but no recommendation on a posology can be made and current data do not yet support its' use in this population.

#### Method of administration

ITULAZAX treatment should be initiated by physicians with experience in treatment of allergic diseases. The first oral lyophilisate should be taken under medical supervision and the patient should be monitored for at least half an hour to enable discussion and possible treatment of any immediate side effect.

ITULAZAX is an oral lyophilisate. The oral lyophilisate should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it will disperse. Swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for the following 5 minutes.

If treatment with ITULAZAX is interrupted for a period of up to 7 days, treatment can be resumed by the patient. If the treatment is interrupted for more than 7 days it is recommended to contact a physician before resuming the treatment.

### **4.3 Contraindications**

Hypersensitivity to any of the excipients (for a full list of excipients, see section 6.1).

Patients with  $FEV_1 < 70\%$  of predicted value (after adequate pharmacological treatment) at initiation of treatment.

Patients who have experienced a severe asthma exacerbation within the last 3 months prior to initiation.

Patients with uncontrolled asthma within the last 3 months prior to initiation.

Patients with active systemic autoimmune disorders (unresponsive to treatment) and patients with immune defects, immunodeficiencies or immunosuppression (see section 4.4).

Patients with malignant neoplasia with current disease relevance.

Patients with acute severe oral inflammation or oral wounds (see section 4.4).

### **4.4 Special warnings and precautions for use**

#### Severe systemic allergic reactions

Treatment should be discontinued and a physician should be contacted immediately in case of severe systemic allergic reactions, severe asthma exacerbation, severe pharyngeal oedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat. The onset of systemic symptoms may include flushing, pruritus, sense of heat, general discomfort and agitation/anxiety.

One option for treating severe systemic allergic reactions is adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.

Patients with cardiac disease may be at increased risk in case of severe systemic allergic reactions. Clinical experience in treatment with ITULAZAX of patients with cardiac disease is limited and allergy immunotherapy should be prescribed with caution in patients with severe cardiovascular disease.

Initiation of ITULAZAX in patients who have previously had a systemic allergic reaction to subcutaneous tree pollen allergy immunotherapy should be carefully considered, and measures to treat potential reactions should be available. This is based on post-marketing experience from a corresponding sublingual tablet product for grass pollen immunotherapy which indicates that the risk of a severe allergic reaction may be increased for patients who have previously experienced a systemic allergic reaction to subcutaneous grass pollen immunotherapy.

#### Asthma

Asthma is a known risk factor for severe systemic allergic reactions.

Severe asthma exacerbation within the last 12 months is a known risk factor for future exacerbations. Limited data is available with Itulazax treatment in this situation.

ITULAZAX has not been studied in patients with severe and/or uncontrolled asthma.

Patients with asthma must be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.

In patients with asthma experiencing an acute respiratory tract infection, initiation of ITULAZAX treatment should be postponed until the infection has resolved.

#### Oral inflammation

In patients with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of ITULAZAX treatment should be postponed and ongoing treatment should be temporarily interrupted to allow healing of the oral cavity.

#### Local allergic reactions

When treated with ITULAZAX the patient is exposed to the allergen that causes the allergic symptoms. Therefore, local allergic reactions are to be expected during the treatment period. These reactions are usually mild or moderate; however, more severe reactions may occur. On the first few days of at-home administration adverse reactions, which were not observed on the first day of treatment, may occur. If the patient experiences significant local adverse reactions from the treatment, allergy pharmacotherapy (e.g. antihistamines) should be considered.

#### Eosinophilic oesophagitis

Cases of eosinophilic oesophagitis have been reported in association with ITULAZAX treatment. In patients with severe or persistent gastro-oesophageal symptoms such as dysphagia or dyspepsia, ITULAZAX should be interrupted and medical evaluation must be sought.

#### Autoimmune diseases in remission

Limited data is available on treatment with allergy immunotherapy in patients with autoimmune diseases in remission. ITULAZAX should therefore be prescribed with caution in these patients.

