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

ODACTRA™ House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
Tablet for Sublingual Use
Initial U.S. Approval: 2017

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

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

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) --------- ---------- 1/2023

Warnings and Precautions (5.1 Severe Allergic Reactions)--- 1/2023

----------INDICATIONS AND USAGE----------
ODACTRA is an allergen extract indicated as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites or by positive skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 12 through 65 years of age. (1)

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

- One tablet daily. (2.1)
- Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of ODACTRA under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

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

- Tablet, 12 SQ-HDM. (3)

----------CONTRAINDICATIONS----------

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

---------- WARNINGS AND PRECAUTIONS ----------

- Inform patients or parents/guardians of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)
- In case of oral inflammation or wounds, stop treatment with ODACTRA to allow complete healing of the oral cavity. (5.6)

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

- The most common solicited adverse reactions reported in ≥10% of adult subjects (18 through 65 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, tongue pain, nausea, throat swelling, stomach pain, tongue ulcer/sore on the tongue, mouth ulcer/sore in the mouth, and food tastes different. The most common solicited adverse reactions reported in ≥10% of adolescent subjects (12 through 17 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc., a subsidiary of ALK-Abelló A/S, at 1-855-216-6497or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: XX/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

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

1 INDICATIONS AND USAGE

ODACTRA™ is an allergen extract indicated as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or by positive skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 12 through 65 years of age.

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

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

One ODACTRA tablet daily.

2.2 Administration

Administer the first dose of ODACTRA in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of ODACTRA, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home. The patient should administer ODACTRA as follows:

- Take the tablet from the blister unit after carefully removing the foil with dry hands.
- Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute.
- Wash hands after handling the tablet.
- Do not take the tablet with food or beverage. Food or beverage should not be taken for 5 minutes after taking the tablet.

Data regarding the safety of restarting treatment after missing a dose of ODACTRA are limited. In the clinical studies, treatment interruptions for up to seven days were allowed.
Prescribe auto-injectable epinephrine to patients prescribed ODACTRA and instruct patients (or their parents/guardians) in the proper use of auto-injectable epinephrine *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

ODACTRA is available as 12 SQ-HDM* tablets that are white to off-white, circular with a debossed pentagon detail on one side.

*SQ-HDM is the dose unit for ODACTRA. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

4 CONTRAINDICATIONS

ODACTRA is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- A history of any severe systemic allergic reaction
- A history of any severe local reaction after taking any sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients contained in this product *[see Description (11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

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

Allergic reactions may require treatment with epinephrine. Prescribe auto-injectable epinephrine to patients receiving ODACTRA. Instruct patients or their parents/guardians to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients or their parents/guardians to seek immediate medical care and to stop treatment with ODACTRA upon use of auto-injectable epinephrine *[see Patient Counseling Information (17).]* See Prescribing Information for epinephrine for complete information.

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

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

5.2 Upper Airway Compromise

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

5.3 Eosinophilic Esophagitis

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

5.4 Asthma

Withhold immunotherapy with ODACTRA if the patient is experiencing an acute asthma exacerbation. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of ODACTRA.

5.5 Concomitant Allergen Immunotherapy

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

5.6 Oral Conditions

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

6 ADVERSE REACTIONS

The most common solicited adverse reactions reported in ≥10% of adult subjects (18 through 65 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, tongue pain, nausea, throat swelling, stomach pain, tongue ulcer/sore on the tongue, mouth ulcer/sore in the mouth, and food tastes different. The most common solicited adverse reactions reported in ≥10% of adolescent subjects (12 through 17 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea.

6.1 Clinical Trials Experience

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

Adults (18 through 65 years of age)

In four double-blind, placebo-controlled, randomized clinical studies, a total of 1279 subjects with house dust mite-induced allergic rhinitis, with or without conjunctivitis, 18 through 65 years of age was treated with at least one dose of ODACTRA 12 SQ-HDM. Of subjects treated with ODACTRA in the four studies, 50% had mild to moderate asthma and 71% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, molds, and animal danders. The study population was 88% White, 6% African American, 4% Asian and 55% female.

