EMADOC-1700519818-2802158
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000321532

PRAC PSUR assessment report

Active substance(s): allergen for therapy: dermatophagoides pteronyssinus / dermatophagoides farina (oromucosal use, products authorised via mutually recognition procedure and decentralised procedure)

EURD list no.: PSUSA/00010582/202509

Data lock point: 22 September 2025

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	23 December 2025	22 December 2025
☐	Start date	08 January 2026	07 January 2026
☐	PRAC Rapporteur AR	09 March 2026	06 March 2026
☐	PRAC/MAH comments	08 April 2026	N/A
☐	Updated PRAC Rapporteur AR	23 April 2026	21 April 2026
☐	Oral explanation at PRAC	N/A	N/A
☒	PRAC outcome	07 May 2026	07 May 2026

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for the following allergen for therapy: dermatophagoides pteronyssinus / dermatophagoides farina (oromucosal use, products authorised via mutually recognition procedure and decentralised procedure).

For an overview of the nationally authorised products for which PSURs were submitted in the context of this EU single assessment, please see the appendix to this assessment report.

2. Assessment conclusions and actions

This is the PSUSA for dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy, covering the reporting period from 23 September 2022 to September 2025.

This assessment report concerns following products, manufactured by ALK Abelló A/S Denmark and Stallergenes Greer SAS France, and with the respective trade names: SQ-HDM-SLIT tablet: Acarizax, AITARO, AMITEND and HDM-SLIT-tablet: ORYLMITE, AITMYTE and ACTAIR.

Dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy is indicated for the treatment of moderate to severe HDM-induced rhinitis, allergic rhinitis or rhinoconjunctivitis and/or intermittent allergic asthma in patients of 12-years and older.

For one product, the following three signals: `Rash`, `Dizziness` and `Malaise` were assessed as new risks and closed, during the reporting interval. One additional signal of `Oral mucosal discolouration` was refuted after evaluation, as well.

The important identified risks for the SQ-HDM-SLIT product is ´Eosinophilic oesophagitis`.

The important identified risk for the HDM-SLIT product is ´Severe laryngopharyngeal reactions´ and ´Pregnant and lactating women` is considered as missing information. `Anaphylactic reactions including anaphylactic shock´ as well as ´Eosinophilic oesophagitis´ are considered as Important identified risk (class effect) and as Important potential risk (class effect) is considered `Autoimmune disorders`.

No additional risk minimisation measures other than routine risk minimisation activities need to be implemented in all products concerned in this assessment. No new and significant information related to benefit and/or risk was identified during the current review period.

Overall, based on the information received during the review period, the benefit-risk balance for dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy remains unchanged and is considered positive.

3. Recommendations

Based on the review of data on safety and efficacy by the Lead Member State and taking into account any comments provided by the PRAC, the PRAC considers that the risk-benefit balance of medicinal products containing the active substance: dermatophagoides pteronyssinus / dermatophagoides farina (oromucosal use, products authorised via mutually recognition procedure and decentralised procedure), remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

5. PSUR frequency

☒ No changes to the PSUR frequency.

The current **3**-year frequency for the submission of PSURs should remain unchanged.

Annex: Lead Member State assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the PSUSA for dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy, covering the reporting period from 23 September 2022 to September 2025.

1.1.1. MAH ALK-Abelló-A/S

This Periodic Safety Update report (PSUR) was prepared for HDM SLIT-tablet, a sublingual allergy immunotherapy tablet (SLIT-tablet) developed for allergy immunotherapy (AIT) treatment of HDM allergy. The HDM SLIT-tablet is an oral lyophilizate and belongs to the pharmaceutical group "Allergen extracts" with the ATC code V01AA03. The drug substances of the HDM SLIT-tablet are allergen extracts from Dermatophagoides pteronyssinus and Dermatophagoides farinae. The allergens are derived from aqueous buffer extraction and purification of the mite body fraction and the faecal fraction of the two species. The composition of the HDM SLIT-tablet is a 1:1 mixture of allergen extracted from the two species and the excipients gelatine (fish source), sodium hydroxide and mannitol.

The purpose of AIT is to repeatedly expose the patient to the allergen that causes the allergic symptoms, to increase the tolerance to this allergen and thereby reduce the allergic symptoms during subsequent natural allergen exposure. The HDM SLIT-tablet is a SLIT-tablet developed to treat HDM allergic disease.

The HDM SLIT-tablet is indicated for patients diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with allergic rhinitis and/or allergic asthma in adolescents (12 – 17 years of age) and adults. In North America and New Zealand, the indication includes adults 18-65 years of age and in Japan children and adults (age not specified).

The product is formulated as an oral lyophilisate for daily sublingual administration. The biological activity is expressed in SQ-HDM and the marketed dose per oral lyophilisate is 12 SQ-HDM for daily sublingual administration (1 SLIT-tablet per day). In Japan, the biological activity is expressed in Japanese Allergy Units (JAU) and the marketed doses are 3,300 JAU and 10,000 JAU (equivalent to 2 and 6 SQ-HDM). In Japan, the HDM SLIT-tablet is administered following an up-dosing regimen; 3,300 JAU is administered daily during the first week and thereafter 10,000 JAU daily. In other markets, the biological activity is expressed in SQ-HDM for daily sublingual administration and the marketed dose is 12 SQ-HDM per lyophilisate.

Approved indication(s) and population(s) being treated and studied: The approved age indication includes children, adolescents and adults (5-65 years of age) in countries in Europe and North America. In Japan, the indication includes children and adults (age not specified). In countries in Rest-of-World, the approved age indication includes adults (18-65 years of age or ≥18 years) and either adolescents (12-17 years of age) or children and adolescents (5-17 years of age). Please see section 2 for a full list of countries and Table 3 for exact wording of the approved indications by country. Populations being studied in non-interventional studies during the reporting period were children and adolescents (5-17 years of age) and adults (≥18 years of age) with allergic rhinitis and/or allergic asthma. Populations being studied in clinical trials during the reporting period were children and adolescents (5-17 years of age) and adults (≥18 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.

The International Birth date is the 23 September 2015.

1.1.2. MAH Stallergenes SAS

House dust mite (HDM) sublingual allergy immunotherapy tablet, referred to as HDM-SLIT tablet, with the tradename Actair, Orylmyte or Aitmyte, is a sublingual tablet of a mixture of allergenic materials from two different HDM species: American (Dermatophagoides farinae or D.far) and European (Dermatophagoides pteronyssinus or D.pte) allergen extracts.

The exact mechanism of action of HDM allergen extracts administered within the course of allergen immunotherapy is not yet completely known. Nonetheless, effects on both humoral and cellular immune responses have been reported consistently and likely contribute to the alleviation of symptoms in allergic disease. The underlying mechanism of action of sublingual immunotherapy is related to numbers of Antigen Presenting Cells carrying peptides derived from allergens, which stimulate resting T cells in the oral lymphoid organs. The immune system is the target for the pharmacodynamic effects of HDM SLIT TABLET. The aim is to induce an immune response against the allergens the patient is treated with.

It is indicated for treatment of moderate to severe HDM-induced Allergic Rhinitis (AR) or rhinoconjunctivitis (RC), (associated or not with intermittent asthma for Australia, New Zealand, Macau, Japan, and South Korea), in patients over 12 years in the European Union and United Kingdom (UK wide). In Australia, New Zealand, Macau and South Korea, the product is authorized in patients over 5 years. In Japan, the product is authorized with no age limit.

Marketing Authorizations have been granted for HDM SLIT TABLET in Japan 2015, Australia 2016, South Korea 2016, New Zealand 2017, United Kingdom 2021, Europe 2021 and Macau 2022.

The treatment should only be initiated by physicians experienced in the treatment of allergic diseases. The first tablet should be taken under medical supervision, and the patient should be monitored for at least 30 minutes.

HDM-SLIT tablet is available as sublingual tablets with 100 and 300 IR which refers to a specific In-House Reference Preparation. The therapy includes a 3-day dose escalation with one tablet of HDM-SLIT tablet 100 IR on Day 1 (D1), two tablets of HDM-SLIT tablet 100 IR on D2 and one tablet of HDM-SLIT tablet 300 IR on D3 continued with one tablet of HDM-SLIT tablet 300 IR per day as maintenance dose.

The strengths of 100 Index of Reactivity (IR) for the initiation treatment and 300 IR for the maintenance treatment are marketed.

Dosage forms: Sublingual tablet: The tablets of 100 IR are white to beige, round and biconvex, brown speckled, engraved "SAC" on one side and "100" on the other and the tablets of 300 IR are white to beige, round and biconvex, brown speckled, engraved "SAC" on one side and "300" on the other. Each sublingual tablet contains 100 IR or 300 IR of HDM allergen extracts from D. far and D. pte in equal parts. The activity of HDM SLIT TABLET is expressed in IR, which refers to a specific In-House Reference Preparation.

The unit IR expresses the allergenicity of Stallergenes (STG) products: an allergen extract has a concentration of 100 IR/ml when, on a Skin Prick Test (SPT) using a Stallerpoint, it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive SPT to either 9% codeine phosphate or 10 mg/ml histamine. This unit is not comparable to the units used by other allergen manufacturers.

Population being treated: The prevalence of atopic disease in general and of AR in particular has increased during the past century. AR is the most common form of non-infectious rhinitis, affecting between 10% and 30% of all adults and as many as 40% of children. The WHO has estimated that 500 million people in the world suffer from AR. Over 100 million people in Europe and North America, over 150 million in Asia-Pacific, over 100 million in India, Pakistan and surrounding countries, over 75 million

in Central and South America, over 30 million in Africa and over 50 million in other countries. Epidemiologic studies show that the prevalence of AR continues to increase worldwide. Its prevalence may vary within and among countries possibly due to geographic differences in the types and potency of different allergens and the overall aeroallergen burden.

According to the EAACI, AR affects up to 40% of the population worldwide with high variations between countries and approximately 100 million of Europeans. According to "Allergic Rhinitis and its Impact on Asthma ARIA guidelines - 2016 revision", the prevalence of confirmed AR in adults in Europe ranges from 17% to 28.5%. Onset of AR is common in childhood, adolescence and early adult years. Treatment is indicated for moderate to severe HDM-induced rhinitis or rhinoconjunctivitis associated or not with intermittent asthma for Australia, New Zealand, Japan and South Korea and Macau, in patients over 12 years in the European Union and UK wide, in patients over 5 years in Australia, New Zeeland, South Korea and Macau and with no age limit in Japan.

The International Birth date is the 26 March 2015.

1.2. Worldwide marketing authorisation status

1.2.1. MAH ALK-Abelló-A/S

During the reporting interval the following marketing authorisations were granted: Serbia on 03 November 2023, Macau on 05 September 2024 and India on 28 November 2024. A new MA was obtained in Russia on 10 November 2023, and the previous MA is no longer valid. During the period covered by this report, MAs were withdrawn for commercial reasons in Portugal on 23 January 2025 and in New Zealand on 29 July 2025. As of DLP, MA procedure was ongoing in Jordan. The HDM SLIT-tablet is currently sold in the following countries under special license: Greece; Singapore (the HDM SLIT-tablet is exempted from the regulatory controls under the Medicines Act and therefore, a product license is not required) and in specific regions of China.

During the period covered by this PSUR, an extension of the indication to include paediatric patients (5-11 years of age) was approved in Europe and North America, and several countries in the Rest-of-World.

ALK is licensor of the HDM SLIT-tablet and is the marketing authorisation holder (MAH) in several territories world-wide. Additionally, ALK has licensed the rights to serve as MAH to the following partners: Torii Pharmaceutical Co, Ltd. in Japan, Biocelect in Australia (the MA was transferred from Seqirus to Biocelect on 01 August 2025), Abbott in Malaysia, Thailand, Philippines, Singapore, Taiwan, Hong Kong, and Republic of Korea, Trupharm in Israel, and Dr. Reddy's Laboratories in India.

The first marketing authorisation for the HDM SLIT-tablet was granted on 23 September 2015 from the regulatory authorities in Denmark and this date is considered the international birth date (IBD). Since then, the HDM SLIT-tablet has been granted marketing authorisation in countries across Europe, North America, Middle East, Asia, and South Pacific.

1.2.2. MAH Stallergenes SAS

The first International MA was granted on 26 March 2015 in Japan. The first European Marketing authorization in the European Union was granted on the 9th of July 2021 in Germany.

The product is indicated for treatment of moderate to severe HDM-induced rhinitis or rhinoconjunctivitis, (associated or not with intermittent asthma for Australia, New Zealand, Macau, Japan, and South Korea), in patients over 12 years in the European Union and United Kingdom (UK wide). In Australia, New

Zealand, South Korea and Macau, the product is authorized in patients over 5 years. In Japan, the product is authorized with no age limit.

OTHER REGISTERED PRODUCTS: STALORAL HDM TABLET is marketed under NPP status in Italy since 03 October 2016. On 22 November 2019, AIFA (Italian Health Agency) considered that STALORAL HDM TABLET was not eligible for the Italian regulation process. Thus, from this date, the physicians are not allowed to initiate the product to new patients. Nevertheless, STALORAL HDM TABLET is marketed for maintenance treatments until 05 May 2025. After this date the product's commercialization is stopped.

HDM SLIT TABLET is distributed under import permit in Hong Kong and Qatar.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

1.3.1.1. MAH ALK-Abelló-A/S

During the reporting period, the following actions have been taken for safety reasons:

In relation to the recently approved indication in children Health Canada has requested ALK to provide educational material for parents / guardians of children 5-11 years old on how to recognise early signs of potential systemic allergic reactions so appropriate treatment can be initiated promptly and the impact of the reaction can be reduced. In relation to this, allergic reactions in children received from post-marketing sources in Canada will be followed up via routine pharmacovigilance activities with a specific questionnaire to collect additional information.

No changes to known risks were identified in the period.

The competent authorities in India have imposed a phase IV post-marketing surveillance study to further assess the safety of the HDM SLIT-tablet in the Indian population. ALK will update the RMP with the inclusion of this commitment study and submit to relevant competent authorities once the details of the surveillance study have been agreed.

1.3.1.2. MAH Stallergenes SAS

No action was taken for safety reason, during the reporting interval.

Four safety variations have been submitted and approved during the reporting period: in European Union: Var DE/H/4913/001-003/IB/001 - Var labelling Type IB c1z corrections post D210 submitted on 29 November 2022 and approved on 12 January 2023 to remove mannitol in the section excipients with known effect.

New Zealand: Extension of indication to the paediatric population 5-12 submitted on 29 June 2022 and approved on 06 April 2023.

Australia: Minor Editorial Changes in accordance with 9D of the ACT for changes in the Product Information PI with variation code PIME PI-Make minor editorial changes submitted 30 November 2023 and approved 10 January 2024.

South Korea: Update of Actair leaflet in South Korea following alignment to Australian leaflet and a post-marketing surveillance submitted 22 April 2025 and approved 16 July 2025.

Lead Member State assessment comment:

MAH ALK-Abelló-A/S

To note:

In Canada, education material to parents / guardians of children 5-11 years old has been implemented, to ensure recognition of early signs of potential systemic allergic reactions so appropriate treatment can be initiated promptly and the impact of the reaction can be reduced.

In India, the competent authorities have imposed a phase IV post-marketing surveillance study to further assess the safety.

MAH ALK-Abelló-A/S comment sent on 25.03.2026 and received via EMA PSUR Repository on 30.03.2026:

ALK hereby submit a comment to provide clarification regarding the Risk Management Plan (RMP) information referenced in section "3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS" in the Periodic Safety Update Report 18 (PSUR) for DE/H/1950/001/MR approved via the Mutual Recognition Procedure; for DE/H/1951/001/MR approved via the Mutual Recognition Procedure and for ACARIZAX DE/H/1947/001/DC, approved via the Decentralised Procedure; for the period 23-Sep-2022 to 22-Sep-2025. Please refer to section 1 "Response to Questions".

MAH COMMENTS TO PRELIMINARY PRAC PSUR ASSESSMENT REPORT

The MAH acknowledges the note that, in India, the national competent authority has imposed a Phase IV post marketing surveillance (PASS) study to further assess the safety of the HDM SLITtablet in the Indian population.

The MAH would like to clarify that, in accordance with Guideline on good pharmacovigilance practices (GVP), EMA/838713/2011 Rev 2, this Indian Phase IV PASS should not be included in the EU Risk Management Plan (RMP) pharmacovigilance plan (Part III). As per GVP guideline, studies required in jurisdictions outside the EU should not be included in the RMP unless they are also imposed as a condition to the EU marketing authorisation, as a specific obligation, or required by the Agency or a national competent authority. Studies not required by the EMA or a national competent authority should not be included in the pharmacovigilance plan in the RMP; this is without prejudice to safety concerns arising from such studies, which must be reported as per the applicable legislation.

Accordingly, the MAH proposes not to update the EU RMP Part III, to include the Indian Phase IV PASS.

The MAH will monitor and evaluate all safety information arising from the Indian PASS study and any safety findings of relevance to the EU benefit–risk profile will be reported via PSURs/signal management.

***Lead Member State statement**:*

The MAH ALK remark is acknowledged.

However, monitoring all safety information arising from the Indian PASS surveillance study imposed by the Indian national competent authority is highly endorsed. Furthermore, monitoring all the cases reported from this PASS surveillance study through routine pharmacovigilance and proactive periodic

signal detection is endorsed as well.

In general, the MAH is kindly reminded that as per GVP Module VII, all clinically important emerging efficacy and safety findings obtained from the clinical trials during the reporting interval, should be provided in future PSURs. In addition, the MAH should include the following information for each clinical trial: study ID, study title, study type, population studied, including country and other relevant population descriptors, study start and study status with CSR.

MAH Stallergenes SAS

To note:

In Europe, a safety variation has been submitted and approved during the reporting period: to remove mannitol in the section excipients with known effect.

In New Zeeland, a safety variation has been submitted and approved during the reporting period for extension of indication to the paediatric population 5-12.

In Australia, a safety variation has been submitted and approved during the reporting period with minor editorial changes in accordance with 9D of the ACT for changes in the Product Information PI.

In South Korea, a safety variation has been submitted and approved during the reporting period: with update of Actair leaflet following alignment to Australian leaflet and a post-marketing surveillance.

In general, during the reporting period, no actions have been taken for safety reasons that affected the risk-benefit balance of dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy.

1.3.2. Changes to reference safety information

1.3.2.1. MAH ALK-Abelló-A/S

The RSI for the HDM SLIT-tablet is the **CCSI, version 11, dated 06 August 2025**. During the reporting interval is was changed two times.

Table 1. Significant safety related changes to the RSI in the period

Reference document	Significant safety related changes
CCSI version 11 06 August 2025	Inclusion of 2 new risks to the tabulated list of adverse reactions: PT Dizziness (SOC Nervous system disorders) with frequency Uncommon PT Rash (SOC Skin and subcutaneous tissue disorders) with frequency Uncommon Both risks were identified during routine signal detection (further details available in section 15).

CCSI version 10 14 September 2023	CCSI updated with paediatric experience following finalisation of 2 paediatric clinical trials (MT-11 and MT-12). Section of paediatric population (5-11 years of age) added to section on undesirable effects.

1.3.2.2. MAH Stallergenes SAS

During the reporting interval, the Reference Safety Information (RSI) has not changed. The reference of the current document remains **CCDS Reference number: STG320_CCDS/CCSI_005-1-22 dated April 2022.**

The combined version of the Company Core Data Sheet (CCDS) and the Company Core Safety Information (CCSI) documents has not been changed.

Lead Member State assessment comment:

For one product, there have been some updates of the RSI, during the reporting period.

1.3.3. Estimated exposure and use patterns

1.3.3.1. MAH ALK-Abelló-A/S

Cumulative Subject Exposure in Clinical Trials

In ongoing and completed clinical trials **5,642 participants have been exposed to the HDM SLIT-tablet** and 3,548 to placebo.

Table 2. Cumulative participant exposure to investigational drug from completed clinical trials by age and sex

Age range	Number of participants		
	Male	Female	Total
Children (< 12 years)	724	369	1,093
Adolescents (12 - 17 years)	596	354	950
Adults (18 - 65 years)	1,672	1,907	3,597
Elderly (> 65 years)	10	10	20
Total	3,002	2,640	5,642

Data from completed trials as of 22 September 2025 Age is calculated at baseline except for the Japanese trials TO-203-1-1 TO-203-3-1 TO-203-3-2 TO-203-3-3 where age is given at screening Trials included MITI 3001 MT-01 MT-02 MT-03 MT-04 MT-06 MT-09 MT-11 MT-12 MT-16 MT-18 P001 P003 P008 P009, TO-203-1-1 TO-203-3-1 TO-203-3-2 TO-203-3-3 TO-206-4-1

Table 3. Cumulative participant exposure to investigational drug from completed trials by racial/ethnic group

Racial / ethnic group	Number of participants
American Indian or Alaska native	8
Asian	1,655
Black or African American	106
Caucasian	3,795
Native Hawaiian or other Pacific islander	1
Multiracial	52
Other	19
Unknown	6
Total	5,642

Data from completed trials as of 22 September 2025 Trials included MITI 3001 MT-01 MT-02 MT-03 MT-04 MT-06 MT-09 MT-11 MT-12 MT-16 MT-18 P001 P003 P008 P009 TO-203-1-1 TO-203-3-1 TO-203-3-2 TO-203-3-3 TO-206-4-1

Two clinical trials (MT-11 and MT-12) were completed in the period, both of which confirmed the existing safety profile for the HDM SLIT-tablet for children and adolescents.

One clinical trial in Chinese subjects (MT-16) was prematurely terminated due to the impact of the corona-virus pandemic starting in 2019.

At DLP, one clinical trial (MT-21) was ongoing with the purpose of investigating efficacy and safety in a Chinese population (12-65 years of age). The clinical trial had first participant first visit (FPFV) on 01 September 2025. During the reporting period, four non-interventional studies were completed or closed. At DLP, three non-interventional studies were ongoing.

Cumulative and Interval Patient Exposure from Marketing Experience

Post-marketing patient exposure is based on sales figures and presented as treatment years TYs. The number of TYs is defined as the theoretical number of patients who could have been treated for 1 year provided that each patient used the product in a standard manner 1 SLIT-tablet per day. Each TY corresponds to 365 SLIT-tablets.

Sales data is available as number of sold or distributed packages. The estimated post-marketing exposure from packages sold / distributed in the reporting period is 876,381 TYs. The estimated **cumulative post-marketing exposure is 1,543,089 TYs**.