#### Simultaneous vaccination

Clinical experience in relation to simultaneous vaccination and treatment with ITULAZAX is missing. Vaccination may be given without interrupting treatment with ITULAZAX after medical evaluation of the general condition of the patient.

#### Fish allergy

ITULAZAX may contain trace amounts of fish protein. Available data have not indicated an increased risk of allergic reactions in patients with fish allergy.

### **4.5 Interaction with other medicinal products and other forms of interactions**

No interaction trials have been conducted in humans and no potential drug interactions have been identified from any source. Concomitant therapy with symptomatic anti-allergic medications may increase the tolerance level of the patient to immunotherapy. This should be considered at discontinuation of such medications.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There is no data on the clinical experience for the use of ITULAZAX in pregnant women. Animal studies do not indicate increased risk to the foetus. Treatment with ITULAZAX should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may continue after evaluation of the general condition (including lung function) of the patient and reactions to previous administration of ITULAZAX. In patients with pre-existing asthma close supervision during pregnancy is recommended.

#### Breastfeeding

No clinical data are available for the use of ITULAZAX during lactation. No effects on the breastfed infants are anticipated.

#### Fertility

There is no clinical data with respect to fertility for the use of ITULAZAX. In a repeat dose toxicity study in naïve mice no effects were observed in the reproductive organs of both genders.

**4.7 Effects on ability to drive and use machines**

Treatment with ITULAZAX has no or negligible influence on the ability to drive or use machines.

**4.8 Undesirable effects**Summary of the safety profile

Patients taking ITULAZAX should primarily expect mild to moderate local allergic reactions to occur within the first few days of treatment and disappear within a few months (in many cases within a week or two). For the majority of events, the reaction should be expected to start within 10 minutes after intake of ITULAZAX on each day of occurrence and abate within an hour. More severe local allergic reactions may occur (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions associated with ITULAZAX obtained from placebo-controlled clinical trials predominantly performed in adults and post-marketing surveillance are tabulated below.

Adverse reactions are divided into groups according to the frequencies: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse Drug Reaction</b>
Infections and infestations	<b>Common</b>	Rhinitis
Immune system disorders	<b>Common</b>	Oral allergy syndrome
	<b>Not known</b>	Anaphylactic reaction
Nervous system disorders	<b>Common</b>	Dysgeusia
Ear and labyrinth disorders	<b>Very common</b>	Ear pruritus
Eye disorders	<b>Common</b>	Symptoms of allergic conjunctivitis*
Respiratory, thoracic and mediastinal disorders	<b>Very common</b>	Throat irritation
	<b>Common</b>	Cough, dry throat, dysphonia, dyspnoea, oropharyngeal pain, pharyngeal oedema, pharyngeal paraesthesia
	<b>Uncommon</b>	Laryngeal oedema, throat tightness
Gastrointestinal disorders	<b>Very common</b>	Oedema mouth, oral pruritus, paraesthesia oral, tongue pruritus
	<b>Common</b>	Abdominal pain, diarrhoea, dyspepsia, dysphagia, gastrooesophageal reflux disease, glossodynia, hypoaesthesia oral, lip oedema, lip pruritus, nausea, oral discomfort, oral mucosal blistering, stomatitis, swollen tongue
	<b>Uncommon</b>	Glossitis, lip blister, mouth ulceration, oesophageal irritation
Skin and subcutaneous tissue disorders	<b>Not known</b>	Eosinophilic oesophagitis
	<b>Common</b>	Urticaria
General disorders and administration site conditions	<b>Uncommon</b>	Angioedema
	<b>Common</b>	Chest discomfort, sensation of foreign body

\* Symptoms of allergic conjunctivitis typically include conjunctival hyperaemia, eye irritation, eye oedema/swelling, eyelid oedema, eye pruritus, lacrimation increased, and ocular hyperaemia.

Description of selected adverse reactions

ITULAZAX allergy immunotherapy involves repeated administration of natural allergen to which the patient is allergic. At initiation of treatment patients should be informed of the adverse reactions they are likely to experience and how to manage these in order to align expectations to treatment and optimise compliance.