Study 1 (NCT01700192) was a randomized, double-blind, placebo-controlled study conducted in the US and Canada evaluating ODACTRA in 1482 subjects 12 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis. Of the 1482 subjects, 640 subjects 18 through 65 years of age received at least one dose of ODACTRA, with a median treatment duration of 267 days (range 1 to 368 days). 631 subjects received placebo. Placebo tablets contained the same inactive ingredients as ODACTRA without allergen extract and were packaged identically so that treatment blind/masking was maintained. Participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of therapy (up to 52 weeks). Participants were monitored for solicited adverse reactions for the first 28 days following treatment initiation.

Study participants were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with ODACTRA or placebo. In Study 1, the most common solicited adverse reactions reported in ≥10% of subjects treated with ODACTRA were: throat irritation/tickle (67.0% vs. 20.8% placebo), itching in the mouth (61.3% vs. 14.1%), itching in the ear (51.7% vs. 11.7%), swelling of the uvula/back of the mouth (19.8% vs. 2.4%), swelling of the lips (18.0% vs. 2.7%), swelling of the tongue (15.8% vs. 2.1%), nausea (14.2% vs. 7.1%),

tongue pain (14.2% vs. 3.0%), throat swelling (13.6% vs. 2.4%), tongue ulcer/sore on the tongue (11.6% vs. 2.1%), stomach pain (11.3% vs. 5.2%), mouth ulcer/sore in the mouth (10.3% vs. 2.9%), and taste alteration/food tastes different (10.0% vs. 3.6%). Table 1 summarizes all solicited adverse reactions reported within the first 28 days of treatment initiation in subjects 18 through 65 years of age using the patient-friendly term.

Table 1: Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with ODACTRA or Placebo (Study 1, Safety Analysis Set) in Subjects 18 through 65 Years of Age (NCT01700192)

Adverse Reaction	**Any Intensity**		**Severe†**	
	ODACTRA (N=640)	Placebo (N=631)	ODACTRA (N=640)	Placebo (N=631)
Ear and labyrinth disorders				
Itching in the ear	51.7%	11.7%	0.3%	-
Gastrointestinal disorders				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth‡	19.8%	2.4%	-	-
Swelling of the lips	18.0%	2.7%	-	-
Swelling of the tongue	15.8%	2.1%	-	-
Nausea	14.2%	7.1%	-	-
Tongue pain	14.2%	3.0%	-	-
Tongue ulcer/sore on the tongue	11.6%	2.1%	-	-
Stomach pain	11.3%	5.2%	0.2%	-
Mouth ulcer/sore in the mouth	10.3%	2.9%	-	-
Diarrhea	6.9%	3.6%	-	-
Vomiting	2.5%	1.4%	-	-
Nervous system disorders				
Taste alteration/food tastes different	10.0%	3.6%	-	-
Respiratory, thoracic and mediastinal disorders				
Throat irritation/tickle	67.0%	20.8%	0.3%	-
Throat swelling	13.6%	2.4%	0.2%	-

In Table 1, the dashes represent no subjects.

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

†Severe adverse reactions were those assessed by the investigator as severe in intensity, which is defined as incapacitating with inability to work or do usual activity.

‡The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).

In Study 1, the timing of the adverse reaction relative to exposure to ODACTRA was evaluated for 7 solicited adverse reactions (itching in the ear, itching in the mouth, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat irritation/tickle, and throat swelling). The median time to onset of these adverse reactions following initiation of treatment with ODACTRA varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions recurred for a median of 2 to 12 days.

In Study 1, the following unsolicited adverse events were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 18 through 65 years of age within 28 days after initiation of treatment with ODACTRA: paresthesia oral (9.2% vs. 3.2%), tongue pruritus (4.7% vs. 1.1%), oral pain (2.7% vs. 0.6%), stomatitis (2.5% vs. 1.1%), dyspepsia (2.2% vs. 0.0%), pharyngeal erythema (2.0% vs. 0.3%), eye pruritus (1.7% vs. 1.4%), oral mucosal erythema (1.7% vs. 0.2%), upper respiratory tract infection (1.6% vs. 1.1%), sneezing (1.6% vs. 0.3%), lip pruritus (1.4% vs. 0.3%), dysphagia (1.4% vs. 0.0%), fatigue (1.3% vs. 1.0%), hypoesthesia oral (1.3% vs. 1.0%), oropharyngeal pain (1.3% vs. 0.6%), chest discomfort (1.3% vs. 0.3%), dry throat (1.3% vs. 0.3%), pruritus (1.1% vs. 1.0%), and urticaria (1.1% vs. 0.3%).