Table 4. Estimated periodic and cumulative exposure* from marketing experience

Region	Dose	Periodic exposure (TY)	Cumulative exposure (TY)
Europe	12 SQ-HDM	257,831	543,641
North America	12 SQ-HDM	33,127	62,711

Rest of World			
Australia & New Zealand	12 SQ-HDM	4,438	12,384
Asia (incl. Middle Eastern countries, excl. Japan)	12 SQ-HDM	26,083	36,468
Japan	2 SQ-HDM	8,912	20,866
Japan	6 SQ-HDM	545,990	867,019
Total		876,381	1,543,089

Please note, due to ongoing maintenance of the sales database, as well as differences in method of stratifying data, there can be minor variations in number of TYs compared to previous periodic reports *Data cut off 31 August 2025 sales data only available for full months Periodic exposure covers 01 September 2022 to 31 August 2025 Cumulative exposure covers 01 September 2015 to 31 August 2025 TY treatment years

Post-authorisation use in special populations

It is not possible to obtain information on demographics based on the sales / distribution numbers.

Relevant information on special populations available from post-marketing use, including spontaneous reporting of ADRs, is presented below. Review of available information did not reveal any new significant safety information.

Age groups

Exposure is estimated by using the assumption that all patients report ADRs with the same frequency irrespectively of age, and that the ADR reporting rate for each age group resembles the exposure rate for each age group.

It should be noted that data from spontaneous reporting of ADRs have limitations that should be considered. Most important is the reporting bias which can be associated with years on the market higher reporting frequency in the first year, age and gender of the patient e.g., higher reporting rates for children compared to adults and for women compared to men, and differences in reporting practices between countries. Furthermore, studies have suggested that the reporting rate of serious ADRs is higher than non-serious ADRs.

Table 5. Estimated cumulative exposure from marketing experience by age group based on reported ADRs

	Children (<12 years*)	Adolescents (12-17 years)	Adults (18-65 years)	Elderly (>65 years)	Unknown
Proportion of cases (%)	23.9	18.9	43.1	1.4	12.7
Exposure (TY)	368,319	291,313	665,555	21,367	196,535

* 3 cases reported for children <5 years of age

Paediatric population

During the reporting period, **1,040 of the 2,197 cases received from post-marketing data sources were in paediatric patients ≤17 years of age.**

Based on the crude estimate for cumulative ADR reporting by age group, **42.8% of all reported cases concerned children and adolescents**, **corresponding to an estimated cumulative exposure of 659,632 TYs.**

Elderly population

During the reporting period, **31 of the 2,197 cases** received from post-marketing data sources **were in elderly patients ≥65 years of age**.

Based on the crude estimate for cumulative ADR reporting by age group, **1.4% of cases concerned elderly patients corresponding to an estimated cumulative exposure of 21,367 TY**.

Reports of pregnancy exposure

During the reporting period, **33 of the 2,197 cases** received from post-marketing data sources **were related to maternal exposure during pregnancy**.

Other post-authorisation use

Off-label use

During the reporting period, **224 of 2,197 cases related to off-label use** were received from post-marketing data sources. Most cases concerned off label use in unapproved age group children or elderly, or fractional dose administered by splitting tablets.

No safety issues were identified from cases of off-label use.

Overdose, abuse and misuse

During the reporting period, **22 of 2,197 cases related to overdose, abuse or misuse** were received from post-marketing data sources, none of them being significant to treatment with the HDM SLIT-tablet.

Use beyond the recommendations

Use beyond the recommendations from post-marketing data sources are captured as medication errors and evaluated in section: Medication errors.

Lead Member State assessment comment:

MAH ALK-Abelló-A/S

Cumulative Subject Exposure in Clinical Trials

In the clinical trial program for the product dermatophagoides pteronyssinus / dermatophagoides farina (ongoing and closed) a total of 5,642 participants has been exposed to the IMP and 3,548 participants to placebo.

To note: Two clinical trials MT-11 and MT-12 were completed in the reporting period: One clinical trial in Chinese subjects MT-16 was prematurely terminated due to the impact of the corona-virus pandemic starting in 2019 and One clinical trial MT-21 was ongoing with the purpose of investigating efficacy and safety in a Chinese population 12-65 years of age.

Cumulative and Interval Patient Exposure from Marketing Experience

The post-marketing exposure, during the current reporting period was 876,381 treatment years, whereof 257,831 in Europe and cumulatively 1,543,089 treatment years, whereof 543,641 in Europe.

In general, analysis of post-marketing use in special population and of cases of off-label use, overdose and misuse identified no safety concern.

1.3.3.2. MAH Stallergenes SAS

Cumulative Subject Exposure in Clinical Trials

Overall, since the DIBD, **5,035 subjects were exposed to HDM SLIT TABLET** at different dosages or placebo in the clinical development program: 4,446 in the rhinitis program and 589 in the asthma program. A total of 3,007 patients were exposed to HDM SLIT TABLET at different dosages, whereof 2,590 in the rhinitis program and 417 in the asthma program. A total of 1,914 subjects were exposed to HDM SLIT TABLET at the 300 IR dose: whereof, 1,845 in the rhinitis program: 1,151 adults, 426 adolescents and 268 children and 69 in the asthma program: 14 adults, 14 adolescents and 41 children.

Table 6. Summary of subjects' exposure in completed clinical studies

Treatment	Exposed subjects, n	
RHINITIS PROGRAM		
HDM SLIT TABLET / (300 IR)	Adults	1,804 / 1,151 [a]
Placebo		1,174
HDM SLIT TABLET / (300 IR)	Adolescents	516 / 426 [a]
Placebo		424
HDM SLIT TABLET / (300 IR)	Children	270 / 268 [a]
Placebo		258
Subtotal in the rhinitis program	4,446	
ASTHMA PROGRAM		
HDM SLIT TABLET / (300 IR)	Adults	362 / 14 [a]
Placebo		116
HDM SLIT TABLET / (300 IR)	Adolescents	14 / 14 [a]
Placebo		13
HDM SLIT TABLET / (300 IR)	Children	41 / 41 [a]
Placebo		43
Subtotal in the rhinitis program	589	

Total	5,035
Subtotal HDM SLIT TABLET	3,007
Subtotal HDM SLIT TABLET 300 IR	1,914A

[a] Figures presented within parentheses represent the numbers of subjects exposed to HDM SLIT TABLET 300 IR

Cumulative and Interval Patient Exposure from Marketing Experience

To date, the methodology to determine these estimates is based on sales figures and treatment regimen which is composed of preferentially an initiation phase with a 3-day dose escalation one 100 IR tablet on D1, two 100 IR tablets on D2, and one 300 IR tablet on D3 and a maintenance phase with one 300 IR tablet per day until the end of treatment. Hence, theoretically, one new patient is to take three 100 IR tablets.

From the worldwide marketing experience, **the estimated number of patients exposed to HDM SLIT** TABLET since the first MA on 26 March 2015 **is 791,774 patients**.

During the period covered by this PBRER, it was estimated that a total of 556,415 patients has been exposed to HDM SLIT TABLET.

POST-AUTHORISATION USES IN SPECIAL POPULATIONS

Since the initial granting of the marketing authorisation in Japan on 26 March 2015, exposure per age group is not available for this product in the Territories outside EU where the product is marketed.

Regarding EU territory, exposure per age group is available for Germany which was the first country where HDM SLIT TABLET was sold after first European Authorisation was obtained for the product.

Table 7. Percentage of sales per age group in Germany from 1er September 2021 to 30th September 2025

Age group	0–4 year old	5–11 year-old	12–17 year-old	18–64 year-old	> 65 year-old	other
Percentage of sales HDM SLIT TABLET	0.02%	2.11%	13.38%	81.95%	2.35%	0.19%

PAEDIATRIC

Interval period children <18 years: **A total of 374 cases of children and adolescents <18 years have been retrieved** among a total of 908 cases during the reporting interval. **38 cases were serious**.

Cumulative period children <18 years: A total of 1,157 cases of children <18 years among 2,553 cases have been retrieved. 74 ICSRs were serious which represents 6.4%.

Cases with associated events were mainly involving gastrointestinal symptoms, including the PTs Oedema mouth 161 events, Oral pruritus 156 events, Abdominal pain 118 events, Nausea 92 events, vomiting 78 events, Lip oedema 55 events, Oral discomfort 52 events, Tongue oedema 42 events, Oropharyngeal discomfort 34 events, Paraesthesia oral 32 events; as well as respiratory symptoms, including the PT Throat irritation 147 events, Dyspnoea 61 events, Pharyngeal oedema 33 events.

All of these PTs are listed in the CCSI for HDM SLIT TABLET.

Among these 74 serious cases: Five cases 201502263, 201800942, 201901659, 202200338 and 2025-AER-02688 involving severe laryngopharyngeal reactions have been analysed and discussed in section: ´Severe laryngopharyngeal reactions`

Twenty cases 201600347, 201600380, 201800922, 201801495, 201801527, 201901715, 202201259, 202201978, 202301314, 202301666, 2023-AER-02723, 2024- AER-00253, 2024-AER-01940, 2024-AER-02384, 2024-AER-02702, 2025-AER- 00935, 2025-AER-01128, 2025-AER-01180, 2025-AER-01241, 2025-AER-01942 involving anaphylactic reaction, and one case 202301809 involving anaphylactic shock have been analysed and discussed in section: ´Anaphylactic reaction including anaphylactic shock`

Two cases 202201630, 2025-AER-00522 involving Eosinophilic oesophagitis have been analysed and discussed in section: ´Eosinophilic oesophagitis`; Two cases 201901440, 202300747 involving autoimmune disorder have been analysed and discussed in section: ´Autoimmune disorders`

The review of these cases did not reveal any new significant safety information on the use of HDM SLIT TABLET in patients under 18 years old.

Interval period children <12 years: **A total of 220 cases of children <12 years have been retrieved**, out of which **thirteen were serious**:

A total of 105 cases 47.7% in patients ≥5 years old; 113 cases 51.4% in children of unknown age and two cases in patients below the age of 5 one patient aged of 2-year-old; one patient aged of 3-year-old 0,9%

A total of 197 88% of these cases occurred in Japan and Australia, where the granting of MA in children is approved. The remaining cases occurred in Austria, Czechia, Slovenia, Spain one case each, France ten cases, Germany seven cases and Romania two cases where MA is approved only for adolescent and adult patients. Therefore, **the cases reported in Europe represent off-label use in paediatric patients**.

Cumulative period children <12 years: A total of 578 cases of children <12 years have been retrieved; among them 27 cases were serious.

The review of these cases did not reveal any new significant safety information on the use of HDM SLIT TABLET in patients under 12 years old.

Interval and cumulative period children <5 years: During the interval period of this report, **two cases were reported in a patient less than 5 years of age.** Cumulatively, four non-serious cases were reported in patients aged less than 5-year-old.

Three cases occurred in Japan, where there is no age limit for administration of HDM SLIT TABLET, and **one case occurred in Germany, which concerned an accidental overdose**.

The first case 201801339: described a 3-year-old male patient who experienced a nonserious adverse reaction of aggravated asthma after receiving HDM SLIT TABLET for AR. Considering the limited information provided for this case, the causal relationship between HDM SLIT TABLET and asthma aggravation was assessed as possible.

The second case 202101276: described a 4-year-old male patient who experienced a non-serious adverse reaction of generalised eczema when HDM SLIT TABLET was started. Dosage administered was 100 IR daily. Symptoms were stable and patients recovered. Considering the limited information provided for this case, the causal relationship between HDM SLIT TABLET and eczema was assessed as possible.

The third case 202300319; Germany: described a 2-year-old female child who developed redness of both cheeks after accidentally taking 4 doses of 300 IR of HDM SLIT TABLET from her mother's treatment. It was reported that exsiccosis and probably redness of both cheeks were pre-existing. The outcome was unknown despite follow-ups attempts. Considering the known safety profile of HDM SLIT and the

compatible chronology, the causal relationship between HDM SLIT TABLET and redness of face was assessed as possible.

The fourth case 202301423: described a 3-year-old male patient who presented with a strange sensation in the mouth after HDM SLIT TABLET was started. Dosage administered was 100 IR daily. Few days later, the patient presented with acute upper respiratory tract infection, mild redness of pharynx, pharyngodynia, pyrexia and cough, treated by tipepidine hibenzate and L-carbocisteine. HDM SLIT TABLET was continued with dosage of 100 IR daily. The patient recovered from acute upper respiratory tract infection and associated symptoms and was recovering from Oral discomfort. Based on available information, the causal relationship was assessed as possible for Oral discomfort. Considering the known safety profile of HDM SLIT TABLET, nature of events (infectious aetiology), the causal role was assessed as unlikely for Upper respiratory tract infection, Pyrexia, Oropharyngeal pain, Cough, Pharyngeal erythema.

The review of these cases did not reveal any new significant safety information on the use of HDM SLIT TABLET in patients under 5 years old.

ELDERLY ≥65 YEARS

Interval period Elderly ≥ 65 years: During the reporting period**, twelve cases have been reported in elderly patients**: **one serious** and eleven non-serious.

Serious case 202301259: This case described a 65-year-old female patient, with medical history of controlled allergic asthma and bronchitis, who experienced lump or swelling in the throat 12 days after HDM SLIT TABLET initiation, and treated with bilastine tablet. The patient also presented with Quincke's oedema. At the time of the report, HDM SLIT TABLET discontinued and the patient recovered.

Therefore, with available data, considering the plausible chronology and the known product profile, the causal relationship between HDM SLIT TABLET and the events, Angioedema and Pharyngeal oedema, was assessed as possible.

The review of the other non-serious cases did not reveal any new significant safety information on the use of HDM SLIT TABLET in patients ≥ 65 years old.

In this context, no new risk or signal have been identified for this population during the interval period.

Cumulative period Elderly ≥ 65 years: A total of 25 cases of elderly patients ≥ 65 years have been retrieved, two were reported as serious and 23 as non-serious. The review of these cases did not reveal any new significant safety information on the use of HDM SLIT TABLET in patients ≥ 65 years old.

OTHER POST-AUTHORISATION USES

OFF LABEL USE

A search of all cases of use beyond recommendations received and registered in the Database using the HLT "Off label uses" and the Preferred Terms "Drug effective for unapproved indication" and "Therapeutic product effective for unapproved indication" has been performed.

A total of 45 cases of off label use associated with the intake of HDM SLIT TABLET have been retrieved during the interval period. Among them, **five cases were serious**.

Overall and since the first marketing of HDM SLIT TABLET, a total of 107 cases has been reported and eleven of them were serious.

Case 201701822: serious hospitalization, spontaneous and not medically confirmed case described a 5-year-old female patient from Italy, treated with HDM SLIT TABLET for mite allergy. HDM SLIT TABLET was

prescribed to a child patient under 12 years old Off label use in unapproved age group. The patient was treated with STALORAL mite sublingual solution before initiating HDM SLIT TABLET. Around 15 minutes after intake of HDM SLIT TABLET 300 IR, patient the patient experienced abdominal pain, vomiting and lip oedema. On the same day, the patient went to the Emergency Room and treated with 1 tablet of Bentelan betamethasone 1 mg and 1 antihistamine, at dosage unknown, by intravenous route. The patient was hospitalized, for observation for 2 days. Treatment was discontinued and patient recovered.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 201801495: serious medically important condition, spontaneous and medically confirmed report, described a 13-year-old male patient from Australia with HDM allergy treated for two and a half years with HDM SLIT TABLET off label use in this territory at the time of reporting due to the initiation of HDM SLIT TABLET before 12 years of age. On 18 September 2018, the patient was given an evening meal of prawn pizza several hours after HDM SLIT TABLET intake. 1 hour after dinner, the patient's mother who was a registered nurse, reported that her son experienced an acute anaphylactic reaction involving the following symptoms: abdominal cramps, hives all over his body neck to ankles, some as large as 10 cm in diameter, swollen lips, itchy throat. The symptoms did not resolve with one Zyrtec cetirizine dihydrochloride. Thus, the patient was conducted to an emergency department where 3-4 oral antihistamines and prednisolone were given. The patient partially recovered from his adverse reactions. A total recovery was obtained after adrenaline injection. The patient was kept in the hospital overnight (< 24 hours) for monitoring then he discharged in the morning and continued HDM SLIT TABLET without any change. As the patient has eaten for many times prawns and other seafood with no allergic reaction, the mother suspected after some literature search that HDM SLIT TABLET could be linked to the development of an allergy to seafood.

This case has been analysed and discussed in section: ´Anaphylactic reaction including anaphylactic shock`.

Case 201901040: serious medically important condition, spontaneous and medically confirmed case described a 54-year-old male patient from Australia, treated with HDM SLIT TABLET for allergic rhinoconjunctivitis. His prescribed protocol was to initiate the dose increase slowly 100 IR over 20 days, then 200 IR over 20 days then eventually 300 IR which corresponds to an off-label use in this territory, with daily concomitant use of antihistamines. During the 3rd day of taking HDM SLIT TABLET at 300 IR, the patient developed right facial angioedema, painless not itchy, that resolved spontaneously over a few days. The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 202000373: serious hospitalisation, spontaneous and medically confirmed case described an 8-year-old male patient from Italy, treated with HDM SLIT TABLET for mite allergy. HDM SLIT TABLET was prescribed to a child patient under 12 years old Off label use in unapproved age group. The patient initiated HDM SLIT TABLET with 1 tablet of 100 IR on the first day, 2 tablets of 100 IR on the second day and 1 tablet of 300 IR on the third day. The therapy continued with 1 tablet of 300 IR twice a week Off label dosing frequency. On day 12 of HDM SLIT TABLET treatment, and 3 hours after intake of HDM SLIT TABLET 300 IR, the patient experienced lipothymia with hypotension. The reactions resolved after few minutes. The physician specified that the patient was hospitalized after the resolution of the adverse reactions and discharged after four days. The patient was not treated with any corrective medication. Treatment was discontinued and patient recovered.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 202000643: serious medically important condition, spontaneous and not medically confirmed case described an adolescent patient exact age unknown from Italy, treated with HDM SLIT TABLET for asthma. HDM SLIT TABLET was prescribed whereas patient has severe asthma, which corresponds to an off-label use. Around 10 minutes after intake of HDM SLIT TABLET, patient presented with dyspnoea, suffocation feeling and burning throat. Treatment was discontinued and patient recovered.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 202101150: serious hospitalisation, solicited, health authority and medically confirmed case described a 10-year-old male patient from Italy, treated with HDM SLIT TABLET for mite allergy. HDM SLIT TABLET was prescribed to a child patient under 12 years old Off label use in unapproved age group. On the first day of HDM SLIT TABLET treatment, the patient experienced epigastralgia. The seriousness of the case was updated to serious since the reporter's comment states that the patient was discharged from the emergency room. it implies an admission to the hospital. As corrective treatment, the patient received pantoprazole tablet 40 mg twice/day for 20 days, macrogol 4000 Onligol at unknown dose via unspecified route, paracetamol Tachipirina via oral route and ibuprofen via unspecified route at an unknown dose. Treatment was discontinued and patient was recovering.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 2024-AER-00887: serious medically important condition spontaneous and not medically confirmed case described a 16-year-old female patient from Spain, treated with HDM SLIT TABLET for mite allergic rhinitis. HDM SLIT TABLET was initiated with 1 tablet per day of 100 IR for 1 month. The patient experienced stomach-ache when swallowing the tablet. Therefore, the physician advised the patient to put the tablets under the tongue until they were almost dissolved and then spit them out off-label use. The patient reached maintenance dose at 1 tablet of 300 IR. Around 4 months after HDM SLIT TABLET start; while eating, the patient choked on food. The Heimlich manoeuvre was performed, after which the patient vomited some liquid, began breathing better, then vomited extensively, stopped choking, and recovered. The patient was taken to the hospital the same day, where an X-ray revealed a clean tract. Eosinophilic oesophagitis was suspected, and a gastroscopy was proposed by the gastroenterologist; however, the procedure was cancelled because the incident was considered isolated and the patient declined. Consequently, eosinophilic oesophagitis could not be confirmed. The patient was not expected to resume treatment with HDM SLIT TABLET and recovered.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 2024-AER-02384: serious medically important, caused-prolonged hospitalization, life threatening spontaneous and medically confirmed case described a 9-year-old male patient from Germany, who developed anaphylaxis grade III with cough specified as barking, hoarseness of voice, dyspnoea and stridor, at day 14 of HDM SLIT TABLET treatment and 10 minutes after HDM SLIT TABLET 300IR administration. Of note, the physician specified that the patient 9 years old chewed and sucked on the tablet Off label use in unapproved age group and medication error. The patient was treated with epinephrine inhalation, salbutamol inhalation, 300 µg of epinephrine via IM route, 4 mg of dimetindene maleate via IV route and 100 mg of prednisolone suppository Rectodelt. The patient was hospitalized. The anaphylaxis lasted for 1 hour. The patient stayed for one night in hospital for monitoring and left the next day without problems. The patient recovered and HDM SLIT TABLET treatment was discontinued on the same day. Based on available information prescription to a 9-year-old patient who chewed and sucked on the tablet: child younger than 12 years; off label use; medication error, the triggering of anaphylaxis as a consequence of the medication error/off label use could not be completely excluded.

This case has been analysed and discussed in section: ´Anaphylactic reaction including anaphylactic shock`.

Case 2025-AER-01241: serious medically important spontaneous and medically confirmed case described an 11-year-old male patient from Spain. HDM SLIT TABLET was prescribed to a child patient under 12 years old Off label use in unapproved age group. The patient experienced an anaphylaxis with symptoms of lip and sublingual oedema, bronchospasm and rhino conjunctivitis during day 13 of HDM SLIT TABLET treatment. It was unknown whether the patient was treated with epinephrine, intravenous fluids, parenteral corticosteroids or antihistamines and inhaled beta agonists. The patient recovered and HDM SLIT TABLET treatment was discontinued on the same day. The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

This case has been analysed and discussed in section: `Anaphylactic reaction including anaphylactic shock`.