Local allergic reactions are manifested in the upper respiratory or gastrointestinal system. Oral pruritus was reported in 39% of the patients, throat irritation in 29% of the patients and tongue pruritus was reported in 13% of the patients.

Systemic allergic reactions, including anaphylactic reactions, are known risks in patients receiving allergy immunotherapy and are considered a class effect.

Symptoms of oral allergy syndrome can occur upon ingestion of certain raw vegetables, fruits or nuts. Treatment with ITULAZAX may worsen the symptoms of existing oral allergy syndrome, and there have been a few new events of oral allergy syndrome reported. Symptoms typically occur at treatment initiation and may resolve with continued treatment.

#### Paediatric population

ITULAZAX is not intended for use in patients <18 years of age. Clinical experience with ITULAZAX in children aged 12-17 years of age is limited. The safety and efficacy of ITULAZAX in children <12 years of age have not been established yet. Reported adverse reactions in 35 adolescents, who were exposed to ITULAZAX in clinical trials, were similar in frequency, type and severity as in adults.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse via HPRA Pharmacovigilance;

Website : [www.hpra.ie](http://www.hpra.ie)

### **4.9 Overdose**

In a phase I trial, adult subjects with allergic rhinitis and/or conjunctivitis induced by birch pollen were exposed to doses of up to 24 SQ-Bet. For adolescents, no data are available for exposure above the recommended daily dose of 12 SQ-Bet.

If doses higher than the recommended daily dose are taken, the risk of side effects may increase, including the risk of severe systemic allergic reactions or local allergic reactions. In case of severe systemic allergic reactions, severe asthma exacerbation, severe pharyngeal oedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated with relevant symptomatic medication.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Allergen extracts, tree pollen

ATC code: V01AA05

#### Mechanism of action

ITULAZAX is an allergen extract for immunotherapy of tree (birch homologous group) pollen-induced allergic rhinitis and/or conjunctivitis. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen.

The pharmacodynamic effects of allergy immunotherapy are exerted on the immune system, but the exact mechanism of action underlying clinical efficacy is not fully understood. However, several studies have shown that the immunological response to allergy immunotherapy is characterised by an induction of allergen specific IgG<sub>4</sub>. Allergen specific IgG<sub>4</sub> competes with IgE for the binding to allergens, and thereby reduces activation of immune cells. The reduction of IgE binding to birch allergen has been confirmed for subjects treated with ITULAZAX and this was accompanied by induction of a treatment induced systemic IgG<sub>4</sub> response specific for birch. Extensive IgE cross-reactivity was observed towards the birch homologous trees before treatment initiation, thus indicating allergic sensitisation to the trees in this group, and a comparable level of IgG<sub>4</sub> cross-reactivity towards the birch homologous trees was observed after treatment with ITULAZAX. The increase in IgG<sub>4</sub> levels is observed after approximately 1 month of treatment and maintained throughout the treatment period.

Treatment with ITULAZAX also results in a rise in serum levels of apple (Mal d 1) specific IgG<sub>4</sub>.

#### Clinical efficacy and safety

The efficacy and safety of ITULAZAX in the treatment of subjects with birch pollen-induced allergic rhinitis and/or conjunctivitis with or without asthma (controlled/partly controlled) has been demonstrated in 2 double-blind, randomised, placebo-controlled clinical trials (1 phase II and 1 phase III). Overall, ITULAZAX was well tolerated in birch pollen allergic subjects with no major safety concerns detected. ITULAZAX leads to improvements in disease control and quality of life reflected by symptom relief and reduced need for allergy pharmacotherapy/symptom relieving medication. Efficacy results from the 2 trials are described below.

*Phase II (TT-03)*

The phase II trial was a randomised, double-blind, placebo-controlled trial conducted in an allergen exposure chamber with doses of 2, 7 and 12 SQ-Bet (ITULAZAX) in 219 adults with birch pollen-induced rhinoconjunctivitis. The ITULAZAX group receiving 12 SQ-Bet included 54 subjects and the placebo group included 56 subjects. Subjects were exposed to birch pollen before treatment initiation and after 8, 16 and 24 weeks of treatment, and to oak pollen before treatment initiation and after 24 weeks of treatment. The primary endpoint was the average total symptom score during the week 24 birch challenge session. Total symptom score was calculated as the sum of the total nasal symptom score and the total ocular score.