Studies 2 (NCT01454544) and 3 (NCT01644617) were randomized, double-blind, placebo-controlled studies of subjects 18 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis, and with or without asthma. Study 4 (NCT01433523) was a randomized, double-blind placebo-controlled study that included subjects 18 years of age and older with house dust mite-induced asthma and allergic rhinitis, with or without conjunctivitis.

Across the four clinical studies, 1279 subjects received at least one dose of ODACTRA, of whom 1104 (86%) completed at least 4 months of therapy.

The percentages of subjects in these studies who discontinued treatment because of an adverse reaction while exposed to ODACTRA or placebo were 8.1% and 3.0%, respectively. The most common adverse reactions (≥1.0%) that led to study discontinuation in subjects who received ODACTRA were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%).

Serious adverse events were reported, 16/1279 (1.3%) among ODACTRA recipients and 23/1277 (1.8%) among placebo recipients. No deaths were reported.

Epinephrine use was reported in 5/1279 (0.4%) subjects who received ODACTRA compared to 3/1277 (0.2%) of subjects who received placebo. Of these subjects, 1 ODACTRA recipient reported a systemic allergic reaction and used epinephrine on the day of treatment initiation compared to 2 placebo recipients who reported anaphylaxis and used epinephrine 6 and 25 days after treatment initiation, respectively.

Of 1279 subjects who received ODACTRA, 34 (2.7%) reported dyspepsia compared to 0/1277 (0%) of subjects who received placebo. Twenty subjects who received ODACTRA (1.6%) reported symptoms of gastroesophageal reflux disease (GERD) compared to 3/1277 (0.2%) of subjects who received placebo.

Adolescents (12 through 17 years of age)

In two clinical studies, a total of 347 adolescent subjects were treated with at least one dose of ODACTRA. Study 1 (NCT01700192) was a double-blind, placebo-controlled, randomized clinical study. Study 5 (NCT04541004) was a single arm, open-label safety study. Because the study design and safety data presentation differ in the studies, adverse reaction rates cannot be directly compared. Overall, the safety profile in adolescents was consistent with the safety profile in adults.

Study 1 was a randomized, double-blind, placebo-controlled study conducted in the US and Canada evaluating ODACTRA in 1482 subjects 12 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis. Of the 1482 subjects, 94 subjects 12 through 17 years of age received at least one dose of ODACTRA, with a median treatment duration of 279 days (range 1 to 353 days). 95 subjects received placebo. Of the adolescent subjects treated with ODACTRA, 53% were male, 39% had asthma, and 72% were polysensitized to other allergens in addition to HDM. The adolescent subject population was 69% White, 13% Black or African American, 10% multiple race, 5% Asian, and 3% American

Indian or Alaska Native. Subject demographics in placebo-treated subjects were similar to the active treatment group.

In Study 1, study participants were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with ODACTRA or placebo. The solicited adverse reactions reported in adolescent subjects 12 through 17 years of age are summarized in Table 2.

Table 2: Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with ODACTRA or Placebo (Study 1, Safety Analysis Set) in Subjects 12 through 17 Years of Age (NCT01700192)

Adverse Reaction (Any Intensity‡)	**ODACTRA (N=94)**	**Placebo (N=95)**
Ear and labyrinth disorders		
Itching in the ear	50.0%	11.6%
Gastrointestinal disorders		
Itching in the mouth‡	73.4%	14.7%
Tongue pain	24.5%	4.2%
Stomach pain	23.4%	15.8%
Swelling of the uvula/back of the mouth†	20.2%	3.2%
Swelling of the lips	20.2%	1.1%
Swelling of the tongue	19.1%	3.2%
Nausea‡	17.0%	9.5%
Tongue ulcer/sore on the tongue	12.8%	4.2%
Mouth ulcer/sore in the mouth	10.6%	3.2%
Diarrhea	7.7%	2.1%
Vomiting‡	4.3%	-
Nervous system disorders		
Taste alteration/food tastes different	4.3%	4.2%
Respiratory, thoracic and mediastinal disorders		
Throat irritation/tickle‡	73.4%	35.8%
Throat swelling	18.1%	8.4%

In Table 2, the dashes represent no subjects.