Case 2025-AER-02660: serious medically important, hospitalization spontaneous and not medically confirmed case described an adult female patient from Australia, who started to experience stomach cramps while taking HDM SLIT TABLET at 300 IR dose. The physician advised the patient to continue treatment and to not swallow the tablet after holding under her tongue i.e., spit them out; off label use. The patient persisted until the tenth day of treatment but discontinued as the stomach cramps continued. After treatment withdrawal, the patient reported having lower gastrointestinal issues and had been admitted to hospital three times with intractable constipation, requiring colonic irrigation. The gastroenterologist diagnosed her with ileus. Colonoscopy was performed without any visible cause of the problem.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

Case 2025-AER-02688: serious life threatening, hospitalization, medically important spontaneous, health authority and medically confirmed case described an 11-year-old male patient from Czechia. HDM SLIT TABLET was prescribed to a child patient under 12 years old Off label use in unapproved age group. The patient experienced an incipient laryngospasm, conjunctivitis, dyspnoea, swelling of the lips and tongue swelling. The events occurred at day 4 of HDM SLIT TABLET treatment and around 5 minutes after administration of HDM SLIT TABLET 300 IR. This authority case was reported as Life Threatening and hospitalization no details provided. It was unknown if the patient received corrective treatments. Drug was discontinued the same day. The patient was recovering at the time of the report.

The causality between the off-label use described in this case and HDM SLIT TABLET was assessed as not applicable.

This case has been analysed and discussed in section: `Severe laryngopharyngeal reactions`.

MAH Conclusion: From the analysis of these data, no signal or risk has been identified. Off label use is not considered as a safety concern with HDM SLIT TABLET.

OVERDOSE

A search for all cases of overdose received and registered in the Database with HDM SLIT TABLET using the HLT "Overdoses NEC" and the PTs "Extra dose administered" and "Accidental overdose" has been performed. Extra dose is defined as the administration of a dose higher than prescribed but less or equal to the maximum recommended dose in the RSI document.

Interval Period: **A total of one case** has been retrieved.

One case 202300319: of accidental overdose has been retrieved with HDM SLIT TABLET during the reference period of this report. This case is **non-serious** and medically confirmed.

A 2-year-old female child who accidentally took the treatment of her mother with four tablets of 300 IR (1200 IR). The child experienced redness of both cheeks. It was reported that exsiccosis and probably redness of both cheeks were pre-existing. Outcome was unknown despite follow-ups attempts.

Cumulative Period: Six non-serious cases of overdose have been retrieved with HDM SLIT TABLET.

Case 202100976: of accidental overdose initiation with 300 IR instead of 100IR, where patient experienced oedema mouth and malaise.

Case 202200214: of accidental overdose initiation with 600 IR instead of 300 IR, where patient experienced oral discomfort.

Case 202300319: described above, of accidental overdose the child accidentally ingested four 300 IR tablets from her mother's treatment, where the child developed redness of both cheeks.

Three cases with no reported adverse reactions

Case 201601312: in a 12-year-old male patient who took 3 tablets of HDM SLIT TABLET 300 IR.

Case 201801446: in a patient of unknown age and gender who experienced prescribed overdose 2 tablets of HDM SLIT TABLET 300 IR).

Case 201801496: in a patient of unknown age and gender who experienced prescribed overdose 2 dosage forms of HDM SLIT TABLET 300 IR.

MAH Conclusion: From the analysis of these data, no signal or risk has been identified. Overdose is not considered as a safety concern with HDM SLIT TABLET.

ABUSE

A search for all cases of abuse received and registered in the Database with HDM SLIT TABLET using the PT "Intentional product use issue" and PT "Intentional overdose" has been performed. The query used to retrieve the cases of abuse has been revised compared to previous PBRER. The SMQ "Drug abuse and dependence" was removed because it included misuses and overdoses, which are already addressed by dedicated queries for those topics. The search was therefore restricted to specific PTs to accurately characterize cases of abuse only.

Interval period: **A total of 27 cases** were identified through the query. All cases were reported by the Japanese partner and were associated with the PT 'Intentional product use issue'. No cases of 'Intentional overdose' were retrieved. These cases correspond to misuse and are discussed in the dedicated section below.

Therefore, no cases of abuse related to the use of HDM SLIT TABLET have been reported.

Cumulative period: A total of 65 cases were identified through the query. All cases were reported by the Japanese partner and were associated with the PT 'Intentional product use issue.' No cases of 'Intentional overdose' were retrieved. These cases correspond to misuse and are discussed in the dedicated section below.

Therefore, no cases of abuse related to the use of HDM SLIT TABLET have been reported.

MAH Conclusion: No signal or risk of abuse with HDM SLIT TABLET has been identified from post marketing experience. Abuse of HDM SLIT TABLET is not considered as a safety concern.

MISUSE

A search for all cases of misuse received and registered in the Database with HDM SLIT TABLET using the HLTs: "Intentional product use issues", "Intentional product misuses" and "Underdoses NEC" has been performed. The query used to identify misuse cases has been updated compared to previous PBRER. Specifically: The HLGT "Overdoses and underdoses NEC" has been replaced by HLT "Underdoses (NEC)" as overdose cases are already addressed in the "Overdose" section under the HLT of "Overdoses NEC". The PT "Poisoning deliberate" has been removed from the query, as it does not align with the definition of misuse.

Interval period: **A total of 30 cases** has been retrieved, whereof **one was serious**.

All cases were reported by the Japanese partner and were associated with the PT "Intentional product use issue" 27 cases or "Intentional product misuse" three cases.

Cases which included associated events mainly described gastrointestinal symptoms, including the PTs Abdominal discomfort, Diarrhoea, Oedema mouth, Oral pruritus, Stomatitis, Vomiting; as well as respiratory symptoms, including the PTs Dysphonia, Laryngeal discomfort, Oropharyngeal discomfort, Pharyngeal oedema, Rhinorrhoea, Throat irritation; all of which are listed in the CCSI for HDM SLIT TABLET.

Serious case 202202154: occurred in a 9-year-old female patient after administration of ACTAIR. The patient had several allergies, for which she was taking ACTAIR and other concomitants or past medications loratadine, levocetirizine, montelukast, cryptomeria japonica pollen, miticure. The patient initiated ACTAIR and experienced on the next day vomiting, sensation of block in ear and deafness. These events were resolved on the same day. Two days after ACTAIR start, the patient experienced diarrhoea and inappetence. These adverse events were resolved on the same day. In consultation with the reported physician over the phone, it was determined that the patient resumed ACTAIR treatment at the dose of 100 IR per day by spit method intentional product use issue. No adverse event was reported in association with the intentional product use issue.

The reported misuses in other cases are: initiation with maintenance dose of 300 IR daily eleven cases, use of spit-method ten cases, patient did not take the entire tablet but a quarter or a half of the tablet five cases, patient swallowed tablet before completely dissolved two cases, initiation with dose of 200 IR daily one case, increase dose from 100 IR to 300 IR one case and patient swallowed tablet with chewing one case.

Cumulative period: A total of 113 cases has been retrieved. **Four of them were serious** seriousness criteria: medically important condition for three of them and hospitalization for one, all of them involving the use of a spit-out method of administration:

Case 201701509: a 43-year-old female patient received ACTAIR and experienced abdominal pain and oesophageal stenosis. The administration of ACTAIR was switched to spit out method. Events resolved following the switch to this spit-out method of administration, and no further adverse events were reported.

Case 202000704: a 6-year-old male patient received ACTAIR by sublingual-spit method. The patient experienced hoarseness and tightness of throat one day after the switch to sublingual-spit method, then the events resolved the day after their onset whereas patient continued to use sublingual-spit method. The events also occurred the same day as the increase of ACTAIR dosage. As the events did not reoccur during the treatment while misuse practice was maintained, t the role of the misuse towards the adverse events reported cannot be assessed.

Case 202201161: a 62-year-old male patient was treated with ACTAIR by sublingual spit method misuse method. Around 1 month after initiation, patient presented with diarrhoea and stomatitis. The patient presented with enterocolitis and was hospitalized due to this event. Patient was recovering from enterocolitis after interruption of all his treatments. ACTAIR was reintroduced at the dosage of 300 IR and diarrhoea reoccurred. Diarrhoea persisted at the dosage of 300IR but resolved when dosage was decreased at 2 doses of 100 IR daily. The reporter assessed the causal relationship between ACTAIR and enterocolitis as Probable. The company assessed the causal relationship as Possible. Enterocolitis is not listed in ACTAIR CCSI, but symptoms observed in this case report such as diarrhoea and stomatitis are listed events. Moreover, gastroenteritis is also a listed event in ACTAIR CCSI. In this context, no further action has been performed.

Case 202202154: a 9-year-old female patient was treated with ACTAIR. The patient had several allergies, for which she was taking ACTAIR and other concomitants or past medications loratadine, levocetirizine, montelukast, cryptomeria japonica pollen and miticure. The patient initiated ACTAIR and experienced vomiting the next day, sensation of block in ear and deafness. These events were resolved on the same day. Two days after ACTAIR started, the patient experienced diarrhoea and inappetence. These adverse events were resolved on the same day. In consultation with the reported physician over the phone, it was determined the patient resumed ACTAIR treatment at the dose of 100 IR per day by spit method intentional product use. No adverse event was reported in association with the intentional product use.

MAH Conclusion: From the review of these cases, no signal or identified risk resulting from misuse has been identified from the post marketing experience of HDM SLIT TABLET. Misuse of HDM SLIT TABLET is not considered as a safety concern.

Lead Member State assessment comment:

Cumulative Subject Exposure in Clinical Trials

A total of 5,035 subjects were exposed to IMP (3,007) or placebo (2,028) in the clinical development program for the product dermatophagoides pteronyssinus / dermatophagoides farina.

Cumulative and Interval Patient Exposure from Marketing Experience

Cumulatively, the estimated number of patients is 791,774 patients, and during the reporting interval a total of 556,415 patients.

In general, analysis of post-marketing use in special population and of cases of off-label use, overdose and misuse identified no safety concern.

1.3.4. Data in summary tabulations

1.3.4.1. MAH ALK-Abelló-A/S

Cumulative summary tabulations of serious adverse events from Clinical trials

A total of 225 treatment-emergent SAEs has been reported from the DIBD to the DLP; 135 of these SAEs were observed in the active treatment group of 5,642 participants exposed to the HDM SLIT-tablet and 90 SAEs were observed in the placebo group of 3,548 participants.

Of the 135 SAEs reported on active treatment, **39 SAEs concerned children and adolescents 5-17 years of age, 92 SAEs concerned adults 18-65 years, and 4 SAEs concerned elderly patients >65 years**.

Cumulatively, eleven SAEs from completed clinical trials were assessed as possibly related either by the investigator or the MAH. Three of the eleven related SAEs PTs oral pain, oral pruritus and throat irritation were reported by adult participants in the clinical trial P001 and were categorised as serious due to protocol defined criteria as the events were reported in connection with overdose protocol defined; the participants took more than 1 HDM SLIT-tablet on the day of the event. Seven of the eleven SAEs considered possibly related to HDM SLIT-tablet were reported for adults and included the PTs for the following trials: MT-02: PTs migraine and dizziness; MT-04: PTs asthma, laryngeal oedema, and arthralgia; MT-06: PT immune thrombocytopenia; and MT-09: PT pharyngeal oedema. One of the eleven related SAEs were reported for a child in MT-11: PT Eosinophilic esophagitis.

None of the SAEs reported with adolescents or elderly patients were assessed as possibly related to IMP.

Cumulative and interval summary tabulations from post-marketing data sources

A total of 7,294 cases with 17,710 ADRs have been reported cumulatively. In the **reporting interval, 2,197 cases with 5,179 ADRs** have been reported.

Cumulatively, **3,118 cases concern children and adolescents <18 years, 3,146 cases concern adults 18-65 years, 101 cases concern elderly patients >65 years**. Age group was unknown in 929 cases.

MAH note: in previous PSURs, the summary tabulations from post-marketing data sources in Appendix 2 included double unlikely AEs if these were included in an overall possibly related case. As of this PSUR, double unlikely AEs are no longer part of the summary tabulations from post-marketing data sources in Appendix 2, in compliance with EMA GVP module VII on PSUR and ICH guideline E2C R2 on PBRER. The term 'double unlikely AEs' is used by the MAH when the causality of a spontaneously reported AE is specifically stated by the reporter to be unrelated to the product unlikely related and where the MAH concurs with this assessment unlikely related.

Member State assessment comment:

MAH ALK-Abelló-A/S

Cumulative summary tabulations of serious adverse events from clinical trials

In clinical trials, there were 225 SAEs reported cumulatively, whereof, 135 SAEs in patients receiving the IMP and 90 SAEs in the placebo group.

Cumulative and interval summary tabulations from post-marketing sources

The MAH presented the Cumulative and interval summary tabulations of all Adverse Drug Reactions (ADRs) from post marketing data sources are presented in Appendix 2.

In the post-marketing experience, there were 374 SAEs during the current reporting interval and 1,421 SEAs cumulatively, retrieved.

Table 8. Reactions of interest (serious event PT) from post-marketing data sources

Event PT	Interval	Cumulative
Immune system disorders	**66**	**190**
Anaphylactic reaction	45	132
Anaphylactic shock	9	20
Anaphylactoid reaction	6	13
Hypersensitivity	4	22
Type I hypersensitivity	1	1
Nervous system disorders	**17**	**47**
Multiple sclerosis	2	2
Presyncope	1	1
Respiratory, thoracic and mediastinal disorders	**74**	**367**
Asthma	6	14
Asthmatic crisis	3	8
Choking sensation	1	2
Laryngeal oedema	11	33
Pharyngeal oedema	1	9
Pharyngeal swelling	9	34
Gastrointestinal disorders	**91**	**388**
Eosinophilic oesophagitis	6	9
Swollen tongue	11	49
Tongue oedema	1	9
Skin and subcutaneous tissue disorders	**32**	**109**
Angioedema	14	47
Erythema	1	8
Pruritus	5	16
Rash	2	9
Pregnancy, puerperium and perinatal conditions	**1**	**4**
Abortion threatened	1	1
General disorders and administration site conditions	**31**	**122**
Chronic fatigue syndrome	1	1
Fatigue	1	5
Malaise	3	11
Grand Total	**374**	**1,421**

In general, no new important safety information is identified, and no safety concern was identified from Data in summary tabulations for the product dermatophagoides pteronyssinus / dermatophagoides farina.

1.3.4.2. MAH Stallergenes SAS

Both SAEs and pregnancies from clinical trials and all post-marketing safety data (serious / non-serious) have been captured in the Global Safety Database, based on the standard regulatory guidelines and by using the MedDRA terminology, version 28.0.

Cumulative summary tabulations of serious adverse events from Clinical trials

Since the beginning of the clinical development programs for rhinitis and asthma, among the 5,035 exposed subjects, **134 SAEs** including nine with causality assigned to the IP (active product or placebo), have been reported in 122 subjects. **Seven SAEs with causality assigned to the IP** - active product**,** were reported in actively-treated subjects.

Table 9. Number of SAEs by product

	Pre-treatment	Placebo run in	Active	Placebo	Total
Number of SAEs	5[a]	3[bc]	95	31[d]	134
Number of drug-related SAEs	0	0	7	2	9

[a] 1 SAE in 1 subject in study 1501D1732 and 4 SAEs in 3 subjects in study SL75.14 were reported before any treatment intake (Pre-treatment AEs) [b] These SAEs were reported during the placebo run-in period of study SL75.14. [c] Subject #616-014-062 withdrew from study SL75.14 during the placebo run-in period due to pregnancy and gave birth to a premature infant with atrial septal defect which was ultimately included as an SAE in the study database. [d] Subject #616-015-006 in the placebo group had an SAE reported as patellofemoral pain syndrome, joint dislocation, and plica syndrome which was reclassified into 3 separate SAEs of chondromalacia, joint dislocation, and plica syndrome.

Table 10. Overview of drug-related SAEs reported since the beginning of clinical development program

Body system / Event PT Active	Active	Placebo
Immune system disorders (10021428)		
Angioedema	1	-
Subtotal	**1**	**-**
Infections and infestations (10021881)		
Pseudocroup	1	-
Subtotal	**1**	**-**
Respiratory, thoracic and mediastinal disorders (10038738)		
Asthma	-	1
Pharyngeal oedema	1	-
Respiratory distress	1	-
Pharyngeal disorder	2	-
Subtotal	**4**	**1**
Skin and subcutaneous tissue disorders (10040785)		
Urticaria	-	1
Eczema	1	-
Subtotal	**1**	**1**
Total	**7**	**2**

Cumulative and interval summary tabulations from post-marketing data sources

Since the IBD, a total of 2,553 Individual Case Safety Reports (ICSRs) has been reported from different sources including **154 serious cases**, including 142 medically confirmed cases, 2,279 non-serious cases and 120 without adverse reactions.

During the reporting interval, a total of 908 ICSRs were received from different sources out of which **83 cases were serious**, 767 cases were non-serious, and 58 cases were without adverse reactions. Particularly, no specific risk was detected in paediatric population compared to adult population.

Table 11. Number of ICSRs from post marketing setting reported during the interval period per source and type

Source	Serious ICSRs	Non-Serious ICSRs	Total
Spontaneous / Health Authorities	78	693	771
Literature	0	3	3
Observational studies	5	129	134
Total	83	825	908

Table 12. Cumulative number of ICSRs from post marketing per source and type

Source	Serious ICSRs	Non-Serious ICSRs	Total
Spontaneous / Health Authorities	130	1913	2043
Literature	3	48	51
Observational studies	21	438	459
Total	154	2399	2553

Table 13. Cumulative and Interval Summary Tabulation from Post-Marketing Data Sources

	Spontaneous, including regulatory authority and literature	Non-Interventional Post-marketing study and other solicited sources
Cumulative Time Period		
Total Number of Cases	2097	456
Interval Time Period		
Total Number of Cases	794	181

Lead Member State assessment comment:

<u>Cumulative summary tabulations of serious adverse events from clinical trials</u>

In clinical trials, there were 134 SAEs reported cumulatively, whereof, 95 SAEs in patients receiving the IMP and 31 SAEs in placebo group.

<u>Cumulative and interval summary tabulations from post-marketing sources</u>

The MAH presented the Cumulative and interval summary tabulations of all Adverse Drug Reactions (ADRs) from post marketing data sources are presented in Chapter 20.2.2.

In the post-marketing experience, there were 218 SAEs reported *in the reporting interval and 336 SEAs cumulatively.*

Table 14. Reactions of interest (serious event PT) from post-marketing data sources

Event PT	Interval	Cumulative
Immune system disorders	**30**	**40**
Anaphylactic reaction	13	27
Anaphylactic shock	10	11
Drug hypersensitivity	1	1
Hypersensitivity	5	5
Oral allergy syndrome	1	1
Nervous system disorders	**8**	**16**
Dizziness	2	2
Facial paralysis	2	2
Syncope	1	2
Respiratory, thoracic and mediastinal disorders	**57**	**89**
Asthma	2	2
Asthmatic crisis	1	1
Bronchospasm	2	2
Choking	2	3
Laryngeal oedema	2	8
Laryngospasm	1	1
Pharyngeal oedema	3	3
Gastrointestinal disorders	**52**	**77**
Tongue oedema	10	13
Skin and subcutaneous tissue disorders	**22**	**34**
Angioedema	10	13
Erythema	5	8
Pruritus	2	3
Rash	1	4
Rash vesicular	1	1
General disorders and administration site conditions	**19**	**24**
Face oedema	1	1
Fatigue	1	1
Malaise	1	2
Grand Total	**218**	**336**

In general, no new important safety information is identified, and no safety concern was identified from Data in summary tabulations for the product dermatophagoides pteronyssinus / dermatophagoides farina.

1.3.4.3. General conclusion on Data in summary tabulations for the product dermatophagoides pteronyssinus / dermatophagoides farina

Lead Member State assessment comment:

The review of the summary tabulations provides by the MAHs revealed no events highlighting a safety issue of the product dermatophagoides pteronyssinus / dermatophagoides farina.

No new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. MAH ALK-Abelló-A/S

Two clinical trials MT-11 and MT-12 were completed in the period, both of which confirmed the existing safety profile for the HDM SLIT-tablet for children and adolescents.

One clinical trial in Chinese subjects MT-16 was prematurely terminated due to the impact of the corona-virus pandemic starting in 2019.

At DLP, one clinical trial MT-21 was ongoing with the purpose of investigating efficacy and safety in a Chinese population 12-65 years of age. The clinical trial had first participant first visit FPFV on 01 September 2025.

During the reporting period, four non-interventional studies were completed or closed. At DLP, three non-interventional studies were ongoing.

Table 15. Listing of interventional and non-interventional studies completed or ongoing during the reporting period

Study ID	Study title	Study type	Population studied	Study start completion date	Status
MT-11	A phase III trial evaluating the efficacy and safety of HDM sublingual immunotherapy SLIT-tablet in children and adolescents 5-17 years with HDM allergic asthma	Randomised (1:1), parallel-group, double-blind, placebo-controlled clinical trial	Children and adolescent patients 5-17 years in Bulgaria France Germany Hungary Poland Russia Spain United Kingdom, USA	22.02.2018 (FPFV) 06.02.2023 (CSR)	Completed
MT-12	A one-year placebo-controlled phase III trial evaluating the efficacy and safety of HDM SLIT-tablet in children 5-11 years of age with HDM allergic rhinitis rhinoconjunctivitis with or without asthma	Randomised 1:1, parallel-group, double-blind, placebo-controlled clinical trial	Child patients 5-11 years in Bulgaria Canada France Germany Lithuania Poland Russia Slovakia Spain USA Ukraine	12.10.2019 (FPFV) 25.09.2023 (CSR)	Completed
MT-16	A phase III trial evaluating the efficacy and safety of HDM sublingual immunotherapy SLIT-tablet in adult Chinese subjects with HDM allergic rhinitis rhinoconjunctivitis using an environmental exposure chamber	Randomised 1:1, parallel-group, double-blind, placebo-controlled clinical trial	Adults ≥18 years in China	06.11.2019 (FPFV) 24.10.2022 (CSR)	Closed*
MT-21	A randomised double-blind placebo-controlled phase III field trial evaluating the efficacy and safety of HDM SLIT-tablet in Chinese participants aged 12-65 years with HDM allergic rhinitis rhinoconjunctivitis with or without asthma	Randomised 1:1 parallel-group, double-blind, placebo-controlled	Adolescents and adults 12-65 years in China	01.09.2025 (FPFV) N/A	Ongoing

Torii 500	Safety of Miticure tick sublingual tablet specific use results survey	Non-interventional	Patients (all ages) in Japan	04.07.2016 08. 2023 (CSR)	Completed
NI-MT-04	A non-interventional observational study assessing the safety and tolerability of ACARIZAX in adults 18-65 years of age	Non-interventional	Adults 18-65 years in the Netherlands	10.2017 27.09.2022	Completed**
NI-MT-06	Post-Market Integrated Electronic Health Record EMR Based Study of Serious Allergic Reactions and EoE in Marketed Use of ODACTRA in US	Non-interventional	Adults 18-65 years in the US	01.03.2017 (FPFV) 17.01.2024*	Closed***
MITI 5001	Post-Marketing Surveillance for Acarizax to Evaluate the Safety and Efficacy in Korean Patients	Non-interventional	Adolescent and adult patients ≥12 years in South Korea	30.05.2020 (FPFV) 30.09.2024 (CSR)	Completed

* MT-16 was prematurely terminated due to the impact of the coronavirus pandemic on trial conduct ** NI-MT-04 was completed on 27.09.2022 NI-MT-04 is registered as a PASS and the results and study report were included in the previous PSUR as late-breaking information *** NI-MT-06 was closed following release from FDA commitment

Completed clinical trials

During the reporting period, three phase III clinical trials were completed or closed: MT-11, MT-12 and MT-16.