Treatment with ITULAZAX resulted in a reduction in total symptom score during birch pollen exposure compared to placebo after 16 weeks of treatment, which was sustained until end-of-trial after 24 weeks of treatment (Table 1). Treatment with ITULAZAX also resulted in a reduction in total symptom score during oak pollen exposure after 24 weeks of treatment (Table 1). The results suggest that the clinical efficacy of ITULAZAX is similar during birch and oak pollen exposure.

**Table 1 Analyses related to symptom scores during birch and oak sessions (TT-03)**

<b>Primary endpoints</b>	<b>N</b>	<b>Adjusted mean</b>	<b>Absolute difference (placebo – ITULAZAX) [95% CL]</b>	<b>% Relative to placebo [95% CL]</b>	<b>p-value*</b>
<b>Average TSS during the week 16 birch session (modified FAS)</b>					
Placebo	56	7.89	---	---	0.02
ITULAZAX	54	6.18	1.70 [0.22 ; 3.18]	22 [3.18 ; 37.28]	
<b>Average TSS during the week 24 birch session (modified FAS)</b>					
Placebo	56	7.10	---	---	0.02
ITULAZAX	54	5.29	1.81 [0.33 ; 3.28]	25 [5.32 ; 42.51]	
<b>Pre-defined secondary endpoint</b>	<b>N</b>	<b>Adjusted mean</b>	<b>Absolute difference (placebo – ITULAZAX) [95% CL]</b>	<b>% Relative to placebo [95% CL]</b>	<b>p-value*</b>
<b>Average TSS during the week 24 oak session (modified FAS)</b>					
Placebo	56	7.47	---	---	0.03
ITULAZAX	54	5.70	1.77 [ 0.18 ; 3.37]	24 [2.96 ; 41.31]	

N = Number of subjects in analysis set, modified FAS = all subjects with observations, \*p-value is for the test of an absolute difference of 0.

The response variable in the analysis was: the square root of the average TSS (results were back-transformed to original scale). The analysis was based on an LME model with treatment, visit (8, 16 and 24 weeks) and their two-factor interaction as fixed class effects, the average TSS at baseline as a fixed regression variable and chamber cohort and subject as random class variables.

TSS= total symptom score. CL = confidence limits.

*Phase III (TT-04)*

The phase III trial was a randomised, double-blind, placebo-controlled, multinational trial in 634 adults and adolescents (age 12-65) with birch pollen induced allergic rhinitis and/or conjunctivitis. Subjects received ITULAZAX (12 SQ-Bet) or placebo for approximately 16 weeks prior to start of the tree pollen season and continued throughout the season with an average treatment duration of 32 weeks.

The primary endpoint was the average total combined score (TCS) of rhinoconjunctivitis symptoms and medication use during the birch pollen season (BPS).

The pre-defined key secondary endpoints were the TCS during the tree pollen season (TPS), which was defined by the combined alder, hazel and birch pollen seasons, and the average rhinoconjunctivitis daily symptom score (DSS) during the BPS and TPS. Pre-defined secondary endpoints included the daily medication score (DMS) during the BPS and TPS.

Treatment with ITULAZAX resulted in a statistically significant treatment effect during both the BPS and the TPS. Subjects on ITULAZAX experienced reductions in symptoms and medication scores compared to placebo for an average of 50 days (average duration of the TPS) (Table 2).