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

†The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).

‡Of those subjects reporting any intensity of: itching in the mouth, nausea, throat irritation/tickle, or vomiting in the ODACTRA group, 1 subject (1.1%) reported severe intensity of the reaction. Adverse reactions were categorized as severe according to the definition ‘incapacitating with inability to work or do usual activity’, as assessed by the investigator.

In Study 1, participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of treatment (up to 52 weeks). Unsolicited adverse events that were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 12 through 17 years of age within 28 days after initiation of treatment with ODACTRA aresummarized in Table 3.

In Study 1, 94 adolescent subjects received at least one dose of ODACTRA, of whom 81 (86%) completed at least 4 months of treatment.

The percentage of adolescent subjects who discontinued from the study because of an adverse reaction while exposed to ODACTRA or placebo was 10% and 1%, respectively. The most common adverse reaction that led to study discontinuation in adolescent subjects who were exposed to ODACTRA were throat irritation (4%), swollen tongue (2%) and nausea (2%).

No adolescent subjects treated with ODACTRA in Study 1 reported serious adverse events, treatment-related systemic allergic reactions, or adverse reactions treated with epinephrine.

Table 3: Unsolicited Adverse Reactions occurring During the Entire Trial After Initiation of Treatment with ODACTRA or Placebo (Study 1, Safety Analysis Set) Reported in ≥1% of Subjects 12 through 17 Years of Age (NCT01700192)

Adverse Reaction	**ODACTRA (N=94)†**	**Placebo (N=95)†**
Ear and labyrinth disorders		
Ear discomfort	1.1%	-
Ear pain	1.1%	-
Eye disorders		
Eye pruritus	1.1%	-
Eye swelling	1.1%	-
Gastrointestinal disorders		
Paraesthesia oral	5.3%	-
Oral pain	4.3%	-
Tongue pruritus	3.2%	-
Stomatitis	2.1%	1.1%
Aphthous ulcer	1.1%	-
Dysphagia	1.1%	-
Eosinophilic esophagitis	1.1%	-
Salivary gland enlargement	1.1%	-
Tongue discomfort	1.1%	-
General disorders and administration site conditions		
Chest discomfort	2.1%	-
Chest pain	1.1%	-
Non-cardiac chest pain	1.1%	-
Infections and infestations		

Adverse Reaction	ODACTRA (N=94)†	Placebo (N=95)†
Acute sinusitis	1.1%	-
Musculoskeletal and connective tissue disorders		
Arthralgia	1.1%	-
Neck pain	1.1%	-
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	1.1%	-
Rhinorrhea	1.1%	-
Throat tightness	1.1%	-
Tonsillar hypertrophy	1.1%	-
Skin and subcutaneous tissue disorders		
Pruritus	2.1%	1.1%
Vascular disorders		
Flushing	1.1%	-

In Table 3, the dashes represent no subjects.
† Due to the population size (ODACTRA; N=94; and placebo; N=95), 1.1% represents one subject.

Study 5 was a single-arm, open label study conducted in Europe, and exposed 253 subjects 12 through 17 years of age with house dust mite-induced allergic rhinitis with or without conjunctivitis and with or without asthma to at least one dose of ODACTRA. The median treatment duration was 28 days (range 11 to 32 days). Of the subjects, 60% were male, 43% had asthma, and 56% were polysensitized to other allergens in addition to HDM. The subject population was 99.6% White and 0.4% Native Hawaiian or Other Pacific Islander.

Study participants were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with ODACTRA or placebo. Participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of the study.

In Study 5, the proportions of subjects reporting solicited adverse reactions during the first 28 days following initiation of treatment with ODACTRA were comparable to those reported during the first 28 days following initiation of treatment with ODACTRA in Study 1.

In Study 5, the following unsolicited adverse reactions occurred in ≥1% of subjects 12 through 17 years of age during the entire study [median treatment duration 28 days (range 11 to 32 days)] after initiation of treatment with ODACTRA: oral pain (3.2%), oral pruritus (2.8%), throat irritation (1.6%), ear pruritus (1.2%), and mouth ulceration (1.2%).