Clinical trial MT-11: a randomised, parallel-group, double-blind, placebo-controlled, multi-national phase III trial evaluating the efficacy and safety of the HDM SLIT-tablet compared to placebo as add-on treatment in children and adolescents 5-17 years of age with HDM allergic asthma based on clinically relevant asthma exacerbations.

The MT-11 trial was finalised on 06 February 2023. The trial was conducted in Europe and US, and a total of 533 subjects were randomised to receive treatment with the HDM SLIT-tablet 12 SQ-HDM or placebo.

Clinical trial MT-12: a randomised, parallel-group, double-blind, placebo-controlled, multi-centre, phase III trial evaluating the efficacy and safety of the HDM SLIT-tablet in children 5-11 years old with HDM allergic rhinitis / rhinoconjunctivitis with or without asthma.

The MT-12 trial was finalised on 25 September 2023. The trial was conducted in Europe and North America and a total of 1460 subjects were randomised to receive treatment with the HDM SLIT-tablet 12 SQ-HDM or placebo.

The MT-11 and MT-12 clinical trial setup included AE solicitation of n=15 pre-specified symptoms / signs identified as local adverse reactions of SLIT. In both trials, an increase in AEs was observed compared to trials without solicitation, as expected.

Clinical trial MT-16: a randomised, parallel-group, double-blind, placebo-controlled, phase III trial investigating the efficacy and safety of the HDM SLIT-tablet compared to placebo in the treatment of HDM allergic rhinitis nasal symptom.

The MT-16 trial was prematurely terminated due to the impact of the coronavirus pandemic on trial conduct; final clinical study report was available 24 October 2022. The efficacy and safety should have been determined during the environmental exposure chamber session at week 24 in adults 18-65 years

of age with HDM allergic rhinitis / rhinoconjunctivitis with or without allergic asthma. The trial was conducted in China and a total of n=13 subjects of the planned 202 were randomised to receive treatment with the HDM SLIT-tablet 12 SQ-HDM or placebo before terminated due to the COVID-19 pandemic.

Overall, the HDM SLIT-tablet 12 SQ-HDM was well tolerated and there were no new or unexpected safety findings observed from the completed clinical trials in the period. The inclusion of AE solicitation in MT-11 and MT-12 was believed to introduce reporting bias, leading to increased reporting of local adverse reactions. However, AE solicitation was not observed to qualitatively influence the safety profile of the HDM SLIT-tablet 12 SQ-HDM. MT-11 and MT-12 showed to be safe and tolerable in the age group 5-17 years of age, indicating a similar safety profile in children and adolescents as in other age groups. Furthermore, there were no deaths reported in the trials, 1 treatment-emergent SAE was reported in the active HDM SLIT-tablet group EoE event in MT-11, and no investigator reports of anaphylaxis were received in the active HDM SLIT-tablet group.

Ongoing clinical trials

At DLP of this PSUR, one clinical trial was ongoing: MT-21.

Clinical Trial MT-21: A randomised double-blind placebo-controlled phase III field trial evaluating the efficacy and safety of the house dust mite (HDM) SLIT-tablet in Chinese participants aged 12-65 years with HDM allergic rhinitis / rhinoconjunctivitis with or without asthma.

The clinical trial had FPFV on 01 September 2025 with randomisation and first IMP exposure planned for November 2025. No clinically important safety information has arisen from the ongoing clinical trial.

Table 16. Ongoing clinical trials

Trial ID	Phase Countries	Dose (SQ-HDM)	Population	Clinical trial title	Status
MT-21	III China	12	Chinese adolescents and adults 12-65 years with HDM AR/C ± asthma	A randomised double-blind placebo-controlled phase III field trial evaluating the efficacy and safety of HDM SLIT-tablet in Chinese participants aged 12-65 years with HDM allergic rhinitis rhinoconjunctivitis with or without asthma	Ongoing

FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting period, three non-interventional studies were ongoing (Torii500, NI-MT-06 MITI5001 and NI-MT-04) and four non-interventional studies were completed or closed.

No new clinically important safety information has arisen from non-interventional studies during the reporting period. A summary of NI-MT-04 was included in the previous PSUR.

Table 17. Non-interventional studies ongoing, completed or closed during the reporting period

Study ID	Country	Number of patients planned or actual	Study Title	Status
Torii 500	Japan	815 (actual)	Safety of Miticure sublingual tablet specific use results survey	Completed
NI-MT-04	The Netherlands	416 (actual)	A non-interventional observational study assessing the safety and tolerability of ACARIZAX in adults 18-65 years of age	Completed*
NI-MT-06	USA	468 (actual)	Post-Market Integrated Electronic Health Record EMR Based Study of Serious Allergic Reactions and EoE in Marketed Use of ODACTRA in US	Closed**
MITI 5001	Republic of Korea	514 safety subjects*** (actual)	Post-marketing surveillance for ACARIZAX to evaluate the safety and efficacy in Korean patients	Completed
NI-MT-08	China	100 (planned)	To evaluate the relevance of measurement instruments in assessing effectiveness of ACARIZAX as treatment for moderate to severe dust mite allergic rhinitis with or without allergic asthma in Chinese adults 18-65 years and adolescents 12-17 years.	Ongoing
NI-MT-09	Japan	50,000 (planned)	Real world evidence of effectiveness of house dust mite sublingual immunotherapy tablets treatment in patients with allergic rhinitis	Ongoing
NI-X-05	Denmark Sweden	1,000,000 (planned)	Comparative real-world effectiveness of SQ sublingual immunotherapy SLIT-tablets vs controls in allergic rhinitis and asthma outcomes from a multinational register study	Ongoing

* The NI-MT-04 study report was completed on 27.09.2022 NI-MT-04 is registered as a PASS and the results and study report were included in previous PSUR as late-breaking information ** NI-MT-06 Post-marketing commitment release obtained on 17.01.2024 *** 514 subjects included in the safety evaluation out of 658 case report forms received ODACTRA is the product name in US ACARIZAX is the product name in Korea and China Miticure is the product name in Japan EoE Eosinophilic oesophagitis.

Clinical Trial Torii500: Safety of Miticure tick sublingual tablet specific use results survey

The primary objective of the study was to investigate the safety and efficacy of HDM SLIT-tablet Miticure during long-term administration and the efficacy after end of administration in patients with allergic rhinitis caused by HDM antigens for a 3-year observation period (up to 4 years), by conducting a specific drug use result survey long-term administration. A total of 815 case report forms were collected from physicians in the study.

Overall, 144 17.7% of patients experienced 209 adverse reactions.

The most frequent adverse reaction was oral pruritus 2.3%, oral swelling 2.2%, ear pruritus and oral discomfort (1.6% each), allergic rhinitis and stomatitis 1.2% each, and throat irritation 1.1%. It should be noted that for all participants experiencing allergic rhinitis, the adverse reaction was assessed as exacerbations of the underlying disease of allergic rhinitis. All reactions, apart from allergic rhinitis are listed in the CCSI for the HDM SLIT-tablet, although symptoms similar to allergic rhinitis are included in the CCSI.

Serious adverse reactions were reported in one participant with dyspnoea and in one participant with anaphylactic reaction, and the treatment was discontinued in these participants. Furthermore, **one pregnancy was reported during the study**, and this participant did not experience any adverse reactions.

Clinical trial NI-MT-06: *Post-Market Integrated Electronic Health Record EMR Based Study of Serious Allergic Reactions and EoE in Marketed Use of ODACTRA in the US*

NI-MT-06 was a post-marketing commitment study. The aim of the study was to provide safety surveillance information for the HDM SLIT-tablet following introduction to the US market, to obtain information about the patient population using the HDM SLIT-tablet, and to estimate the incidence of serious allergic reactions and EoE when using the HDM SLIT-tablet in order to describe potential baseline risk factors for serious allergic reactions and EoE.

The planned completion date for the post-marketing commitment Electronic Health Record study was scheduled for February 2024, however as of February 2023 only 468 patients were recruited. **Due to the low recruitment rates the MAH applied for a release from the commitment in 17 July 2023, which was granted by the FDA on 17January 2024**.

Summary of data from the study: As of 28 February 2023, there were 468 patients treated with HDM SLIT-tablet identified in the Electronic Health Record database and **four reports related to the safety concerns of interest**. The 4 reports included one report of non-serious EoE in a 25-year-old patient and three reports of serious hypersensitivity: one in a 59-year-old patient and two for patients below the indicated age 13 and 14-year-old (the adolescent indication was approved in US on 20.01.2023), respectively of treatment with HDM SLIT-tablet. All four reports included very limited information and were assessed as possibly related to HDM SLIT-tablet by both reporter and sponsor. In general, serious allergic reactions and EoE are considered well characterised risks for HDM SLIT-tablet and are considered listed according to the USPI.

Clinical Trial MITI5001: Post-Marketing Surveillance for Acarizax to Evaluate the Safety and Efficacy in Korean Patients

The MITI5001 was a post-marketing drug use-results survey which were conducted as part of active surveillance. It is an approval condition for the HDM SLIT-tablet, proposed in the Korean Risk Management Plan in accordance with the enforcement regulation on the safety of medicinal products, regulations on the approval, notification and review of medicinal products, standards for post-marketing safety management of medical products, etc. Korean GPV, and standards for re-examination of new drugs, etc.

The objectives of the study were to identify the variation in the frequency of occurrence of adverse events/adverse drug reactions and efficacy profile under actual use status, and to identify any unexpected adverse events/adverse drug reactions, and to identify serious adverse events/adverse drug reactions. In addition, the study aimed to confirm the efficacy and safety profile in special patient groups (paediatric and geriatric patients, pregnant or breastfeeding patients, renal and hepatic impaired patients) and after long-term use.

Summary of data from the study: A total of 658 patients was included in the study of which 514 were included in the safety evaluation. **564 adverse events were reported in 268 participants** corresponding to an adverse event reporting rate of 52.14%. 41.63% of the adverse events were assessed as possibly related to treatment with the HDM SLIT-tablet. **Only three serious adverse events in three patients were reported** in the study and among them, two events in two patients were reported as adverse drug reactions. One patient reported anaphylactic reaction, and another patient reported abdominal pain. The majority of all reported events were mild to moderate in severity and expected according to RSI. Most frequently reported unexpected adverse reactions were rash 8 reactions, gastritis, macule and swelling face 3 reactions each.

Rash has recently been identified as a potential signal in the post-marketing pharmacovigilance activities.

In the long-term effectiveness evaluation ≥ 24 weeks, 96% of the patients with allergic rhinitis 217 / 226 patients, 100% of the patients with allergic asthma 2/2 patients, and 93% of the patients with allergic rhinitis and allergic asthma 13/14 patients reported an improvement.

MAH conclusion: this post-marketing surveillance survey confirmed the positive benefit-risk balance of the HDM SLIT-tablet. In comparison with the current approved prescribing information, no new specific trends in the safety or the effectiveness of the HDM SLIT-tablet was observed in Korean paediatric and adult patients aged 12 years and older throughout the post-marketing surveillance study. Therefore, it is considered that the use of the HDM SLIT-tablet is effective and well tolerated in Korean patients with allergic rhinitis and/or asthma caused by house dust mites.

Medication errors

MAH Note: the search criteria applied to identify cases related to medication errors were changed during the reporting period to increase accuracy of identifying relevant terms. In previous PSURs, 'Medication errors and other product use errors and issues' was applied.

425 medication error events were reported for the HDM SLIT-tablet during the review period, and 1,028 events cumulatively from post-marketing sources.

Table 18. Medication errors reported in the period and cumulatively

MedDRA PT	Number of events	
	Period	Cumulative
Accidental exposure to product by child	2	4
Accidental overdose	2	6
Accidental underdose	1	2
Contraindicated product administered	13	16
Contraindication to medical treatment*	1	2
Documented hypersensitivity to administered product	0	1
Drug monitoring procedure incorrectly performed	0	1
Drug monitoring procedure not performed	10	38
Expired product administered	1	4**
Inappropriate schedule of product administration	16	48

Incorrect dosage administered	0	1
Incorrect dose administered	0	64
Incorrect product administration duration	4	4
Incorrect route of product administration	4	26
Intercepted product administration error	0	1
Intercepted product dispensing error	0	3
Intercepted product monitoring error	0	1
Intercepted product prescribing error	1	3
Medication error	7	9
Overdose*	17	27
Prescribed underdose*	0	1
Product adhesion issue*	0	1
Product administered at inappropriate site	10	18
Product administered to patient of inappropriate age	162	290
Product administration error	3	5
Product administration interrupted	0	1
Product communication issue	0	1
Product dispensing error	1	2
Product dose omission in error	2	3
Product dose omission issue	4	5**
Product packaging difficult to open*	3	3
Product preparation issue	0	1
Product prescribing error	1	4
Product prescribing issue	1	1
Product selection error	0	1
Product use complaint	1	1
Product use in unapproved indication	4	10
Product use issue	49	224
Underdose*	19	37
Wrong product administered	1	2
Wrong technique in product usage process	85	156
Total	425	1,028

* New PT included compared to previous PSURs due to the change in search criteria ** Fewer events cumulatively since previous PSUR due to exclusion of double unlikely events as described in section 6.3

Overall, the reported medication errors in the period resembles those reported cumulatively, revealing no new unexpected patterns for the medication errors.

162 events of PT Product administered to patient of inappropriate age were received in the period. Of the 162 events, 141 events concerned children <12 years of age, five events concerned adolescents 12-17 years of age and n=16 events concerned elderly >65 years of age. Of the 140 cases with 141 events of inappropriate use in children, 20 cases included co-reported adverse reactions in relation to the administration of which 19 were non-serious and one was serious.

Based on results from recently finalised clinical trials in children that confirmed the existing safety profile for the HDM SLIT-tablet in for children and adolescents, an extension of the indication to include paediatric patients 5-11 years of age has been approved in Europe, North America and several countries in Rest of world. Cases of PT Product administered to patient of inappropriate age constituting off label use in children were primarily received before the HDM SLIT-tablet indication included this age group and no safety issues were identified from these cases.

85 events of PT Wrong technique in product usage process and 49 events of PT Product use issue were reported in the period. Cases were primarily related to deviations from the recommended dose; primarily by splitting the tablet in 2 or by up-dosing from 3,300 JAU to 10,000 JAU at a slower pace than recommended.

No specific safety issues warranting further actions in relation to medication errors were identified.

LITERATURE: A general literature search for published safety data related to treatment with HDM SLIT-tablet and other products containing the same active substance and / or is of the same drug class has been performed on a regular basis as part of the ongoing safety surveillance.

MAH Note: during the search for publications in EMBASE, metadata from 65,000 clinical trial records were being added to the database, making the data entry date recent for older trials. To exclude these, NOT 'clinical trial': dtype were added to the search string.

The following one publication with significant new safety findings was identified during the reporting period:

Sasamoto et al. 2024. During the reporting period Sasamoto et al. published the results of a single-centre, non-randomised, controlled, open-label, prospective clinical study investigated the efficacy and safety of HDM SLIT-tablet in children aged 1-4 years with allergic rhinitis in Japan. The HDM SLIT-tablet is approved without an age limit in Japan. The participants were divided into SLIT n = 22 and control n = 12 groups based on their guardians' preferences. The SLIT group received a daily dose of 10,000 JAU of HDM SLIT-tablet for 12 months, whereas the control group received symptomatic treatment only. The baseline median age was 41 months in the active group and 34 months in the control group. The median AR symptom score was 4 for both groups. Compared with baseline, the AR symptom score decreased significantly in the active group after 12 months of treatment from score 4 to 3, p = 0.002, whereas it tended to increase in the control group from score 4 to 6, p = 0.08. During the study period, the number of adverse reactions attributed to HDM SLIT-tablet per total number of dose intakes was 1.1% 72 adverse reactions per 6401 doses in 8 participants 36%. All adverse reactions were mild. The most frequently occurring adverse reactions were oral pruritus/discomfort, tongue pruritus/discomfort, skin pruritus, and sneezing, each occurring in 3 14% of the participants. Anaphylaxis was not observed in any cases. In the active group, Dermatophagoides (D.) farina -specific IgE (sIgE) levels increased during the first 6 months and decreased to baseline levels after 12 months of treatment. In the control group, D. farina -sIgE levels

had increased significantly at 12 months compared to baseline (p = 0.01). D. farina -specific IgG4 and HDM IgE-blocking factor levels were significantly increased 12 months after treatment compared to baseline in the active group only (p <0.001). A lower wheezing frequency was seen in the active group (0.3%) compared to the control group (0.7%).

MAH conclusion: this pilot study demonstrated the efficacy, safety, and immunomodulatory effects of HDM SLIT-tablet in preschoolers with AR.

Lead Member State assessment comment:

MAH ALK-Abelló-A/S

During the reporting period, two phase III clinical trials were completed: MT-11 (randomised, parallel-group, double-blind, placebo-controlled, multi-national phase III trial evaluating the efficacy and safety of the HDM SLIT-tablet compared to placebo as add-on treatment in children and adolescents 5-17 years of age with HDM allergic asthma based on clinically relevant asthma exacerbations.) and MT-12 (a randomised, parallel-group, double-blind, placebo-controlled, multi-centre, phase III trial evaluating the efficacy and safety of the HDM SLIT-tablet in children 5-11 years old with HDM allergic rhinitis / rhinoconjunctivitis with or without asthma). The clinical trial in Chinese subjects: MT-16 (a randomised, parallel-group, double-blind, placebo-controlled, phase III trial investigating the efficacy and safety of the HDM SLIT-tablet compared to placebo in the treatment of HDM allergic rhinitis nasal symptom) was prematurely terminated due to the impact of the coronavirus pandemic.

One clinical trial MT-21 (A randomised double-blind placebo-controlled phase III field trial evaluating the efficacy and safety of the house dust mite (HDM) SLIT-tablet in Chinese participants aged 12-65 years with HDM allergic rhinitis / rhinoconjunctivitis with or without asthma) was ongoing, during the reporting interval.

During the reporting period, four non-interventional studies were completed: Torii500 (Safety of Miticure sublingual tablet specific use results survey); NI-MT-04 (summary was included in the previous PSUR); and MITI5001 (Post-marketing surveillance for ACARIZAX to evaluate the safety and efficacy in Korean patients) or closed: NI-MT-06 (Post-Market Integrated Electronic Health Record (EMR) Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis (EoE) in Marketed Use of ODACTRA in the US).

Three non-interventional studies were ongoing: NI-MT-08 (To evaluate the relevance of measurement instruments in assessing effectiveness of ACARIZAX as treatment for moderate to severe dust mite allergic rhinitis with or without allergic asthma in Chinese adults 18-65 years and adolescents 12-17 years); NI-MT-09 (Real world evidence of effectiveness of house dust mite sublingual immunotherapy tablets treatment in patients with allergic rhinitis) and NI-X-05 (Comparative real world effectiveness of SQ sublingual immunotherapy (SLIT)-tablets vs. controls in allergic rhinitis and asthma – outcomes from a multinational register study).

There were no relevant safety findings on patterns of medication errors and potential medication errors, identified, which would require specific risk minimization measures at this time. Cases of medication error will continue to be closely monitored, and this is endorsed.

There was no safety signal recognised from the literature identified, during the current reporting interval.

In general, no information relevant to the benefit-risk assessment has been obtained from clinical trials or other study sources during the reporting interval.

1.3.5.2. MAH Stallergenes SAS

FINDINGS FROM NON-INTERVENTIONAL STUDIES

NEWLY IDENTIFIED INFORMATION ON EFFICACY / EFFECTIVENESS

During the reporting period, a final analysis report of a NIS Study "Post marketing surveillance for long term use ACTAIR 100 IR/ 300 IR" conducted in Japan was published by Okamoto et al. A 2-year interim analysis was also published prior the reporting period.

During treatment with ACTAIR, physicians recorded the severity of patient's allergic rhinitis on a 5-point scale 0 = asymptomatic; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe using the Practical Guideline for the Management of Allergic Rhinitis in Japan. Effectiveness was determined according to the change from baseline start of treatment in the mean rhinitis severity score and the proportion of patients in each severity category at each observation time point. Patients also reported a global evaluation of treatment effectiveness using the Patient Global Impression of Improvement PGI-I scale relative to baseline, and which defines 'improvement' as 'very much better', 'much better' or 'a little better' and 'no improvement' as 'no change' or 'worse'.

This study confirmed the safety and effectiveness of ACTAIR in real-life setting up to 4 years of treatment.

One NIS was completed during the reference period and **one Post-Authorisation Safety Study (PASS) with HDM SLIT TABLET HDM tablets was ongoing** during the reference period:

Non-interventional study in Japan

The study "**Safety and effectiveness of a 300 IR house dust mite sublingual tablet: descriptive 4-year final analysis of a post-marketing surveillance in Japan**" conducted in 116 sites in Japan was completed in November 2021. The objectives of this NIS were to evaluate the safety and effectiveness of long-term use up to 4 years of ACTAIR in routine clinical practice in Japan, and to assess effectiveness after discontinuation, in 538 patients including patients from 3 age group: < 15 years; ≥ 15 to < 65 years and ≥ 65 years. Patients with HDM-associated AR starting treatment with ACTAIR between December 2015 and November 2017 were registered in the survey. Treatment was administered in accordance with the approved labelling in force in Japan. Observation time points were specified at 6 months and at 1, 2, 3 and 4 years of treatment.