**Table 2 Analyses related to symptom and medication scores during pollen seasons (TT-04)**

<b>Primary endpoint</b>	<b>N</b>	<b>Adjusted mean</b>	<b>Absolute difference (placebo – ITULAZAX) [95% CL]</b>	<b>% Relative to placebo [95% CL]</b>	<b>p-value*</b>
<b>Average TCS during the BPS (FASBPS)</b>					
Placebo	292	7.62	---	---	
ITULAZAX	283	4.61	3.02 [1.99 ; 4.05]	40 [28.24 ; 49.51]	<0.0001
<b>Pre-defined key secondary endpoints</b>	<b>N</b>	<b>Adjusted mean</b>	<b>Absolute difference (placebo – ITULAZAX) [95% CL]</b>	<b>% Relative to placebo [95% CL]</b>	<b>p-value*</b>
<b>Average TCS during the TPS (FASBPS)</b>					
Placebo	292	6.22	---	---	
ITULAZAX	283	3.95	2.27 [1.44 ; 3.11]	37 [24.99 ; 46.62]	<0.0001
<b>Average DSS during the BPS (FASBPS)</b>					
Placebo	292	3.60	---	---	
ITULAZAX	283	2.28	1.32 [0.84 ; 1.81]	37 [25.29 ; 46.70]	<0.0001
<b>Average DSS during the TPS (FASBPS)</b>					
Placebo	292	3.02	---	---	
ITULAZAX	283	2.03	0.99 [0.60 ; 1.38]	33 [21.45 ; 42.56]	<0.0001
<b>Pre-defined secondary endpoints</b>	<b>N</b>	<b>Adjusted mean</b>	<b>Absolute difference (placebo – ITULAZAX) [95% CL]</b>	<b>% Relative to placebo [95% CL]</b>	<b>p-value*</b>
<b>Average DMS during the BPS (FASBPS)</b>					
Placebo	292	3.21	---	---	
ITULAZAX	283	1.63	1.58 [0.94 ; 2.22]	49 [33.38 ; 62.41]	<0.0001
<b>Average DMS during the TPS (FASBPS)</b>					
Placebo	292	2.58	---	---	
ITULAZAX	283	1.37	1.20 [0.69 ; 1.72]	47 [30.47 ; 60.29]	<0.0001

Average TCS during the alder/hazel pollen season (FASBPS)					
Placebo	286	4.07	---	---	
ITULAZAX	278	2.87	1.21 [0.46 ; 1.96]	30 [12.61 ; 43.80]	0.0015

N = number of subjects with observations, CL = confidence limits, TCS = total combined score, BPS = birch pollen season, TPS = tree pollen season, FASBPS = subjects in full analysis set with observations during the BPS, DSS = daily symptom score, DMS = daily medication score, \*p-value is for the test of an absolute difference of 0.

DSS was the sum of 4 rhinitis and 2 conjunctivitis symptoms (range 0-18).

DMS was the sum of rescue medication provided by the sponsor (range 0-20).

TPS: Defined as days included in any of the hazel, alder and birch pollen seasons.

BPS: The start date was defined as the first day of 3 consecutive days with birch pollen counts  $\geq 30$  grains/m<sup>3</sup> and the stop date was defined as the last day in the last occurrence of 3 consecutive days with birch pollen count  $\geq 30$  grains/m<sup>3</sup>.

Alder and hazel seasons: The start date was defined as the first day of 3 consecutive days with pollen counts  $\geq 10$  grains/m<sup>3</sup> and the stop date was defined as the last day in the last occurrence of 3 consecutive days with pollen count  $\geq 10$  grains/m<sup>3</sup>.

Additional secondary endpoints supported the overall treatment effect of ITULAZAX. Subjects treated with ITULAZAX reported more days with minimal allergic rhinoconjunctivitis symptoms compared to placebo subjects (mild days) and fewer days with severe rhinoconjunctivitis symptoms during the BPS (Table 3). Rhinitis quality of life as measured by RQLQ(S) was also improved for subjects in the ITULAZAX group compared to placebo during the BPS (Table 4). Similar results were obtained for mild/severe days and RQLQ during the TPS. The results indicated an overall improved well-being for subjects treated with ITULAZAX.