In Study 5, 253 adolescent subjects received at least one dose of ODACTRA, of whom 248 (98%) completed 28 days of treatment. The percentage of subjects who discontinued from the study because of an adverse reaction while exposed to ODACTRA was 1%.

No adolescent subjects in Study 5 reported serious adverse events, treatment-related systemic allergic reactions, or adverse reactions treated with epinephrine.

Across eight clinical studies of varying durations which enrolled individuals 5 through 85 years of age and which were conducted with different doses of ODACTRA, eosinophilic esophagitis was reported in 2/2737 (0.07%) subjects who received ODACTRA compared to 0/1636 (0%) subjects who received placebo. Of these eight clinical studies, 2416 subjects received different doses of ODACTRA in four clinical studies with durations of 12 months or longer [2 cases/2416 subjects (0.08%) who received ODACTRA for 12 months or longer]. One case of eosinophilic esophagitis assessed as related to treatment occurred on Day 99 in an adult subject receiving ODACTRA. One case of eosinophilic esophagitis assessed as related to treatment occurred on Day 204 in an adolescent subject receiving ODACTRA.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ODACTRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Gastrointestinal disorder*: esophageal irritation
- *General Disorders and Administration Site Conditions:* sensation of foreign body
- *Immune System Disorders:* serious systemic allergic reactions, including anaphylaxis
- *Respiratory, Thoracic and Mediastinal Disorders:* asthma exacerbations, cough, dysphonia
- *Skin and Subcutaneous Tissue Disorders:* angioedema, erythema.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on ODACTRA administered to pregnant women are insufficient to inform associated risks in pregnancy.
In an embryo/fetal developmental toxicity study performed in mice, administration of ODACTRA during gestation did not reveal adverse developmental outcomes in fetuses (*see 8.1 Data*).

Data

Animal Data
In a developmental toxicity study, the effect of ODACTRA on embryo/fetal development was evaluated in mice. Animals were administered ODACTRA subcutaneously daily from day 6 to day 17 of the gestation period at doses up to 5 times the human sublingual dose. There were no ODACTRA-related post-implantation losses, fetal malformations or variations.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of ODACTRA have been established in adolescents 12 through 17 years of age. The safety and effectiveness have not been established in persons below 12 years of age.

8.5 Geriatric Use

Safety and effectiveness have not been established in persons older than 65 years of age.

10 OVERDOSAGE

Symptoms of overdose may include hypersensitivity reactions such as systemic allergic reactions or severe local allergic reactions *[see Warnings and Precautions (5.1)]*. In case of severe adverse reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated as medically indicated, including the use of epinephrine as appropriate *[see Warnings and Precautions (5.1)]*.

11 DESCRIPTION

ODACTRA tablets contain house dust mite allergen extract from *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. ODACTRA is a sublingual tablet that dissolves within 10 seconds.

ODACTRA is available as a tablet of 12 SQ-HDM [6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*]. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy have not been fully established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ODACTRA has not been evaluated for carcinogenic potential or impairment of fertility in animals. Two *in vitro* chromosome aberration assays, an *in vitro* bacterial mutagenesis assay and a combined *in vivo* Comet and micronucleus assay for mutagenicity in rats were performed using HDM (*D. farinae* and *D. pteronyssinus*) allergen extracts. One *in vitro* chromosome aberration assay was positive. Based on the aggregated results, the weight of evidence indicates that this finding is unlikely to be of clinical relevance.

14 CLINICAL STUDIES

The efficacy of ODACTRA for the treatment of HDM-induced allergic rhinitis was investigated in two double-blind, placebo-controlled, randomized clinical field efficacy studies (Studies 1 and 2) and one environmental exposure chamber (EEC) study.

Adolescents and Adults

Study 1 (North American Field Efficacy Study)

Study 1 was a double-blind, placebo-controlled, randomized field efficacy study conducted in the United States and Canada for a duration of up to 12 months, that compared the efficacy of ODACTRA (N=741) compared to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects 12 through 85 years of age were enrolled if they had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE. Subjects were required to be symptomatic and were not taking symptom-relieving allergy medications at enrollment.

Subjects with mild to moderate asthma, defined as asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid, were enrolled in the study.