As of DLP of this report, 547 patients actually aged between 11 and 66 years old had been enrolled and case report forms for 545 patients had been collected. The first patient first visit was on 05-Jan-2016. The investigation period started from 01 December 2015 to 18 February 2022, and the study was analysed in 2022 as planned. In the most recent Japanese PSUR JPSUR, reporting period March 26, 2021, to March 25, 2022, and according to the study's CSR dated 28 September 2022 the safety analysis set comprised 538 patients. There were 156 cases with adverse drug reaction. Incidence of adverse drug reaction (ADR) was 29.00%. The Adverse drug reactions occurred in at least 2% of the cases were "Oral pruritus" 3.72% n=20 cases in 538 cases, "Throat irritation" 3.35% n=18 cases in 538 cases, "Mouth swelling" 2.97% n=16 cases in 538 cases, "Oedema mouth" 2.79% n=15 cases in 538 cases and "Ear pruritus" 2.6% n=14 cases in 538 cases. Three serious ADRs asthma, abdominal pain and chest discomfort were reported in one patient each, and all resolved. No shock or anaphylaxis occurred during the study.

383 patients were included in the efficacy analysis set. Improvements were defined as those that could be classified into "slightly improved", "moderately improved", and "remarkably improved" to calculate improvement rates. Improvement rate in patient global assessment was 83.7% at 6-month point n=283,

94.9% at 1-year point n=256, 95.9% at 2-year point n=172, 97.8% at 3-year point n=138, and 95.6% at 4-year point n=113.

This study confirmed the safety and effectiveness of ACTAIR® in real-life setting up to 4 years of treatment.

Post-Authorisation Safety Study

VORAN Study ORY-MIT-PAS-01-DE in Germany and Austria: "Study of the safety and tolerability of ORYLMYTE in routine medical practice in adolescents and adults".

The main objective was to further describe the safety and tolerability of ORYLMYTE at the recommended dose of 300 IR for 12 months i.e. patients' first treatment year) in adolescents and adults suffering from moderate to severe HDM-induced AR or allergic rhinoconjunctivitis, with or without mild controlled asthma. At the time of this report, 782 patients have been included out of the total planned number of 1,500 patients. The FPFV was in November 2021. The LPLV for treatment year 1 was on 29 May 2024. The study has been extended to treatment year 2 and 3 since the last PBRER. LPLV for treatment year 3 is planned for April 2026.

To date, 195 cases have been collected in the frame of this study. The study is ongoing.

INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

OTHER CLINICAL TRIALS: During the reporting period, **one investigator-initiated study was completed, and one investigator-initiated study was ongoing**.

Investigator-initiated study IIS in Australia: "Patient stratification and monitoring of ACTAIR treatment efficacy using new objective immune markers" Principal Investigators: Prof Menno van Zelm and Prof. Robyn O'Hehir.

This is a prospective controlled two-arm trial of 18 months of ACTAIR treatment in HDM-allergic individuals - adult patients with a clinical history of perennial rhinitis with or without stable asthma spirometry >70% predicted and laboratory-confirmed HDM allergy to examine immunological markers and predictors of efficacy: ACTAIR n = 21 / Pharmacotherapy only n = 17. The study objectives are to explore: novel immunological mechanisms of AIT using ACTAIR, to guide development of new therapeutic strategies addressed by analyses of data from patients on ACTAIR vs pharmacotherapy only controls: increase in specific serum IgG2/4 and IgG2/4+ B cells and Immunological prediction of responses to HDM AIT using ACTAIR to guide future patient selection addressed by analyses of molecular patterns stratified by subsequent clinical response within an ACTAIR treated group: allergen binding intensity on basophils, serum IgE and IgG subclasses specific for HDM and Der p 1/Der p 2, changes in Der p 1/Der p 2 specific B-cell immunophenotypes IgG subclasses. Clinical measurements are ImmunoCAP, ELISA and SPT at t=0, FeNO at t=0, t=4, t=12 and t=18 months, and Visual Analogue Score [VAS], Medications scores, Symptoms Diary score t=0, 4, 12, 18mo. Overall, HDM SLIT produced marked symptom improvement over 18 months and a biphasic remodelling of allergen-specific B memory cells suggesting B memory reprogramming as a basis for clinical benefit. The FPFV was planned in 2021. The LPLV was in 2025. 38 patients were included in the study. The study is now completed.

Investigator-initiated study IIS in Australia: "Effect of Allergy Immunotherapy on Turbinate Surgery", Principal Investigator: Prof. Richard Harvey.

This is an open label, controlled, multi centre n=3 observational study with 300 IR HDM SLIT tablet ACTAIR vs standard pharmacotherapy in patients with HDM perennial allergic rhinitis and turbinate hypertrophy n=120 who are candidates for turbinate surgery. The inclusion criteria: diagnosis confirmed by RAST or SPT; age >12 yrs; failed INCS to relieve nasal obstruction. The study design is as follows:

turbinate reduction with 300 IR HDM SLIT tablets 'AIT'; n= 60 3 months pre surgery with patient-initiated use of pharmacotherapy and 9 months post-surgery 12 months SLIT vs standard pharmacotherapy 'Control'; n=60 3 months pre / 9 months post. Revised recruitment targets agreed 2024: AIT, n = 35, Control, n = 35. The Primary outcome is the patient-reported satisfaction with combined approach of turbinate surgery and AIT indexed using the NOSE questionnaire, VAS and RQLQ.

The secondary outcomes are the impact of AIT on nasal obstruction, allergic symptoms and nasal reactivity after turbinate surgery, impact of AIT in the 3 months prior to turbinate surgery in HDM allergic rhinitis. The FPFV is planned in 2022. The LPLV is scheduled in 2026. The study is ongoing.

Table 19. Listing of all MAH-sponsored noninterventional studies

Study Title Country	Objectives	Study population	Nb of patients *	Study period
Post marketing surveillance for long term use of ACTAIR 100 IR 300 IR Japan	To survey the safety and effectiveness of long-term use up to 4 years of ACTAIR in routine clinical practice in Japan and to survey effectiveness after treatment discontinuation	Children < 15 years adolescents and adults ≥ 15 and < 65 elderly ≥ 65	Planned 500 Enrolled: 547 With collected CRFs 545 Safety analysis set 538 Effectiveness analysis set 383	01.12.2015 to 18.02.2022
Study of the safety and tolerability of ORYLMYTE in routine medical practice in adolescents and adults VORAN Study ORY-MIT-PAS- 01-DE Austria Germany	To further describe the safety and tolerability of ORYLMYTE at the recommended dose of 300 IR for 3 years in adolescents and adults suffering from moderate to severe HDM- induced allergic rhinitis or allergic rhinoconjunctivitis, with or without mild controlled asthma	Adolescents and adults Patient ≥12 years	Planned 1,500 Included 782	Actual FPFV 11.2021 LPLV for Treatment year 1 05.2024 Planned LPLV for year 3 04.2026

* Interim results as of March 2021

MEDICATION ERRORS

Clinical development program: During the reporting interval, no case of medication error was reported as no clinical trials were completed or ongoing during this period.

Post marketing experience: A search for all cases of medication errors received and registered in the Database has been done using the SMQ "Medication errors" and the following PTs: ´Therapy change` and `Product advertising issue´. The PTs "Product expiration date issue" and "Treatment noncompliance" have been removed from the query as these PTs are already included in the SMQ "Medications errors".

Cases of overdose, abuse, misuse and off label use are not considered in the analysis of medication errors and have been discussed in the section `OTHER POST-AUTHORISATION USES` of this report.

Interval period: A total **33 cases of medication errors** have been reported. Among them, **one serious**, fifteen non-serious with adverse reaction and seventeen of them were without any adverse reaction.

Serious case 2024-AER-02384: serious medically important, caused-prolonged hospitalization, life threatening spontaneous and medically confirmed case described a 9-yearold male patient from Germany, who developed anaphylaxis grade III with cough specified as barking, hoarseness of voice, dyspnoea and stridor, at day 14 of HDM SLIT TABLET treatment and 10 minutes after HDM SLIT TABLET 300IR administration. Of note, the physician specified that the patient 9 years old chewed and sucked on the tablet Off label use in unapproved age group and medication error. The patient was treated with epinephrine inhalation, salbutamol inhalation, 300 µg of epinephrine via IM route, 4 mg of dimetindene maleate via IV route and 100 mg of prednisolone suppository Rectodelt. The patient was hospitalized. The anaphylaxis lasted for 1 hour. The patient stayed for one night in hospital for monitoring and left the next day without problems. The patient recovered and HDM SLIT TABLET treatment was discontinued on the same day.

Based on available information prescription to a 9-year-old patient who chewed and sucked on the tablet: child younger than 12 years; off label use; medication error, the triggering of anaphylaxis as a consequence of the medication error/off label use could not be completely excluded.

This case has been analysed and discussed in section: `Anaphylactic reaction including anaphylactic shock`.

Cumulative period: A total of **124 cases of medication errors have been retrieved**: 78 cases 62.9 % were reported with adverse reactions; 46 cases 37.1 % were not associated with adverse reactions. **Four cases were assessed as serious** 201600004, 201800730, 202000643 and 2024-AER-02384:

Serious case 201600004: a 53-year-old male patient swallowed HDM SLIT TABLET unmelted without keeping it 2 minutes under the tongue (wrong technique in product usage process) and immediately experienced hoarseness. Patient was taken to the hospital and received corrective treatment. Event resolved the same day.

Serious case 201800730: a 27-year-old male patient incorrectly administered 150 IR/day during 3 days per week incorrect dose administered. Around 3 months after start of product and around 30 minutes after last intake of the product, he experienced lip oedema and went to emergency department. The patient was treated with corrective intravenous treatment and event resolved the same day.

Serious case 202000643: an adolescent male patient with medical history of severe asthma received the product whereas severe asthma is a contraindication of the product contraindicated product prescribed. The patient experienced severe dyspnoea, suffocation feeling and burning throat around 10 min after his last intake of the product. HDM SLIT TABLET was discontinued and patient recovered the same month.

Serious case 2024-AER-02384: This case has been analysed and discussed in section `Anaphylactic reaction including anaphylactic shock´.

MAH Conclusion: The analysis of the cases retrieved during the reporting interval of this PBRER did not detect any specific signal or risk of medication error with HDM SLIT TABLET.

From the cumulative analysis of the 124 cases RR: 0.16/1,000, no pattern of medication error or potential medication error with the use of HDM SLIT TABLET has been identified. The warnings and precautions for use mentioned in the current HDM SLIT TABLET CCDS/CCSI are considered appropriate to prevent a wrong use of the product and the onset of adverse reactions.

LITERATURE: The literature search methodology was based on the articles cited by EMBASE PVWizard and PUBMED from 23 September 2022 to 22 September 2025. The available information was analysed for ACTAIR/ORYLMYTE/AITMYTE and other SLIT containing relevant data of safety, lack of efficacy and any useful information likely to have an impact on our product benefit-risk balance.

NATURAL ALLERGEN

Safety topics: Asthma & Allergic Rhinoconjunctivitis: A multicentre pooled analysis of eight randomized controlled trials and post-marketing data over seven years evaluated the safety of an HDM sublingual immunotherapy tablet 300 IR HDM in more than 235,000 patients aged 5–65 years with allergic rhinitis, with or without controlled asthma. Most treatment-related adverse events were mild or moderate local reactions oral pruritus, throat irritation, mouth edema, mainly occurring during the first days of treatment and decreasing over time. Severe or serious reactions were rare, with no deaths or anaphylactic shock reported. Post-marketing data confirmed these findings, showing only very few anaphylaxis cases that resolved safely. Overall, the HDM SLIT tablet demonstrated a favourable and consistent safety profile across age groups and asthma status. A multicentre phase 3 trial was conducted in adolescents aged 12–17 years with house dust mite–induced allergic rhinitis with or without conjunctivitis AR/C, with or without asthma. Participants received daily doses of an HDM sublingual immunotherapy tablet SQ HDM for up to one month, and results were compared with existing long-term datasets in similar populations. The treatment demonstrated a favourable safety profile, with no cases of anaphylaxis, epinephrine use, or severe systemic reactions. Most adverse events were mild to moderate local reactions occurring early in treatment, and safety was consistent in adolescents with or without asthma. Overall, the HDM SLIT tablet was well tolerated in adolescents with AR/C, confirming a reassuring safety profile across regions.

Asthma: A retrospective study in 217 children ≤15 years assessed the safety of HDM sublingual immunotherapy tablet SQ HDM in those with controlled HDM-driven allergic asthma. Only two mild asthma exacerbations were observed, both resolving without treatment interruption. No severe or systemic reactions occurred. The findings indicate that HDM SLIT-tablets are well tolerated in paediatric patients with controlled allergic asthma.

Case report: Nonepisodic angioedema with eosinophilia: A case report described a 32-year-old man with HDM-induced allergic rhinitis who developed intense chest pain and odynophagia shortly after taking the HDM sublingual immunotherapy tablet (SQ HDM) the day following multiple travel vaccinations. No systemic allergic symptoms occurred, and symptoms resolved after discontinuing treatment for several days. SLIT was later resumed without recurrence.

Relevant publication on specific population setting: A randomised, double-blind, placebo-controlled phase III trial evaluated the efficacy and safety of HDM sublingual immunotherapy tablet SQ HDM in 1,458 children aged 5 to 11 years with HDM-induced allergic rhinitis/rhinoconjunctivitis, with or without asthma. The safety profile was favourable, with most treatment-related adverse events being mild or moderate local application-site reactions such as oral or throat pruritus. No serious systemic reactions were reported. A prospective, controlled study in Japan evaluated the safety of a HDM sublingual immunotherapy tablet SQ-HDM in 34 children aged 1–4 years with perennial allergic rhinitis.

Mild local adverse reactions occurred in 36% of patients, mainly oral or tongue pruritus, sneezing, and skin itching. No moderate, severe, or systemic reactions, including anaphylaxis, were observed, and no treatment discontinuations occurred, indicating a favourable safety profile of HDM SLIT in preschool children.

Other route of administration: A prospective study conducted in China on 242 patients aged 4 to 65 years with house dust mite–induced allergic rhinitis evaluated the early safety and efficacy of SLIT using standardized Dermatophagoides farinae drops Chanllergen, Zhejiang Wolwo Bio-Pharma over 6 months.

Adverse events were mostly mild and occurred during the first month of treatment, primarily consisting of local rashes, gastrointestinal reactions, and oral or tongue pruritus. No severe or systemic reactions were reported, and no patient discontinued treatment due to adverse events. A phase 3 randomized, double-blind, placebo-controlled trial in 767 adults aged 18–64 years with HDM-induced allergic rhinoconjunctivitis, with or without controlled asthma, showed that subcutaneous HDM immunotherapy was well tolerated. Most adverse events were mild to moderate local reactions, with few systemic events and no severe anaphylaxis. Overall, the treatment demonstrated a favourable and consistent safety profile.

Lack of effectiveness: A systematic review including 15 studies and more than 43,000 patients with HDM-driven asthma evaluated the HDM sublingual immunotherapy tablet SQ HDM. Most studies reported improvements in asthma symptom control and a reduction in inhaled corticosteroid use, particularly in patients with less well-controlled asthma. However, findings on lung function and overall treatment efficacy were inconsistent, with some trials showing no significant benefit. Overall, the review concluded that the HDM-SLIT tablet provides moderate improvements in asthma control, but that evidence remains heterogeneous across studies despite an overall favourable safety profile.

ALLERGOIDS: No publication was identified during the reporting period providing new or relevant safety information on HDM allergoid immunotherapy.

Lead Member State assessment comment:

MAH Stallergenes SAS

One NIS was completed (Safety and effectiveness of a 300 IR house dust mite sublingual tablet: descriptive 4-year final analysis of a post-marketing surveillance in Japan) during the reference period and one Post-Authorisation Safety Study (PASS) (VORAN Study (ORY-MIT-PAS-01-DE) in Germany and Austria: "Study of the safety and tolerability of ORYLMYTE in routine medical practice in adolescents and adults) with HDM SLIT TABLET HDM tablets was ongoing during the reference period.

Additionally, during the reporting period, one investigator-initiated study (Investigator-initiated study (IIS) in Australia: "Patient stratification and monitoring of ACTAIR treatment efficacy using new objective immune markers", Principal Investigators: Prof Menno van Zelm and Prof. Robyn O'Hehir) was completed and one investigator-initiated study (Investigator-initiated study (IIS) in Australia: "Effect of Allergy Immunotherapy on Turbinate Surgery", Principal Investigator: Prof. Richard Harvey) was ongoing.

There were no relevant safety findings on patterns of medication errors and potential medication errors, identified, which would require specific risk minimization measures at this time. Cases of medication error will continue to be closely monitored, and this is endorsed.

There was no safety signal recognised from the literature identified, during the current reporting interval.

In general, no information relevant to the benefit-risk assessment has been obtained from clinical trials or other study sources during the reporting interval.

1.3.6. Lack of efficacy in controlled clinical trials

Lead Member State assessment comment:

No cases of lack of efficacy were reported in ongoing clinical trials and no clinical trial results indicated lack of efficacy for dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy, during the reporting period.

1.3.7. Late-breaking information

Lead Member State assessment comment:

No new and relevant safety or efficacy / effectiveness findings were received between the DLP and the submission of this PBRER for for dermatophagoides pteronyssinus / dermatophagoides farina allergen for therapy.

2. Signal and risk evaluation

2.1. Summary of safety concerns

2.1.1. MAH ALK-Abelló-A/S

A summary of the important safety concerns included in the HDM SLIT-tablet RMP at the beginning of this PSUR reporting period, RMP version 6.0, dated 21 March 2022.

During the period the HDM SLIT-tablet RMP was updated to version 7.0 dated 13 December 2024. The safety concerns remain unchanged.

Table 20. Summary of safety concerns RMP version 6.0

Important identified risk	Eosinophilic oesophagitis
Important potential risk	None
Missing information	None

2.1.2. MAH Stallergenes SAS

Table 21. Summary of safety concerns

Important identified risk	Severe laryngopharyngeal reactions
Important identified risk (class effect)	Anaphylactic reaction including anaphylactic shock
	Eosinophilic oesophagitis
Important potential risk (class effect)	Autoimmune disorders
Missing information	Pregnant and lactating women

2.2. Signal evaluation

2.2.1. MAH ALK-Abelló-A/S

In the PSUR reporting period, four signals were opened for the HDM SLIT-tablet or for SLIT products in general. Three were evaluated to be a new risk to treatment with the HDM SLIT-tablet and one was refuted due to lack of sufficient evidence in available data. The signal Rash was monitored closely for a year in an attempt to obtain more detailed information in the reported cases before the final evaluation.

Table 22. Tabular overview of signals: new, ongoing or closed during the reporting interval 23 September 2022 to 22 September 2025

Signal term	Date detected	Status new ongoing or closed	Data closed for closed signals	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Oral mucosal discolouration	24 October 2023	Refuted	22 February 2024	Periodic signal detection	During routine signal detection, 59 cases related to oral mucosal discolouration for ALK SLIT products were detected in the GSDB in addition to a publication describing 3 cases in children with gum pigmentation considered related to SLIT	Review of cases from the GSDB and from clinical trials for selected PTs, in addition to a literature review	None
Rash	21 December 2023	Closed	01 July 2025	Periodic signal detection	During routine signal detection a high number of cases with PT Rash assessed as unlisted and possibly related to treatment was detected in the cumulative review of cases in the GSDB	Review of cases from the GSDB and from clinical trials under the HLTs Rashes, eruptions and exanthems NEC and Dermatitis and eczema	After a period of additional monitoring Rash was assessed as a new risk and added to CCSI version 11.0. The local label will be updated subsequently where relevant.
Dizziness	26 February 2025	Closed	01 July 2025	Periodic signal detection	During routine signal detection a high number of cases with PT Dizziness assessed as unlisted and possibly related to treatment was detected in the cumulative review of cases in the GSDB	Review of cases from the GSDB and from clinical trials with PT Dizziness and PTs Vertigo, Pre-syncope and Balance disorder as supporting data	Dizziness was assessed as a new risk and added to CCSI version 11.0. The local label will be updated subsequently where relevant
Malaise	26 February 2025	Closed	01 July 2025	Periodic signal detection	During routine signal detection a high number of cases with PT Malaise assessed as unlisted and possibly related to treatment was detected in the cumulative review	Review of cases from the GSDB and from clinical trials with PT Malaise and with PTs	Malaise was assessed as a new risk, however, considered covered by the already listed

Signal term	Date detected	Status new ongoing or closed	Data closed for closed signals	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					of cases in the GSDB	Asthenia and Fatigue as supporting data	event of PT Fatigue.

2.2.1.1. Refuted signal

2.2.1.1.1. Oral mucosal discolouration

Summary of signal evaluation: During a routine periodic signal detection with DLP 30 September 2023, a new case with PT Pigmentation was reported. Based on this case, a search was made to identify scientific literature describing these types of events during allergy immunotherapy in addition to a search for other similar cases in the GSDB. Due to an identified literature report and the number of cases in the GSDB, a signal was suspected for the SLIT products: SLIT tablets and drops, including the HDM SLIT-tablet.

The assessment was initiated to investigate if oral mucosal discolouration could potentially be a class effect of SLIT administration, regardless of allergen and product formulation. Cases with the following MedDRA PTs were included in the performed analyses: PTs Administration site discolouration, Application site discolouration, Gingival discolouration, Gingival hyperpigmentation, Lip discolouration, Mucosal discolouration, Oral mucosal discolouration, Oral pigmentation, Oropharyngeal discolouration, Pigmentation disorder, Pigmentation lip, Tongue discolouration, Tongue pigmentation, and Vaccination site discolouration.

As of DLP, **a total of 30,751 cases were received** in the GSDB, **including a total number of 74,132 adverse events**. ALK SLIT included SLIT-tablets (HDM, grass, tree and ragweed) and SLIT drops (OSIRIS, SLIToneULTRA, and Pangramin with multiple allergens represented).

Cumulatively, 65 cases with 71 events have been received for SLIT products in the GSDB until DLP 30 November 2023. Six events of PT Pigmentation disorder did not describe discolouration in the mouth, but instead skin reactions on the chest, legs, ears etc. These events have been excluded from further analysis.