**Table 3 Analyses of estimated proportion of mild and severe days during the BPS (FASBPS) (TT-04)**

Pre-defined secondary endpoints	N	Estimate	95% CL	p-value
<b>Estimated proportion of mild days during the BPS (%)</b>				
Placebo	292	42.65		
ITULAZAX	283	58.80		
	OR	1.92	[1.79 ; 2.06]	<0.0001
<b>Estimated proportion of severe days during the BPS (%)</b>				
Placebo	292	22.62		
ITULAZAX	283	12.12		
	OR	0.47	[0.43 ; 0.52]	<0.0001

BPS = birch pollen season, FASBPS = subjects in full analysis set with observations during the BPS, N = number of subjects with observations, CL = confidence limits, OR = odds-ratio.

OR: calculated as placebo/active.

Mild day: day without intake of antihistamines or olopatadine eye drops and no individual symptom scores higher than 1 (mild).

Severe day: day with DSS $\geq 6$  and at least 2 moderate or 1 severe symptom.

**Table 4 Analysis of seasonal overall RQLQ during the BPS (FASBPS) (TT-04)**



Pre-defined secondary endpoint	N	Adjusted mean	Absolute reduction	p-value
			(ITULAZAX - placebo) [95% CL]	
<b>Seasonal overall RQLQ during the BPS</b>				
Placebo	292	1.45		
ITULAZAX	283	0.99	-0.45 [-0.63 ; -0.28]	<0.0001

RQLQ = rhinoconjunctivitis quality of life, BPS = birch pollen season, FASBPS = subjects in full analysis set with observations during the BPS, N = number of subjects with observations, CL = confidence limits.

#### Paediatric population

The efficacy of ITULAZAX in adolescents with birch pollen induced allergic rhinitis and/or conjunctivitis was also investigated in the TT-04 trial (n=25 ITULAZAX, n=32 placebo). Treatment with ITULAZAX resulted in a 31% relative reduction (absolute reduction 1.94) in TCS compared to placebo during the birch pollen season for the adolescent subgroup, but data are limited. The safety of ITULAZAX in adolescents with birch pollen induced allergic rhinitis and/or conjunctivitis was investigated in the TT-02 (phase II) and the TT-04 trial. A descriptive comparison of pooled safety data indicated that tolerability for ITULAZAX is similar in adults and adolescents, but data on adolescents are limited.

The European Medicines Agency has waived the obligation to submit the results of studies with ITULAZAX in children under the age of 5 years in birch pollen-induced allergic rhinitis/rhinoconjunctivitis (treatment of allergic rhinitis/rhino-conjunctivitis).

The European Medicines Agency has deferred the obligation to submit the results of studies with ITULAZAX in children 5 years or older in birch pollen-induced allergic rhinitis/rhinoconjunctivitis (treatment of allergic rhinitis/rhino-conjunctivitis) (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

No clinical studies investigating the pharmacokinetic profile and metabolism of ITULAZAX have been conducted. The effect of allergy immunotherapy is mediated through immunological mechanisms, and there is limited information available on the pharmacokinetic properties.

The active molecules of an allergen extract are composed primarily of proteins. For sublingually administered allergy immunotherapy products, studies have shown that no passive absorption of the allergen through the oral mucosa occurs. Evidence points towards the allergen being actively taken up through the oral mucosa by dendritic cells, in particular Langerhans cells. Allergen which is not absorbed in this manner is expected to be hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract. There is no evidence to suggest that the allergens present in ITULAZAX are absorbed into the vascular system after sublingual administration to any significant extent.

## 5.3 Preclinical safety data

Conventional studies of general toxicology, genotoxicity and toxicity in relation to reproduction in mice have revealed no special hazards to humans.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Gelatine (fish source)  
Mannitol  
Sodium hydroxide (for pH adjustment)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

#### **6.4 Special precautions for storage**

Store in the original blister in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

#### **6.5 Nature and contents of container**

Aluminium/aluminium blister cards in outer carton. Each blister card contains 10 oral lyophilisates.

Pack sizes: 30 and 90.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### **7 MARKETING AUTHORISATION HOLDER**

ALK-Abello A/S  
Boge Alle 6-8  
DK-2970 Horsholm  
Denmark

### **8 MARKETING AUTHORISATION NUMBER**

PA1255/007/001

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 13<sup>th</sup> September 2019

### **10 DATE OF REVISION OF THE TEXT**

February 2022