In this study, 31% of subjects had asthma, 48% had conjunctivitis, and 76% were polysensitized to other allergens in addition to HDM, including trees, grasses, weed, animal danders and molds. The subject population was 76% White, 11% African American, 7% Asian, and 59% female. The mean age of subjects was 35 years.

The efficacy of ODACTRA in the treatment of HDM-induced allergic rhinitis was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were

calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study 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 primary endpoint was the difference between the treatment and placebo groups in the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Other secondary endpoints in this study included the average rhinitis DSS, the average rhinitis DMS, and the Total Combined Score (TCS). The TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS, which was then averaged during approximately the last 8 weeks of treatment.

Subjects in this study were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm. The results of this study are shown in Table 5. Consistent results across age groups were observed, supporting a similar treatment effect in adolescent and adult subgroups.

Table 5: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 12 Years of Age and Older (Study 1, Field Efficacy Study) (NCT: NCT01700192)

Endpoint*	ODACTRA (n=566)† Score‡	Placebo (n=620)† Score‡	Treatment Difference (ODACTRA-Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
Primary Endpoint				
TCRS¶	4.10	4.95	-0.80	-17.2% (-25.0%, -9.7%)
Secondary Endpoints				
Rhinitis DSS	3.55	4.20	-0.60	-15.5% (-24.4%, -7.3%)
Rhinitis DMS	0.65	0.79	-0.15	-18.4% (-41.0%, 4.3%)
TCS	5.50	6.60	-1.10	-16.7% (-24.6%, -4.0%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

Analyses were based on the full analysis set (FAS), which included all randomized and treated subjects. Subjects were analyzed according to the treatment group to which they were randomized.

*Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints; Parametric analysis using zero-inflated log-normal model for Rhinitis DMS endpoint.

†Number of subjects in analyses.

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

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

¶The pre-specified criteria for demonstration of efficacy was defined as a TCRS difference relative to placebo less than or equal to -15 percent, and the upper bound of the 95 percent confidence interval (CI) of TCRS difference relative to placebo less than or equal to -10 percent.

Adults

Study 2 (European Field Efficacy Study)

This double-blind, placebo-controlled, randomized field efficacy study evaluated adult subjects 18 through 66 years of age comparing ODACTRA (N=318) and placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this study had a history of symptomatic allergic rhinitis when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing. At study entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the baseline period.

In this study, 46% of subjects had asthma, 97% had conjunctivitis and 67% were polysensitized to other allergens in addition to HDM, including trees, grass, weeds, animal danders and molds. The study population was 98% White, <1% African American, and <1% Asian; 50% of subjects were female. The mean age of subjects in this study was 32 years. The primary efficacy endpoint was the difference relative to placebo in the average TCRS during the last 8 weeks of treatment. The mean Rhinitis DSS at baseline was 7.95 out of 12 for the treatment arm and 8.00 out of 12 total points for the placebo arm. The results of this study are shown in Table 6.

Table 6: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 18 Years of Age and Older (Study 2, European Field Efficacy Study) (NCT01454544)

Endpoint*	ODACTRA (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
Primary Endpoint				
TCRS¶	(318) 5.71	(338) 6.81	-1.09	-16.1% (-25.8%, -5.7%)
Secondary Endpoints				
Rhinitis DSS¶	(318) 2.84	(338) 3.31	-0.47	-14.1% (-23.8%, -3.9%)
Rhinitis DMS¶	(318) 2.32	(338) 2.86	-0.54	-18.9% (-34.7%, -1.3%)
TCS#	(241) 7.91	(257) 9.12	-1.21	-13.2% (-23.7%, -1.5%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

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

†Number of subjects in analyses.

‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

¶Analysis based on FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the study before the efficacy assessment period as placebo subjects. For the primary analysis (FAS-MI) only the absolute difference was pre-specified. Additional analyses describing the corresponding pre-specified relative differences to placebo for the full analysis set (FAS): TCRS: -18.1% (-27.6%, -7.7%); rhinitis DSS: -16.2% (-25.7%, -5.8%); and rhinitis DMS: -21.4% (-36.6%, -3.2%).