A total of 59 cases with 65 events included events related to oral mucosal discolouration; 32 cases were reported from patients using SLIT-tablets, among which n=16 cases were reported for the HDM SLIT-tablet, and 27 from patients using SLIT-drops. The most frequently reported AIT allergens were house dust mite and grass, but other allergens such as cypress, ragweed and ribwort plantain were also presented.

Oral mucosal discolouration and tongue discolouration were among the most frequently reported events but also lip and gingival discolouration were reported. De-challenge was positive in eight cases with ten events, and re-challenge was positive for three cases with 4 events. One of the cases were reported for HDM SLIT-tablet, however the positive re-challenge did not concern the reported event of black discolouration, but sublingual swelling occurring at the same time.

Table 23. Overview of adverse events from post-marketing sources

PT	Event count	Event frequency per cases* / per events**	Causality possible by MAH	De-challenge Positive / negative	Re-challenge Positive / negative
Oral mucosal discolouration	19	0.00062 / 0.00026	16	6 / 2	4 / 0
Tongue discolouration	17	0.00055 / 0.00023	16	0 / 0	0 / 0
Gingival discolouration	5	0.00016 / 0.00007	4	1 / 0	0 / 0
Mucosal discolouration	5	0.00016 / 0.00007	5	0 / 1	0 / 0
Application site discolouration	5	0.00016 / 0.00007	1	0 / 1	0 / 0
Lip discolouration	5	0.00016 / 0.00007	4	2 / 0	0 / 0
Oral pigmentation	3	0.00010 / 0.00004	3	0 / 0	0 / 0
Pigmentation lip	3	0.00010 / 0.00004	2	1 7 0	0 / 0
Tongue pigmentation	2	0.00007 / 0.00003	2	0 / 0	0 / 0
Oropharyngeal discolouration	1	0.00003 / 0.00001	1	0 / 0	0 / 0
Total	65	-	54	10 / 4	4 / 0

*Event frequency per cases calculated based on the cumulative number of cases 30,751 received for ALK SLIT products in the GSDB as of DLP **Event frequency per events calculated based on the cumulative number of events 74,132 received for ALK SLIT products in the GSDB as of DLP

All 65 events, in 59 cases, were divided into the following colour-categories based on the reported description: White: n=19 events; Dark: dark, black, brown, brown-black: n=19 events; Yellow: n=4 events; Purple: purple, blue: n=4 events; Greyish: n=1 event and Unspecified: n=18 events.

Oral pigmentation may be physiologic or pathologic. Pathologic pigmentation can be classified into exogenous and endogenous based upon the cause. Exogenous pigmentation could be induced by drugs, tobacco/smoking, amalgam tattoo or heavy metals induced. Endogenous pigmentation can be associated with endocrine disorders, syndromes, infections, chronic irritation, reactive or neoplastic. For many cases, limited information was available regarding the event, which makes it challenging to make a thorough medical evaluation and assess a cause-and-effect relationship and for 18 events, the type and colour of discolouration was unspecified.

For 25 events, time to onset occurred within 1 month, in n=10 events between 1 month and 12 months, and for n= 3 events onset occurred after 12 months of treatment. In 27 of the 65 events time to onset were unknown.

In n=19 of the 59 cases, alternative aetiologies or important confounding factors were described: Concomitant use of other sublingual allergen product (STALORAL SLIT BIRCH); Concomitant medication of inhaled Antihistamines and/or oral antihistamines; Concomitant medication of inhaled β2 adrenergic receptor agonists; Concomitant medication of inhaled and oral corticosteroids; Concomitant medication of oral angiotensin-converting enzyme inhibitor; Concomitant oral mycosis with prescribed antifungal treatment; Concomitant medication of oral penicillin and Thorough tooth brushing (indicated as alternative aetiology in n=2 cases).

The reporting rates were considered low across all the products, ranging from 0.0011% to 1.2903%. The

reporting rate was highest for Osiris 342 Ribwort plantain, English plantain, Osiris 312 Mugwort, and SLITone 188 Grass mix. For the HDM SLIT-tablet the reporting rate was 0.0016%. Clinical trial data obtained from 53 completed clinical trials with HDM, tree, grass or ragweed SLIT-tablets, phase I-IV including children, adolescents and adults, were included for further analysis. Very few events were reported in clinical trials and for the HDM SLIT-tablet, n=6 (in 5 participants) versus n=2 events (in 2 participants) were reported for active versus placebo, respectively. Of the n=6 events, n=3 were reported as related to treatment by the investigator, n=3 as not related. Furthermore, n=4 recently completed phase III clinical trials (n=2 HDM SLIT-tablet, n=1 tree SLIT-tablet and n=1 5-grass mix SLIT drops) included oropharyngeal examinations at most visits; no discolouration or pigmentation changes were reported in these trials. A literature search identifying a total of 22 publications did not reveal any further cases of suspected AIT-induced oral mucosa discolouration. A search was conducted on PubMed on 'oral cavity mucosa discolouration' limited to the last 10 years to investigate competing aetiologies described as causes of acute discolouration of the oral mucosa.

The search produced 41 results with a multitude of causes for discolouration of various types and several of the articles described case studies with descriptions and/or images not dissimilar to some of the reported events in the GSDB and with proposed aetiologies ranging from COVID-19 to smoker's melanosis, physiological pigmentation, post-inflammatory hyperpigmentation including lichen planus and manifestation of systemic disease. Further, searches were performed in the European suspected adverse reactions database and in the FAERS dashboard. The results from the searches did not identify information which could potentially support a signal of oral mucosal discolouration in relation to treatment with SLIT. The in-depth review of the spontaneous data, clinical trial data, data from external databases, and the literature did not point to a specific cause of the discolouration and therefore did not reveal new information which could support the suspected signal of 'Oral mucosal discolouration'. Pigmentations are commonly found in the mouth. They represent various clinical patterns that can range from just physiologic changes to oral manifestations of systemic diseases and malignancies. Colour changes in the oral mucosa can be attributed to the deposition of either endogenous or exogenous pigments as a result of various mucosal diseases. Many of the post-marketing cases contained limited information and large diversity/inconsistency in colour of the discolouration reported (white, black, blue etc.) suggesting different causes. Although the clinical data for the HDM SLIT-tablet showed a higher proportion of participants in the active treatment group experiencing discolouration compared to placebo, the discolouration was not described in detail and with the few events reported, a clear causal relationship to treatment could not be established. Limited information was available in the literature and in the external regulatory databases where it was found that several other drug products could be an aetiology for oral mucosal discolouration, but not AIT.

MAH conclusion: no clear causal relationship between oral mucosal discolouration and any of the products, including the HDM SLIT-tablet, was established.

Consequently, the signal was refuted and closed in February 2024.

Lead Member State assessment comment:

One signal `Oral mucosal discolouration` was triggered by a routine signal detection. During the reporting period the signal was refuted and closed. To note, very few events were reported in clinical trials. During the signal assessment, there was no clear causal relationship between oral mucosal discolouration and any of the concerned products, recognised.

The assessment of the signal of `Oral mucosal discolouration` by the MAH is endorsed.

2.2.1.2. Confirmed signals

2.2.1.2.1. Rash

Summary of signal evaluation: The suspected signal of rash was discovered during routine signal detection covering the period 01 June 2023 to 30 November 2023. The signal was triggered by the high number of cases of PT Rash in the cumulative period assessed as possibly related to **treatment 164 cases of 10,328 cases in total**. The initial signal evaluation was inconclusive, and the signal was put under monitoring for an additional year. A specialized follow-up questionnaire was sent to the reporter whenever rash was reported to ALK with the aim of obtaining more descriptive information on the events. During this period, 34 new cases within the HLT Rashes, eruptions and exanthems NEC were received. Rash is defined as an eruption in the skin that can be itchy, red, scaly, swollen, painful and irritated. It can have various causes including underlying diseases, infections, irritants, allergies and medicinal products. Immediate drug hypersensitivity reaction is normally associated with an IgE-mediated response and occurs within 1-6 hours after medicinal administration, whereas delayed reaction can occur many days after treatment and is associated with a T lymphocyte mediated response. In respect to AIT, it is well known that allergy symptoms are common reactions to the treatment and IgE-mediated rash is clinically plausible in this context. It is difficult to estimate the background prevalence of rash due to the nonspecific manifestation that can reflect a variety of conditions. The prevalence of self-reported itchy rash lasting longer than 3 days has been reported to be 51.7% of the general population over a lifetime. A slight overrepresentation of women reported itchy rash compared to men, although this could be biased by a higher frequency of consultation and greater use of skin products. The signal analysis has been performed on events from the HLT Rashes, eruptions and exanthems NEC. In addition, as rash could be a part of an anaphylactic reaction and therefore not coded as a separate event, all case narratives related to PT Anaphylactic reaction and PT Anaphylactic shock from post-marketing cases were reviewed.

The cumulative search with HLT Rashes, eruptions and exanthems NEC resulted in 235 cases of which the majority 153 cases included events assessed as probably or possibly related to treatment. The 23 probably related cases showed a short time to onset between tablet intake and rash onset, and positive de-challenge. Further, n=2 cases presented with positive re-challenge and in n=3 cases rash re-occurred after each tablet intake, all factors supporting a causal relationship to treatment with the HDM SLIT-tablet. The most prevalent location of rash was in the face or generalised or not further specified. In 93 cases, onset of rash occurred within the first 2 weeks of treatment and 37 on the first day of treatment, indicating that rash could be a symptom of an allergic reaction with rapid onset.

A total of n=14 cases (nine events) were assessed serious for multiple reasons such as co-reported events, adrenaline treatment and hospitalisation, but only **in n=1 case the patient was hospitalised due to rash as a solitaire event**. From these data, there is therefore no reason to suggest that rash alone should be considered serious. Frequencies from clinical trials did not indicate a causal relationship for rash either as single term or as selected terms from the HLT Rashes, eruptions and exanthems NEC, as distribution of events were almost similar across the treatment groups placebo versus active. These results suggested that the underlying allergic disease was the main reason for the patient experiencing rash.

Table 24. Adverse events related to Rash reported from clinical trials

Rash (Grouped term)	Placebo	Active (12 SQ-HDM)	Active (all treatment doses
Number of participants (n/N)	36/3,479	25/3,336	46/5,454
Frequency (n%)	1.03%	0.75%	0.84%

Number of events (E)	45	30	56
Serious events	0	0	0
Severe events	0	0	0
IMP-related events	5	7	13
Time to onset	From 1 to 448 days with median 114 days	From 1 to 773 days with median 180.5 days	From 1 to 773 days with median 118 days
Time to onset for IMP-related events	From 2 to 34 days with median 5 days	From 1 to 394 days with median 16 days	From 1 to 394 days with median 12 days

Rash included the following PTs from HLT Rashes eruptions and exanthems NEC PT Rash PT Rash erythematous PT Rash macular PT Rash maculo-papular PT Rash popular PT Rash pruritic PT Rash vesicular

MAH conclusion: despite rash being an unspecific term with many possible pathophysiological mechanisms, and despite lack of evidence from clinical trials, the high proportion of probably and possibly related cases, and some strong index cases presenting de-challenge/re-challenge and re-occurrence after each tablet intake provide evidence of a new risk to treatment with the HDM SLIT-tablet. The evidence was supported by literature with presented rash as a symptom of a systemic allergic reaction. The severity and duration of rash presented in the cases varied considerably resulting in both treatment discontinuation and in cases the rash resolved without intervention, thus the impact on the benefit-risk balance is limited.

Lead Member State assessment comment:

One signal `Rash` was triggered by a routine signal detection, that have highlighted a high number of PT cases Rash. During the signal assessment, a total of n=14 cases with n=9 events were assessed as serious with one case requiring hospitalisation. To note, few events were reported in clinical trials.

During the reporting interval the signal was closed. In conclusion, `Rash` was evaluated as a new risk. The RSI was updated accordingly to the CCSI version 11.0.

The assessment of the signal of `Rash` by the MAH is endorsed.

2.2.1.2.2. Dizziness

Summary of signal evaluation: During periodic signal detection, a cluster of dizziness events were observed in the period covering 01 June 2024 to 31 January 2025, leading to the suspicion of a signal of dizziness from treatment with the HDM SLIT-tablet. Dizziness is described as a disturbed sense of relationship to space. It is a term that people use to describe a range of sensations, such as feeling faint, woozy, weak or wobbly and is considered a chief complaint commonly used to describe many conditions and may occur with or without vertigo, which is a sense where you or your surroundings are spinning or moving.

In general, there are four main types of dizziness, all of which have been analysed in this signal assessment: Light-headedness PT: Dizziness; Vertigo PT: Vertigo; Disequilibrium PT: Balance disorder and Presyncope PT: Presyncope.

A variety of conditions may produce subjective feelings of dizziness without vertigo pseudo-vertigo that correspond to presyncope or nonspecific "light-headedness". Examples of conditions can be stress (e.g. a vasovagal response), anaemia, thyroid disease, low blood pressure, etc. Also, conditions that affect the

inner ear, motion sickness and medicine side effects are known to cause dizziness. The pathophysiologic mechanism behind this will vary for the different conditions. Dizziness is among the most common signs and symptoms of anaphylaxis. Dizziness is also listed in the EACCI guideline on anaphylaxis as a symptom to be aware off in the diagnosis and treatment of anaphylaxis.

The MAH database included **124 cases with 127 events of dizziness among 11,929 reported cases** for the HDM SLIT-tablet. 58 of the 124 cases were assessed as probably related to treatment primarily due to the close temporal relationship with rapid onset 1-15 days of treatment initiation + n=1 case with on day 26 of treatment initiation. Of the 58 cases, n=9 cases were identified with positive de-challenge and n=4 cases with positive re-challenge. Dizziness can be linked to allergic symptoms, potentially serving as a precursor to anaphylaxis in rare instances.

Additional 33 of 124 cases were assessed as possibly related to treatment due to lack of sufficient detailed information, or a weaker temporal relationship, making it difficult to rule out a causal relationship. The remaining cases were assessed as unlikely related or un-assessable. Few cases with vertigo n=19, presyncope n=11 or balance disorder n=2 have been received for treatment with the HDM SLIT-tablet and only n=6 were assessed as probably related to treatment n=2 and n=4, for vertigo and presyncope, respectively. Many of the cases with vertigo resembled the cases with dizziness in terms of rapid onset 1 to 14 days in n=10 cases and short duration minutes to hours. Though the majority of dizziness incidents were classified as non-serious, their impact was significant enough to lead to treatment discontinuation in 73 cases. Very few events of dizziness were reported in clinical trials, and the reporting was slightly higher for placebo 0.6% compared to 12 SQ-HDM 0.5%, thus not supporting a causal relationship. It is noted that dizziness is a prevalent condition in the general population, affecting 20–30% of individuals. This naturally complicates the process of ascribing the symptom directly to the HDM SLIT-tablet. However, the rapid onset of dizziness in many of these cases following treatment serves as supporting evidence of an association with the HDM SLIT-tablet.

MAH conclusion: the cases reported to the MAH provides evidence of a new risk to treatment with the HDM SLIT-tablet, despite lack of evidence from clinical trials. This was supported by literature which presented dizziness as a symptom of a systemic allergic reaction. The severity and duration of dizziness presented in the cases were often intolerable for the patients and led to treatment discontinuation, thus affecting the benefit-risk balance negatively. However, with the low reporting rate and the fact that the patients recovered when discontinuing treatment, the impact on the overall benefit-risk balance is evaluated to be minor. The ADR dizziness is absent from the CCSI, due to lack of evidence from clinical trials, but **dizziness is already presented as an ADR in several local labels, including the EU SmPC**. Dizziness is also mentioned as a symptom associated with risk of systemic allergic reactions in some labels.

Lead Member State assessment comment:

One signal `Dizziness` was triggered by a routine signal detection. During the signal assessment, the majority of the events were assessed as non-serious, but nevertheless treatment discontinuation was reported in 73 cases. To note, very few events were reported in clinical trials.

During the reporting interval the signal was closed. In conclusion, `Dizziness` was evaluated as a new risk. The RSI was updated accordingly to the CCSI version 11.0.

The assessment of the signal of ` Dizziness` by the MAH is endorsed.

2.2.1.2.3. Malaise

Summary of signal detection: During periodic signal detection, a cluster of malaise events were observed in the period covering 01 June 2024 to 31 January 2025, leading to the suspicion of a signal of malaise from treatment with the HDM SLIT-tablet. Malaise is a general feeling of being unwell. It is a symptom of multiple health conditions, reactions to medications, or other causes. Malaise may be caused by inflammatory proteins called cytokines, which deploy when the immune system activates or doesn't work properly. According to the Cambridge Academic Content Dictionary, malaise is also defined as a general feeling of bad health or lack of energy in a person, group, or society. It often occurs with fatigue and an inability to restore a feeling of health through proper rest. A person may feel this way for various reasons. Some causes are transient and relatively benign, while others are more chronic and severe. Sometimes, malaise happens suddenly. During an allergic reaction, the body's immune system releases chemicals like histamines, which can lead to inflammation and discomfort, contributing to a feeling of malaise. Malaise belongs to the MedDRA HLT Asthenic conditions, which also includes the PTs Fatigue, Asthenia and Decreased activity, all of which have been included in this signal assessment.

The MAH database included **127 cases with 128 events of malaise among 11,929 reported cases** for the HDM SLIT-tablet. 51 of the 127 cases were assessed as probably related to treatment primarily due to a close temporal relationship to onset 1-10 days of treatment initiation of which 37 cases occurred at the first day of treatment. N=17 cases included evidence of de-challenge. Additional 26 cases were assessed as possibly related to treatment primarily due to lack of sufficient detailed information or a weaker temporal relationship.

Of the 127 cases, n=11 cases with n=11 events of malaise were assessed as serious due to hospitalisation, adrenaline treatment or because they were assessed as medically significant. In the n=4 cases where the patients were treated with adrenaline, malaise was just one of many symptoms reported indicating that the patient experienced a systemic allergic reaction. Although few events were serious, the impact was significant enough to lead to treatment discontinuation in 74 cases. To broaden the analysis events in HLT Asthenic conditions were included in the assessment. This added 146 cases of PT Fatigue, 41 cases of PT Asthenia and n=1 case of PT Decreased activity. Fatigue is already a listed event for the HDM SLIT-tablet and was therefore not investigated further. 29 of the 41 cases with PT Asthenia were assessed as probably/possibly related to treatment supporting a causal relation to treatment. Very few events of malaise were reported in clinical trials, and the reporting was slightly higher for placebo (0.2%) compared to 12 SQ-HDM (0.1%), thus not supporting a causal relationship. The definition of malaise is somewhat imprecise, and this is also the case for the terms fatigue and asthenia. They can sometimes occur simultaneously and even though they are not covering entirely the same group of symptoms the terms are used interchangeably in both medical and lay contexts.

In the literature malaise is a recognised adverse event to vaccination; and classified as a common minor vaccine reaction often appearing alongside fever and headache. It is believed to be a non-allergic systemic reaction, to be distinguished from systemic IgE-mediated reactions. However, allergic reactions lead to biochemical changes inflammatory cytokines which affects the central nervous system. This can, when suffering from symptomatic allergic rhinitis, lead to sleep disturbance, fatigue and depressive symptoms such as e.g. malaise, weakness, and decreased activity.

MAH conclusion: despite malaise being an unspecific term with different physiological mechanisms, and the lack of evidence from clinical trials, the high proportion of probably related cases and cases with de-challenge, provides evidence of a new risk to treatment with the HDM SLIT-tablet. Going forward, the PT Malaise will, together with PT Asthenia be considered part of the grouped term PT Fatigue, which is listed in the CCSI. The literature supports this by describing that allergic reactions/allergy can give symptoms such as fatigue, malaise, weakness, and decreased activity. These events have impact on patients, and treatment discontinuation is expected. However, since the events are anticipated to resolve after

treatment discontinuation, together with the low reporting rate and the fact that most patients recover when discontinuing treatment, the impact on the overall benefit-risk balance is evaluated to be minor.

Lead Member State assessment comment:

One signal `Malaise` was triggered by a routine signal detection. During the signal assessment, the majority of the events were assessed as non-serious with just few events assessed as serious. However, treatment discontinuation was reported in 74 cases. To note, few events were reported in clinical trials.

During the reporting interval the signal was closed. In conclusion, `Malaise` was evaluated as a new risk. Nevertheless, it is already a listed event.

The assessment of the signal of `Malaise` by the MAH is endorsed.

2.2.2. MAH Stallergenes SAS

Considering the size of the HDM SLIT TABLET data set, use of a statistical method was not considered appropriate. Signal detection is performed by regular review on a case-by-case basis of all cases from the Global Safety Database and by a periodic review of cumulative data including in the context of the preparation of aggregate reports. Upon detection of a potential signal, additional information is reviewed to confirm or refute the signal. This includes cumulative review of data from all sources related to the concerned ADRs, extended to other products of the same class and literature review, where relevant.

During the reporting period, there was no ongoing or closed signal, and no new signal has been detected.

No safety signal was closed during the reporting interval of this PBRER. The assessment of cases reported during the period did not raise any additional safety concern or signal with HDM SLIT TABLET.

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. MAH ALK-Abelló-A/S

New information on important potential risks

No safety concerns are defined as important potential risks in the RMP for the HDM SLIT-tablet.

New information on important identified risks

2.3.1.1. Eosinophilic oesophagitis EoE

EoE is a chronic allergen-induced, type 2 immune-mediated disease of the oesophagus characterised by symptoms of oesophageal dysfunction and an eosinophilic predominant infiltrate in the oesophagus and is believed to be associated with the allergic disease process, often occurring in patients with other atopic conditions. In the period covered by this report, no events of EoE have been reported from clinical trials.

During the reporting period, **31 cases of EoE were received from spontaneous sources: n=6 serious cases** and 25 non-serious cases. N=12 of the 31 cases of EoE were medically confirmed by further diagnostics such as endoscopy and histopathology. In the remaining cases, either no diagnostics were performed n=4 cases or it was unknown if any diagnostics were performed n=15 cases.

At the time of reporting, n=15 of the reported events were recovered, n=5 events were recovering, n=1 event was resolved with sequelae not further specified, n=1 event was not recovered, and for n=9 events

the outcome was unknown. The n=6 serious cases were serious due to medical significance n=4 cases, hospitalisation n=1 case and n=1 case reported as life-threatening with very limited information available.

MAH conclusion: the cases received during the period of this report did not provide new, significant safety information concerning the risk of EoE.

New information on other potential risks not categorised as important

There are no potential risks not categorised as important for the HDM SLIT-tablet.

New information on other identified risks not categorised as important

2.3.1.2. Serious systemic allergic reactions, including anaphylactic shock

Serious systemic allergic reactions, including anaphylactic reactions and anaphylactic shock, have not been reported in the clinical trial program but are considered class effects for AIT. Serious systemic allergic reactions, anaphylactic reactions and cases of anaphylactic shock have been reported from spontaneous sources reflecting the risk in clinical practice for the HDM SLIT-tablet. In the period covered by this report, no serious systemic allergic reaction, including anaphylactic shock have been reported from clinical trials.

During the reporting period**, 88 cases with 120 events related to serious systemic allergic reactions including anaphylactic shock were received** from spontaneous sources or included in cases with significant follow-up. At the time of reporting, 79 of the reported events were recovered, n=10 events were recovering, n=1 event was resolved with sequelae not further specified, n=2 events were not recovered, and for 28 events, the outcome was unknown.

In 35 of the 88 cases, use of adrenaline was reported suggesting a more severe reaction. N=7 of the cases were immediate reactions within 30 minutes after the initial dose, suggesting that the patients were treated in the clinic. N=14 cases were reported on the same day of the initial dose but exact time to onset was unknown n=13 cases or reported to occur 5 hours after initial dose n=1 case. The remaining cases were reported to occur later than day 1 n=12 cases or with unknown time to onset n=2 cases. Outcome in the 35 cases with reported use of adrenaline was recovered in 26 cases, recovering in n=3 cases, and unknown in n=5 cases. In n=1 of the 35 cases, outcome was not recovered at the time of reporting; in this case respiratory distress occurred more than 2 years after initiation of treatment and was co-reported with various other symptoms indicating an unlikely causal relationship to the HDM SLIT-tablet.

MAH conclusion: no significant new safety information or changes in frequency or severity have been identified for the risk based on the information received in the period.

2.3.1.3. Serious laryngo-pharyngeal reactions

Local allergic reactions of varying severity are considered a SLIT class effect. The main clinically relevant concerns with regards to local allergic reactions are serious laryngo-pharyngeal reactions that may potentially compromise airways and lead to life-threatening situations due to airway obstruction. In the period covered by this report, no serious laryngo-pharyngeal reactions have been reported from clinical trials.

During the reporting period, **53 cases with 78 serious laryngo-pharyngeal reactions were reported** from spontaneous sources. At the time of reporting, 51 of the reactions were recovered, N=5

reactions were recovering, n=1 reaction was recovered with sequelae not further specified, n=1 reaction was not recovered, and for n=20 reactions outcome was unknown. In n=11 of the 53 cases received in the period, treatment with adrenaline was reported suggesting a more severe reaction.

MAH conclusion: no significant new safety information has been identified for the risk based on the information received in the period.

2.3.1.4. Acute worsening of asthma symptoms (exacerbations)

Although data for the HDM SLIT-tablet supports a reduced risk of asthma exacerbations for patients with allergic asthma, the risk of an acute worsening of asthma symptoms does exist for patients with risk factors. In the period covered by this report, no events of acute worsening of asthma symptoms (exacerbations) have been reported in clinical trials. **During the reporting period, 68 cases with 72 events related to acute worsening of asthma symptoms have been reported** from spontaneous sources. At the time of reporting, 38 events were recovered, n=2 events were recovering, n=3 events were not recovered, and for 29 events the outcome was unknown. N=12 of the 68 cases reported serious events related to acute worsening of asthma symptoms exacerbations due to medical significance n=7 cases, and hospitalisation n=5 cases.

No overall changes to the risk, such as increased frequency or severity, have been identified based on data from spontaneous sources nor from the clinical trials.

Update on missing information

No safety concerns are defined as missing information in the RMP for the HDM SLIT-tablet.

Lead Member State assessment comment:

MAH ALK-Abelló-A/S

Taking into consideration the review of the risks presented by the MAH, no further action is considered warranted at this stage.

2.3.2. MAH Stallergenes SAS

NEW INFORMATION ON IMPORTANT IDENTIFIED RISK

2.3.2.1. SEVERE LARYNGOPHARYNGEAL REACTIONS

Since Severe LP reactions are under close monitoring, a cumulative review of cases has been performed using the SMQ "Oropharyngeal allergic conditions" as well as at least one of the following PTs: Laryngeal obstruction; Laryngeal oedema; Laryngeal tremor; Laryngospasm; Laryngotracheal oedema; Oropharyngeal oedema; Sensation of foreign body; Tracheal obstruction and Tracheal oedema. Or at least two of the following MedDRA PTs: Aphonia; Dysphagia; Dysphonia; Laryngeal dyspnoea; Odynophagia; Oropharyngeal pain; Oropharyngeal spasm and Throat tightness.

Identified Risk: Severe laryngopharyngeal reactions: Frequency with 95% CI: Eight cases of severe laryngopharyngeal reactions were reported in seven patients in the completed clinical trials. Of these, five patients were receiving HDM SLIT TABLET 300 IR (4 patients included in the rhinitis program and one patient included in the asthma program) and two patients included in the rhinitis program were treated with HDM SLIT TABLET at 500 IR. Six cases of severe laryngopharyngeal reactions were spontaneously reported with HDM SLIT TABLET (RR 0.076/10,000). Serious cases of laryngopharyngeal reactions have

been reported in HDM SLIT TABLET -treated patients. **No case with fatal outcome has been reported in clinical trials or post-marketing.**

Post marketing experience: To select the severe LP reactions, a focus on serious cases, with at least one of the seriousness criteria as per ICH E2D, containing at least 1 of the PTs of the above list was performed. Therefore, the following cases were excluded from the analysis: Cases without respiratory symptoms and Cases resolving without intervention effective in the acute management of severe LP reactions (e.g., epinephrine, intravenous fluids, parenteral corticosteroids or antihistamines, inhaled beta agonists, oxygen therapy). This section focuses on severe LP reactions, as they may lead to obstruction of upper airways.

Interval Period**: One case describing events pertaining to severe LP reaction was identified** during the interval period of this PBRER. which corresponds to a RR of 0.018 per 10,000 patients.

Case 2025-AER-02688: described a 11-year-old patient (unspecified gender) who experienced an incipient laryngospasm, conjunctivitis, dyspnoea, swelling of the lips and tongue swelling. The events occurred at day 4 of ACTAIR treatment and around 5 minutes after administration of ACTAIR 300 IR. This authority case was reported as Life Threatening and hospitalization (no details provided). It was unknown if the patient received corrective treatments. Drug was discontinued the same day. The patient was recovering at the time of the report. Company causality was assessed as Possible.

Cumulative Period: A total of six cases (201502263, 201600004, 201800942, 201901659, 202200338, 2025-AER-02688) since the first marketing of HDM SLIT TABLET have been identified.

Table 25. The cumulative overview of cases of severe LP reactions

Case Id Seriousness Criteria Source Country HCP Sex Age	Reaction/event (PT)	Outcome	Time to onset after treatment Introduction after last intake	Action (s) taken Corrective treatments	MAH causality
201502263 Other Medically important Condition Spontaneous Japan Y M 12	Laryngeal oedema	Recovered	Not stated	Drug withdrawn betamethasone	Possible
201600004 Other Medically important Condition Spontaneous Japan Y M 53	Pharyngeal swelling Dysphonia Wrong technique in product usage process	Recovered	The same day patient received last dose.	Drug withdrawn IV steroid	Probable
201800942 Other Medically important Condition Spontaneous Japan Y F 9	Laryngeal oedema	Recovered	5 minutes	Not reported Not reported	Probable
201901659 Other Medically important condition and hospitalization Spontaneous Japan Y M 14	Throat tightness Throat irritation Dyspnoea	Recovered	Few minutes	Not reported inhaled salbutamol IV prednisolone IM adrenaline	Possible

202200338 Life threatening Spontaneous DE Y F 13	Mouth swelling tongue oedema dysphagia	Recovered	10 minutes after administration	Drug discontinued IV prednisolone	Possible
2025-AER-02688 Life Threatening Caused prolonged hospitalization Medically Important Spontaneous Czechia Y UNK 11	Laryngospasm Conjunctivitis Allergic Dyspnoea Lip Oedema Tongue oedema Off label use	Recovering	5 minutes	Drug Discontinued Not reported	Possible

MAH Discussion

Significant medical history: Regarding medical history, two patients had a known medical history: food allergy, asthma and atopic dermatitis (201901659); multiples allergies (2025-AER-02688).

Corrective treatment and outcome: Corrective treatments were administered as follows: one adult patient (201600004) was treated by steroid injection; one adolescent patient (201502263) was treated with betamethasone; one adolescent patient (201901659) received inhaled salbutamol, intravenous prednisolone and inhaled adrenaline. Moreover, intramuscular adrenaline was administered for persistent throat; one adolescent patient (202200338) received intravenous prednisolone and for two child patients, corrective treatment was unknown. The adult patient (201600004) was admitted to emergency unit. Three adolescent patients (201502263, 201901659, 202200338) were admitted to hospital; two were admitted to the emergency unit only and one remained overnight for observation. The child patient (201800942) was not hospitalized. The second child patient (2025-AER- 02688) was hospitalized and considered by the reporter as life-threatening (no further details available). None of patients required intensive care. Favourable evolution observed in all cases: five patients recovered, and one patient was recovering.

MAH Conclusion: The cumulative analysis shows no change in the pattern of the severe LP reactions reported with HDM SLIT TABLET. Since the first marketing of HDM SLIT TABLET, six cases were retrieved. The cumulative RR as of the current data lock point is 0.076/10,000 patients, compared to 0.2 per 10,000 patients in the previous PBRER. All patients showed favourable clinical evolution. No cardiovascular events have been observed, and time of hospitalization was less than one day. This safety concern is considered as an important identified risk and **is described in the sections 4.4 and 4.8** of the CCSI/CCDS.

No further regulatory action is required at this point. Severe LP reactions will remain closely monitored.

2.3.2.2. ANAPHYLACTIC REACTION INCLUDING ANAPHYLACTIC SHOCK

Search criteria for anaphylactic reaction: The SMQs Anaphylactic reaction, Hypersensitivity and Angioedema were used to identify cases pertaining to anaphylactic reaction with HDM SLIT TABLET in the database. Only serious cases have been considered in the query.

A total of 126 cases pertaining to the query were found cumulatively, including **66 cases during the reporting period**. From this search, serious cases that do not meet the clinical criteria for diagnosing anaphylaxis and those resolving without effective intervention in the acute management of anaphylaxis (e.g., epinephrine, intravenous fluids, parenteral corticosteroids or antihistamines) were excluded from the analysis.

Search criteria for anaphylactic shock: As anaphylactic shock is an important potential class effect risk of AIT, a cumulative review of cases using the SMQ "Anaphylactic/anaphylactoid shock conditions" was performed. Only serious cases have been considered in the query. According to the query results, 42 cases pertaining to the query were found cumulatively, including **24 cases during the reporting period**. From this search were considered as potential anaphylactic shock: Life threatening anaphylactic reactions leading to administration of epinephrine, supplemental high flow oxygen, IV fluid resuscitation with a crystalloid such as 0.9% isotonic saline, and cardiopulmonary resuscitation or anaphylactic reactions with fatal outcome.

Identified Risk class effect Anaphylactic reaction including anaphylactic shock Frequency with 95% CI: No cases of severe anaphylactic reaction including anaphylactic shock were reported in clinical trials. Thirty-three cases of anaphylactic reaction were spontaneously reported with HDM SLIT TABLET (RR 0.42/10,000). Two cases of anaphylactic shock were spontaneously reported with HDM SLIT TABLET (RR 0.025/10,000).

Anaphylactic reactions have been reported in HDM SLIT TABLET-treated patients. **No case with fatal outcome has been reported in clinical trials or post marketing.**

Post marketing experience: Interval Period: **Cases reporting anaphylactic reaction**:

According to the query results, 66 cases were retrieved from the query during the reporting period. Considering the criteria presented above, **21 cases of anaphylactic reaction were selected**. The RR as of the current period is 0.38 per 10,000 patients, compared to 0.14 per 10,000 patients in the previous PBRER.

Case 202201978: described an 11-year-old female patient who experienced an anaphylaxis unspecified time after ACTAIR initiation/administration. The patient went to the hospital. It was not reported whether the patient was treated with corrective medication. ACTAIR was discontinued. The outcome was unknown. No additional information was provided, and thus the case is selected as a conservatory measure. The MAH causality was assessed as Possible.

Case 202300555: described a 31-year-old female patient who presented with an anaphylaxis grade 3 at day 3 of ORYLMYTE treatment 300 IR and 10 minutes after administration of ORYLMYTE 300 IR. The patient received adrenaline. The patient discontinued ORYLMYTE treatment. The patient experienced a second episode of an acute anaphylaxis with lip and tongue oedema 16 days after ORYLMYTE withdrawal which required hospitalization. The patient recovered. The MAH causality was assessed as Possible for the first episode of anaphylaxis.

Case 202301109: described a 19-year-old female patient who experienced tingling of tongue, mouth and lips, increasing hoarseness objective, dyspnoea subjective and itching of upper body without reddening. The events occurred around 5 minutes after the first administration of ORYLMYTE 100 IR. The patient was admitted to hospital. The vital signs and oxygen saturation were without abnormalities throughout the complete events. The patient received epinephrine hydrochloride Fastjekt 300 by Intramuscular route, prednisolone 250 mg by Intravenous route, sodium lactate Ringer solution 500 ml by Intravenous route. In the initial report the physician had reported anaphylactic shock. After evaluating the reactions, the physician confirmed that it was not an anaphylactic shock but an oral local reaction and a vocal cord dysfunction. The physician reported the recurrence of events two to three times after rebeginning of ORYLMYTE (date not specified). Drug was discontinued. The patient recovered on the same day. The reporter assessed the causality as Probable. The MAH causality was assessed as Probable.

Case 202301314: described a 6-year-old male patient who experienced a decrease in blood pressure 30 minutes after the first administration of ACTAIR treatment (100IR). The physician considered this event as an anaphylactic shock. Disturbed consciousness, respiratory symptoms, cutaneous symptoms or

digestive symptoms were not observed. Blood pressure was 133 mm Hg and 88 mmHg measured twice and at the time of outcome, it was 108 mmHg. The symptom improved by subcutaneous injection of adrenaline. Of note, the patient's medical history included otitis media, sinusitis and upper respiratory tract inflammation. The patient's concomitant medications included clarithromycin, carbocisteine and tipepidine hibenzate. It was not reported that the patient was hospitalized or presented with a life-threatening condition. The patient recovered. ACTAIR was discontinued. The physician assessed the causality as Certain. The MAH causality was assessed as Possible given the available data. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock, since no evidence of respiratory compromise or end organ dysfunction (such as cardiovascular collapse or syncope) was reported. The event was not considered life-threatening.

Case 202301666: described a 12-year-old male patient who presented with glossal oedema, dysphonia, sublingual oedema during day 11 of ORYLMYTE treatment, abdominal pain, lip oedema, ocular pruritus and auricular pruritus on an unknown date, and anaphylactic shock during day 12 of ORYLMYTE treatment. The patient was treated with budesonide via inhalation route and 60 mg of corticosteroids unspecified active substance and route of administration. The patient recovered and ORYLMYTE treatment was discontinued. The MAH assessed the causality as Possible. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock. This assessment is supported by the absence of documented administration of intramuscular adrenaline, supplemental high flow oxygen, intravenous fluids. Furthermore, no evidence of respiratory compromise or end-organ dysfunction (e.g., cardiovascular collapse or syncope) was reported, and the event was not considered life-threatening.

Case 2023-AER-02723: described a 14-year-old male patient who experienced anaphylaxis (shock) at the first day of ACTAIR treatment 100IR. Partial pressure of oxygen was 98-99 mmHg. Main findings were decrease in blood pressure (values: 93–107 mmHg) and skin symptom erythema. Pulse rate measurement was 76–85 bpm. There were no findings of disturbed consciousness, respiratory symptom or digestive symptoms. After blood pressure decreased due to anaphylaxis, adrenaline was subcutaneously administered. The patient recovered from the event of anaphylaxis (shock). ACTAIR was discontinued. The physician assessed the causality as Possible. The MAH causality was assessed as Possible. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock, since no evidence of respiratory compromise or endorgan dysfunction such as cardiovascular collapse or syncope was reported. The event was not considered life-threatening.

Case 2024-AER-00253: described an 11-year-old male patient who experienced decreased blood pressure no information on measurements, cold sweat, chill and tremor, queasiness and vomiting at day 10 of ACTAIR treatment. The physician considered these reactions as an anaphylactic shock. The patient was transported to hospital and was treated with drip infusion details were unknown. The patient went home on the same day without hospitalization. Since then, the patient did not receive ACTAIR. The patient recovered. The physician assessed the causality as Possible. The MAH causality was assessed as Possible. Based on the available information, the MAH considered this case more consistent with the onset of an anaphylactic reaction rather than an anaphylactic shock. This assessment is supported by the absence of documented administration of intramuscular adrenaline, supplemental high flow oxygen, intravenous fluids, or parenteral corticosteroids. Furthermore, no evidence of respiratory compromise or end-organ dysfunction such as cardiovascular collapse or syncope was reported.

Case 2024-AER-01235: described a 31-year-old male patient who experienced facial pallor and cold sweat for which he was placed in a lateral position, 16 minutes after the first administration of ACTAIR treatment (100IR). The blood pressure was 78/43 mmHg, and the heart rate was 59 bpm. The physician considered the clinical manifestation as an onset of anaphylactic reaction with decreased blood pressure. Numbness in hands and cold sweat were present. Subsequently, blood pressure and heart rate were

measured multiple times, at 18 min, 30 min, 40 min, 50 min and 55 min: BP: 78/53 mmHg; heart rate: 66 bpm, BP: 85/54 mmHg; heart rate: 62 bpm, BP: 96/59 mmHg; heart rate: 57 bpm, BP: 99/68 mmHg; heart rate: 60 bpm, BP: 108/68 mmHg; heart rate: 89 bpm. The patient was positioned in a semi-sitting posture then in a sitting position. At 11:10 a.m., 75 minutes later, blood pressure was 108/69 mmHg and heart rate were 64 bpm. The patient returned home. It was not reported whether the patient was treated with corrective medication. The patient was recovering at the time of the report. ACTAIR was discontinued. The physician assessed the causality as Possible. The MAH causality was assessed as Probable based on suggestive chronology.

Case 2024-AER-01537: described a 22-year-old male patient who developed allergic shock leading to hospital admission, respiratory disorder, dyspnoea, nausea, vomiting, shivering of the whole body, swelling at the base of the tongue, throat swelling and globus sensation during the third day of ORYLMYTE treatment and 1 hour after ORYLMYTE administration. The patient was treated with prednisolone 100 mg by IV route, cimetidine 200 mg by IV route, 500ml of IV fluids Sterofundin and 1mg of dimetindene maleate via IV route. The patient recovered and ORYLMYTE treatment was discontinued. The physician assessed the causality as Certain. The MAH causality was assessed as Possible based on the available information. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock. This assessment is supported by the absence of documented administration of intramuscular adrenaline or supplemental high flow oxygen. Furthermore, no evidence of end-organ dysfunction (e.g., cardiovascular collapse or syncope) was reported, and the event was not considered life-threatening.

Case 2024-AER-01566: described a 62-year-old female patient who experienced circulatory collapse, hives, vomiting, abdominal cramps, itching, light headedness, intestinal spasm, rhinitis, nausea, eyes tearing and sleep disorder 37 days after ORYLMYTE treatment initiation. No additional information was available regarding this authority case. Thus, this case was selected as a conservatory measure. It was not reported whether the patient was treated with corrective medication. The patient was recovering at the time of the report. ORYLMYTE was discontinued around 16 days after the occurrence of events. The MAH causality was assessed as Possible. Of note, the events were not considered life-threatening. There is no available information on the administration of adrenaline.

Case 2024-AER-01940: described a 13-year-old female patient who experienced allergic reaction with a serious criteria life-threatening at the first day of ACTAIR treatment and 10 minutes after ACTAIR administration. No additional information was available regarding this authority case. Thus, this case was selected as a conservatory measure. It was not reported whether the patient was treated with corrective medication. ACTAIR was discontinued and the patient recovered on the same day. The MAH causality was assessed as Probable.

Case 2024-AER-02384: described a 9-year-old male patient who developed anaphylaxis grade III with cough specified as barking, hoarseness of voice, dyspnoea and stridor, at day 14 of ORYLMYTE treatment and 10 minutes after ORYLMYTE 300IR administration. Of note, the physician specified that the patient 9 years old chewed and sucked on the tablet Off label use in unapproved age group and medication error). The patient was treated with epinephrine inhalation, salbutamol inhalation, 300 µg of epinephrine via IM route, 4 mg of dimetindene maleate via IV route and 100 mg of prednisolone suppository Rectodelt. The patient was hospitalized. The anaphylaxis lasted for 1 hour. The patient stayed for one night in hospital for monitoring and left the next day without problems. The patient recovered and ORYLMYTE treatment was discontinued on the same day. The physician assessed the causality as Certain. The MAH causality was assessed as Probable based on the suggestive chronology. It should be noted that ORYLMYTE was prescribed to a 9-year-old patient child younger than 12 years; off label use who chewed and sucked on the table instead of leaving it to dissolve sublingually. The possibility that the reported anaphylaxis was triggered by this medication error/off-label use cannot be completely excluded.

Case 2024-AER-02424: described a 28-year-old female patient who developed itching in her mouth and difficulty in breathing during day 14 of ACTAIR treatment, for which she was emergently transported to hospital and received drip infusion. These events were considered as anaphylactic reaction by the physician. The patient received treatment at the outpatient department. The symptoms were resolved within the day. ACTAIR treatment was discontinued. The physician assessed the causality as Certain. The MAH causality was assessed as Possible based on the available information.

Case 2024-AER-02702: described a 12-year-old male patient who initially experienced mild oral reactions (tingling and swelling under tongue) during first days of treatment with ORYLMYTE. On day 7 of treatment and 30 minutes after administration of ORYLMYTE, the reactions worsened to anaphylactic reaction grade 2 with symptoms of reddening in face and thorax, swelling of face, nasal congestion, mild dyspnoea, shivering and feeling of tightness. The anaphylactic reaction grade 2 led to call of Emergency medical service and hospitalization. The patient received prednisolone sodium succinate 250mg via IV route, dimetindene maleate via IV route, salbutamol inhalation and adrenaline inhalation. The patient recovered and ORYLMYTE treatment was discontinued. The physician assessed the causality as Certain. The MAH causality was assessed as Probable based on the available information.