#Subjects from Serbia and Croatia were excluded from the analysis of TCS because the preferred formulations of antihistamine eyedrops were not available in these countries at the time the study was conducted. The TCS analysis is based on the full analysis set (FAS). All available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.

Study 3 (Environmental Exposure Chamber Study)

This double-blind, placebo-controlled, randomized EEC study evaluated adult subjects 18 through 58 years of age comparing ODACTRA (N=42) and placebo (N=41) administered as a sublingual tablet daily for approximately 24 weeks. Subjects had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE. In this study, 23% of subjects had asthma, 87% had conjunctivitis, and 84% were polysensitized to other allergens in addition to HDM, including tree, grass, weed, animal danders and molds. The subject population was 90% White, <1% African American, 8% Asian, and 43% female. The mean age of subjects was 27 years.

The primary endpoint was the difference relative to placebo in the average TNSS at Week 24. The Total Nasal Symptom Score (TNSS) represents the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints were the differences relative to placebo in the average TNSS at Weeks 8 and 16 and average Total Symptom Score (TSS) at Week 24, which represents the sum of TNSS plus 2 ocular symptoms (gritty/itchy eyes and watery eyes). Baseline TNSS following house dust mite EEC challenge prior to treatment was 7.74 out of 12 total points for ODACTRA and 7.32 out of 12 total points for placebo. The results of this study are shown in Table 7.

Table 7: Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (Study 3, Environmental Exposure Chamber Study) (NCT01644617)

Endpoint*	ODACTRA (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
Primary Endpoint				
TNSS – Week 24	(36) 3.83	(34) 7.45	-3.62	-48.6% (-60.2%, -35.3%)
Secondary Endpoints				
TNSS – Week 8	(40) 5.34	(39) 6.71	-1.37	-20.4% (-33.3%, -6.8%)
TNSS – Week 16	(39) 4.82	(38) 6.90	-2.08	-30.1% (-42.3%, -16.8%)
TSS – Week 24	(36) 4.43	(34) 9.27	-4.84	-52.2% (-65.0%, -37.0%)

TNSS=Total Nasal Symptom Score; TSS=Total Symptom Score (TNSS + total ocular symptom score); CI=Confidence Interval

*Parametric analysis using analysis of covariance for all endpoints.

†Number of subjects in analyses.

‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

16 HOW SUPPLIED/STORAGE AND HANDLING

ODACTRA 12 SQ-HDM tablets are white to off-white, circular freeze-dried sublingual tablets with a debossed pentagon detail on one side.

ODACTRA is supplied as follows:
3 blister packages of 10 tablets (30 tablets total). NDC 52709-1701-3

Store at controlled room temperature, 20ºC-25ºC (68ºF-77ºF). Store in the original package until use to protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

Severe Allergic Reactions

- Advise patients (or their parents/guardians) that ODACTRA may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients (or their parents/guardians) about the signs and symptoms of these allergic reactions *[see Warnings and Precautions (5.1)]*. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.
- Ensure that patients (or their parents/guardians) have auto-injectable epinephrine and instruct patients (or their parents/guardians) in its proper use. Instruct patients (or their parents/guardians) who experience a severe allergic reaction to seek immediate medical care, discontinue ODACTRA, and resume treatment only when advised by a physician to do so *[see Warnings and Precautions (5.1).]*
- Advise patients to read the patient information for epinephrine.
- Inform patients (or their parents/guardians) that the first dose of ODACTRA must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of life-threatening systemic or local allergic reaction *[see Warnings and Precautions (5.1)]*.
- Because of the risk of upper airway compromise, instruct patients (or their parents/guardians) with persistent and escalating adverse reactions in the mouth or throat to discontinue ODACTRA and to contact their healthcare professional *[see Warnings and Precautions (5.2)].*
- Because of the risk of eosinophilic esophagitis, instruct patients (or their parents/guardians) with severe or persistent symptoms of esophagitis to discontinue ODACTRA and to contact their healthcare professional *[see Warnings and Precautions (5.3)].*

Asthma

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

Administration Instructions

- Instruct patients (or their parents/guardians) to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve within 10 seconds. Instruct patients to avoid swallowing for at least 1 minute. Also instruct patients to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet *[see Dosage and Administration (2.2)].*

Manufactured for: ALK-Abelló A/S

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