Case 2025-AER-00481: described a 25-year-old female patient who presented with anaphylaxis at the first day of ORYLMYTE treatment and after administration of one tablet of ORYLMYTE 100 IR. No additional information was available regarding this authority case. It was unknown whether patient was received corrective treatment epinephrine or IV corticosteroid. ORYLMYTE was withdrawn. The patient recovered on the same day. The MAH causality was assessed as Possible. See note below.

Case 2025-AER-00494: described a 25-year-old female patient who presented with diagnosis of anaphylaxis signs and symptoms: itchy hyperaemia on the chin, neck and decollete; change in tone of voice, dysphagia, dyspnoea, polypnea, sensation of laryngeal obstruction, uvula oedema, at the first day of ORYLMYTE treatment. The patient had no known risk factor at the time of events. Blood pressure was normal: 134/82 mmHg. The patient was treated with epinephrine, IV fluids, 40mg of methylprednisolone via IM route and 20mg of bilastine via oral route. The patient recovered and ORYLMYTE treatment was discontinued. The physician assessed the causality as Certain. The MAH causality was assessed as Probable given the available data. Of note, this case is identified as a duplicate of the authority case 2025-AER-00481 ITMINISAL02- 1024241 as it was reported in same country of detection (Italy), same age of patient 25-year-old, same batch number of ORYLMYTE 303174434545 and with same start/end therapy date, 04 February 2025. A request to report a suspected duplicate case was performed thorough Report Duplicates Service Desk EudraVigilance. Only the case 2025-AER-00494 is retained.

Case 2025-AER-00935: described a 12-year-old male patient who experienced tongue edema, dysphonia, latter aphonia, difficulty swallowing, cough, swelling of the right cheek, throat irritation (red throat) and abdominal pain. The events occurred 10 days after ACTAIR initiation. The patient was admitted to hospital. The diagnosis was anaphylactic shock. Adrenaline via intramuscular route and Budesonide via inhalation were administered. The symptoms were resolved within 1 hour. The patient was hospitalized during 24 hours for observation. Drug was discontinued. The patient recovered on the same day. The reporter assessed the causality as Probable. Company causality was assessed as Possible based on the available information. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock, given the absence of respiratory compromise or end organ dysfunction e.g., collapse or syncope.

Case 2025-AER-01128: described a 16-year-old male patient who experienced an anaphylactic reaction: generalized facial angioedema, facial erythema, generalized oedema of the tongue, foreign body sensation, voice change, difficulty swallowing, difficulty breathing and shortness of breath choking, tachycardia, nausea, dizziness, and scintillating scotomas at the day 3 of ACTAIR treatment 300IR and despite premedication. The physician recommended to take double premedication at the second dose of

ACTAIR 300IR. The patient presented with more serious anaphylaxis. The patient was treated with antihistamines unspecified active substance and unspecified route of administration and inhalator corticosteroids unspecified active substance. The patient recovered. ACTAIR treatment was withdrawn. The physician assessed the causality as Certain. The MAH causality was assessed as Probable given the recurrence of event.

Case 2025-AER-01180: described a 15-year-old female patient who presented with pharyngeal oedema, dyspnoea, nausea, vomiting, jaw numbness (oral paraesthesia), chest tightness, asthenia and somnolence, on the day 7 of ACTAIR treatment and 5 minutes after administration of ACTAIR 300 IR. These events have been classified as anaphylactic shock by the physician. It was not reported whether the patient was treated with corrective medication. The patient recovered and ACTAIR treatment was discontinued. The physician assessed the causality as Probable. The MAH assessed the causality as Probable. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock. This assessment is supported by the absence of documented administration of intramuscular adrenaline, intravenous fluids, or parenteral corticosteroids. Furthermore, no evidence of respiratory compromise or end-organ dysfunction (such as cardiovascular collapse or syncope) was reported.

Case 2025-AER-01241: described an 11-year-old male patient who experienced an anaphylaxis with symptoms of lip and sublingual oedema, bronchospasm and rhino conjunctivitis during day 13 of ORYLMYTE treatment. It was unknown whether the patient was treated with epinephrine, intravenous fluids, parenteral corticosteroids or antihistamines and inhaled beta agonists. The patient recovered and ORYLMYTE treatment was discontinued on the same day. The MAH assessed the causality as Possible.

Case 2025-AER-01942: described a 11-year-old male patient who developed the event of anaphylaxis (reported as anaphylactic shock but without any detail) at day 3 of ACTAIR treatment. The reporter specified that it could not be determined whether anaphylaxis was serious or non-serious because it was treated at another facility. It was not reported that the patient was hospitalized or presented with a life-threatening condition. It was not reported whether the patient was treated with corrective medication, the case is selected as a conservatory measure. The patient was recovering at the time of the report. ACTAIR was discontinued. The MAH assessed the causality as Possible. Based on the available information, the MAH considered this case as an anaphylactic reaction rather than anaphylactic shock. This assessment is supported by the absence of documented administration of intramuscular adrenaline, supplemental high flow oxygen. intravenous fluids, or parenteral corticosteroids. Furthermore, no evidence of respiratory compromise or end-organ dysfunction (such as cardiovascular collapse or syncope) was reported, and the event was not considered life-threatening.

Cases reporting anaphylactic shock: According to the query results**, 24 cases were retrieved during the reporting period**. **Two cases of anaphylactic shock were selected considering the criteria** presented above, which correspond to a RR of 0.04 per 10,000 patients. In both cases, the diagnosis was made by physicians, but no detailed information was provided regarding the symptoms of anaphylactic shock.

Case 202301809: described an 11-year-old female patient who experienced an anaphylactic shock due to a food allergy, for which she had previously consumed and only experienced minor symptoms. The patient transferred to the reporting physician's hospital. The patient required adrenaline treatment. Although the patient's condition improved with treatment for anaphylactic shock, the patient subsequently experienced repeated anaphylactic shock due to food allergy. The patient recovered at the time of the report. Action taken with ACTAIR was unknown. The physician assessed the causality as Possible. The MAH causality was assessed as Unlikely with regards of the food allergy history. Based on the available information, anaphylactic shock is considered more likely related to the patient’s food allergy than ACTAIR administration.

Case 2024-AER-00226: described a 37-year-old female patient who developed dyspnoea after the second day of ORYLMYTE treatment (200IR) and experienced anaphylactic shock 4 minutes after ORYLMYTE 200IR administration. The patient was admitted to hospital. The patient received inhalation of adrenaline (6 drops in 10 ml NaCl), prednisolone 200mg via IV route and 500 ml sodium chloride solution via IV route. The patient recovered and ORYLMYTE treatment was discontinued. The physician assessed the causality as Certain. The MAH assessed the causality as Probable.

Cumulative period: After internal review, the case 201800657 was medically reassessed and excluded as an anaphylactic case: This case concerned a child patient who was receiving HDM SLIT TABLET for about 2 and a half years for the treatment of perennial allergic rhinitis. The patient experienced urticaria and dyspnoea and then was taken to the emergency outpatient department. The patient received treatment with an inhalant and prednisolone tablet. It was assumed that the events of urticaria and dyspnoea were not caused by HDM SLIT TABLET because the patient was also having allergies besides AR (atopic dermatitis and food allergy) which were worsening during this season. The reporting physician considered that the events of urticaria and dyspnoea were due to other allergies. The MAH assessed the causal relationship as possible based on the compatible chronology between HDM SLIT TABLET intake and adverse reactions occurrence. Based on Sampson criteria, this case does not meet the definition of anaphylaxis.

The case 2025-AER-00481 is excluded (duplicate of case 2025-AER-00494)

In total, and up to the DLP of this report, **33 cases of anaphylactic reaction have been reported**. The cumulative RR is 0.42 per 10,000 patients, compared to 0.59 per 10,000 patients in the previous PBRER. In total, and up to the DLP of this report, **two cases of reporting anaphylactic shock** have been reported, corresponding to a RR of 0.025/10,000.

To Note: The tabular cumulative overview of all cases of anaphylactic reaction is presented by the MAH in the PSUR report from page 63 up to page 81.

Table 26. A cumulative overview of cases of anaphylactic shock

Case Id Seriousness Criteria Source Country HCP Sex Age	Reaction event PT	Outcome	Time to onset after treatment Introduction after last intake	Action (s) taken Corrective treatments	MAH causality	Comment
202301809 Medically important Life-threatening Spontaneous Japan Y F 11	Anaphylactic shock Food allergy	Recovered	Not reported (same day)	Unknown Adrenaline	Unlikely	Based on available information anaphylactic shock is more likely related to patient's food allergy than administration of HDM SLIT TABLET No detailed information on symptoms of anaphylactic shock was provided to fully confirm the diagnosis
2024-AER-00226 Medically Important Hospitalization Life Threatening	Anaphylactic shock Dyspnoea	Recovered	4 minutes	Discontinued inhalation of adrenaline prednisolone IV and IV fluids	Probable	Physician reported onset of anaphylactic shock 4 minutes after administration. Patient's medical history included asthma. No details were provided on

Spontaneous DE Y F 37						symptomatology Anaphylactic shock was treated with adrenaline by inhalation Given time relationship MAH assessed causality as related

MAH Discussion about **anaphylactic reaction**:

Age group: Thirteen cases were reported in the adult population 201601559, 201700952, 201800730, 201801338, 201601380, 201601325, 202300555, 202301109, 2024-AER-01235, 2024-AER- 01537, 2024-AER-01566, 2024-AER-02424, 2025-AER-00494, four patients were male and nine were female. Twelve cases were reported in the adolescent population 201600347, 201600380, 201801495, 201801527, 202201259, 202301666, 2023-AER-02723, 2024-AER-01940, 2024- AER-02702, 2025-AER-00935, 2025-AER-01128, 2025-AER-01180, nine patients were male and three were female. Eight cases were reported in the children population less than 12 years old 201800922, 201901715, 202201978, 202301314, 2024-AER-00253, 2024-AER-02384, 2025-AER-01241, 2025-AER-01942, six patients were male and two were female. RR by age group could not be calculated due to the lack of age-specific exposure data. The only available exposure information was derived from German sales, which represent approximately 3.4% of the total estimated patient exposure. In addition, Japan accounts for about 72% of overall exposure; however, age-stratified data are not available for this market. Consequently, calculation of reporting rates per age group was not feasible.

Significant medical history: Medical history considered as significant for this analysis are previous treatment with SLIT, asthma and other concomitant allergy. No patient had been treated with SLIT. Five patients from the adult population reported concomitant relevant medical history: Asthma was reported in two patients 202300555, 202301109 and Other allergies were reported in three patients 201601380, 201801338, 2024-AER-01537. Six patients from the adolescent population reported having suffered from at least one of atopic conditions such as asthma, other allergy or airborne allergy– in detail: Asthma was reported in three patients 201600347, 201600380, 2025-AER-00935 and Other allergy or airborne allergies pollen/mites/danders were reported in three patients 201801495, 201801527, 202301666. One patient from the children population reported concomitant relevant medical history of bronchial asthma and allergy to early bloomers 2024-AER-02384.

Life-threatening cases: **Eight cases were reported as life-threatening**. Epinephrine was administered in five cases 201600347, 201600380, 202300555, 2024-AER-02384, 2025-AER-00935, while corrective treatment was unknown in three cases 2024-AER-00253, 2024-AER-01940, 2025-AER- 01180. All patients recovered

MAD Discussion about anaphylactic shock: Two cases of anaphylactic shock were identified. One in child patient 202301809 and one in adult patient 2024-AER-00226. These cases were considered as life threatening requiring administration of epinephrine. Both patients recovered.

Case 202301809: food allergy may have contributed to the onset of anaphylactic shock, which subsequently recurred due to food allergy.

Case 2024-AER-00226: the diagnosis of anaphylactic shock was made by the physician.

However, no details on specific symptoms of anaphylaxis were provided. The patient received epinephrine via inhalation rather than the recommended injectable route.

MAH Conclusion: Since the first marketing of HDM SLIT TABLET, 33 cases of anaphylactic reaction were reported corresponding to a RR of 0.42/10,000. This adverse reaction is an identified risk with the use of HDM SLIT TABLET and **is described in the sections 4.4 and 4.8** of CCSI/CCDS. Since the first marketing of HDM SLIT TABLET, two cases of anaphylactic shock were reported in patients treated with HDM SLIT TABLET corresponding to a RR of 0.025/10,000. This adverse reaction is an identified risk with the use of HDM SLIT TABLET and **is described in the sections 4.4 and 4.8** of CCSI/CCDS.

No additional action is required at this point. Anaphylactic reaction including anaphylactic shock will remain closely monitored.

2.3.2.3. EOSINOPHILIC OESOPHAGITIS

In the literature, several case reports were published suggesting a possible association between SLIT and EoE.

Identified Risk class effects Eosinophilic oesophagitis Frequency with 95% CI: Two cases were reported in study SL75.14. Seven cases of EoE without biopsy to confirm the diagnosis were spontaneously reported with HDM SLIT TABLET RR 0.09/10,000. The two cases retrieved in clinical trials and the five cases retrieved in postmarketing experience were not serious. Among the seven post-marketing cases, the outcome was unknown in four cases, recovering in one case, and recovered in two cases. Both cases reported in clinical trials were recovered. Background incidence and prevalence: Among both paediatric and adult patients with EoE, it has consistently been found that 50% to 75% have AR.

Post marketing experience: **Two non-serious cases of EoE, medically confirmed, have been retrieved during the interval period** following an analysis performed in the Database using the MedDRA PT "Eosinophilic oesophagitis".

Case 2025-AER-00267: concerns a 31-year-old male patient treated with HDM SLIT TABLET and experienced chest pain in the morning, retrosternal burns during the day, chest discomfort and burns in the evening around 20 days after HDM SLIT TABLET start. The physician suspected eosinophilic esophagitis. The patient discontinued HDM SLIT TABLET for 1 week and contacted his physician. The patient took sachet/gel for burns, but he did not know the name of the drug. HDM SLIT TABLET was discontinued. The patient recovered. The diagnosis of eosinophilic esophagitis was not confirmed by biopsy or endoscopy. The MAH causality was assessed as possible

Case 2025-AER-00522: concerns a 7-year-old male patient treated with HDM SLIT TABLET and presented with eosinophilic oesophagitis around 12 days after HDM SLIT TABLET start. The diagnosis was made based on symptoms that may be suggestive of eosinophilic oesophagitis. The symptoms were vomiting (variable time), ear itch, abdominal pain and what sounded like dysphagia in the evening. The patient took an antihistamine and ice cream before bed for dysphagia. HDM SLIT TABLET was discontinued. The vomiting remained the only symptom but was less frequent. HDM SLIT TABLET was resumed and similar symptoms emerged about a week into the 300 IR dose. The physician performed a routine clinical examination, which was unremarkable. The physician discussed the possibility of inflammatory reaction to the HDM SLIT TABLET and recommended to perform an endoscopy. At the end, the endoscopy was not performed as the patient was not compromised, and the parents were not fussed. The patient recovered. The diagnosis of eosinophilic esophagitis was not confirmed by biopsy or endoscopy. The MAH causality was assessed as possible

From the cumulative analysis, seven cases of EoE have been retrieved.

Table 27. EOSINOPHILIC OESOPHAGITIS cumulative analysis

Case Id Seriousness Criteria Source Country HCP Sex Age biopsy	Reaction/event (PT)	Outcome	Time to onset after treatment Introduction after last intake	Action (s) taken Corrective treatments	MAH causality
201701131 Not serious Spontaneous Australia Y M Unk No	Eosinophilic oesophagitis	Unknown	2-3 months	Drug withdrawn	Possible
202201032 Not serious Spontaneous Australia Y Unk Unk No	Eosinophilic oesophagitis	Unknown	Unknown	Unknown	Possible
202201255 Not serious Spontaneous DE Y M Adult No	Eosinophilic oesophagitis nausea chest pain	Recovering	Unknown	Drug discontinued	Possible
202201628 Not serious Spontaneous Australia N M 37 No	Eosinophilic oesophagitis dyspepsia pharyngeal oedema chest pain throat irritation pruritis dysphagia choking	Unknown	Around 1 week after initiation	Drug discontinued	Possible
202201630 Not serious Spontaneous Australia Y F Ado No	Eosinophilic oesophagitis gastroesophageal reflux disease	Unknown	Around 3 years after initiation	Drug discontinued	Possible
2025-AER-00267 Not serious Spontaneous France Y M 31 No	Eosinophilic oesophagitis chest pain chest discomfort	Recovered	Around 20 days after initiation	Drug discontinued	Possible
2025-AER-00522 Not serious Spontaneous Australia Y M 7 No	Eosinophilic oesophagitis Vomiting ear pruritus Abdominal pain Dysphagia	Recovered	Around 12 days after initiation	Drug discontinued	Possible

Six of these seven cases have been medically confirmed. No results of gastroscopy or biopsy have been reported. Moreover, in four cases, physicians reported that they were concerned about eosinophilic oesophagitis because patients presented respectively with symptoms of oesophageal symptoms 202201628, gastroesophageal reflux 202201630, chest pain and discomfort, persisting retrosternal burns 2025-AER-00267, vomiting, abdominal pain and dysphagia 2025-AER-00522. Due to plausible chronology for five cases 201701131, 202201628, 202201630, 2025-AER-00267, 2025-AER-00522 and because they were no other confounding factors, causality was assessed as Possible for all these case reports.

MAH Discussion: Extrinsic eosinophilia is a common finding in clinical practice of allergy. Depending on the underlying disease, various organs (e.g., skin, heart, gastrointestinal tract, central nervous system,

lungs) are affected by eosinophilia, inducing chronic inflammation. The reported incidence of EoE in the general population ranges from 0.00001% to 0.004%. The aetiologies of EoE are not fully identified, but an association between EoE and food allergies is recognized, suggesting that food antigens may represent a possible cause. Environmental allergens have also been implicated as possible contributors in the evolution of the disease, as described in a published case of an EoE exacerbation during pollen season. It is noteworthy that most patients developing EoE have underlying allergic disease suggesting a strong allergic component of this disease.

MAH Conclusion: From the above information, it is still considered that EoE represents an identified safety risk associated with all SLIT products and as such is considered as a class effect risk. CCSI/ CCDS for all company's SLIT products were modified accordingly. Since first marketing of HDM SLIT TABLET and as of today, seven cases of EoE have been retrieved corresponding to a RR of 0.09/10,000. No biopsy or gastroscopy have been done to confirm the EoE, thus the cases were kept conservatively.

No additional action is required at this point. EoE will remain closely monitored.

NEW INFORMATION ABOUT POTENTIAL IMPORTANT RISKS

2.3.2.4. AUTOIMMUNE DISORDERS

To better identify and detect possible auto immune disorders associated with HDM SLIT TABLET, a search for all cases received and registered in the Database using the SMQ Immune-mediated autoimmune disorders, HLGT Autoimmune disorders and HLGT Immune disorders NEC, HLT Multiple sclerosis acute and progressive and PT Psoriasis area severity index increased has been performed. The PT Gastritis was excluded from the query.

Potential Risk Class effect Autoimmune disorders Frequency with 95% CI: Four cases of autoimmune disorders were reported in the clinical development programme: one case in a patient treated with ACTAIR and three cases in patients on placebo. Four cases of autoimmune disorder were spontaneously reported with HDM SLIT TABLET RR 0.1/10,000.

Post marketing experience: **Two cases of autoimmune disorders have been reported during the interval period**:

Case 202300747: concerns a 13-year-old male patient treated with HDM SLIT TABLET and experienced new confirmed allergy to shellfish, mouth ulcers ("aphthous"), knee pain and lichen sclerosus around 4 months after HDM SLIT TABLET start. Several specialists have examined the patient no further information. Corrective treatment was not reported. At time of the report, the patient did not recover and HDM SLIT TABLET was discontinued.

Case 2024-AER-01902: concerns a 41-year-old female patient treated with HDM SLIT TABLET and experienced alopecia areata 410 days after HDM SLIT TABLET start. Corrective treatment was not reported. At time of the report, the patient did not recover. Action taken with HDM SLIT TABLET was unknown at the time of the report.

Since the first marketing of HDM SLIT TABLET, four cases of autoimmune disorders have been retrieved.

Table 28. Cumulative cases of autoimmune disorders

Case Id Seriousness Criteria Source Country HCP Sex Age	Reaction/event (PT)	Outcome	Time to onset after treatment Introduction after last intake	Action (s) taken Corrective treatments	MAH causality

201700602 serious Spontaneous Australia Y F Unk	Autoimmune disorder Rash	Not recovered	Unknown	Unknown	Unlikely
201901440 hospitalisation and medically important Spontaneous Japan Y F 17	IgA nephropathy	Not recovered	3 years	Drug discontinued	Possible
202300747 Non-serious Spontaneous Belgium Y M 13	Food allergy Mouth ulceration Arthralgia Lichen sclerosus	Not recovered	Around 4 months	Drug discontinued	Possible
2024-AER-01902 Non-serious Spontaneous Health authority DE N F 41	Alopecia areata	Not recovered	410 days	Drug discontinued	Possible

MAH Conclusion: Since HDM SLIT TABLET launch, four cases of autoimmune disorders were reported in patients treated with HDM SLIT TABLET corresponding to a RR of 0.1/10,000. This is very low compared to approximate prevalence of autoimmunity in the general population 3-5 %. The Reporting Rate of autoimmune disorders remains stable over time. In these cases, the data collected does not allow a formal conclusion on the potential role of HDM SLIT TABLET in the occurrence or relapse of autoimmune diseases. Autoimmune disorders were considered as a class safety concern and an important potential risk for all allergen immunotherapy AIT since 2009.

Autoimmune disorders AID were considered as a class safety concern and an important potential risk for all allergen immunotherapy AIT since 2009. During the process of an evaluation of RMPs for two others AIT products Staloral Birch and Staloral Birch/Halder/Hazel, the Paul-Ehrlich Institute PEI requested that 'Autoimmune disorders' be removed as a key potential risk following an assessment of the current scientific knowledge and publications. The MAH agreed to this change, and the removal was approved on 28 October 2024. AID being considered as class effect, as a result, 'Autoimmune disorders' will not be listed as an important potential risk for HDM SLIT TABLET in the next PBRER report.

Immune deficiency diseases or active forms of autoimmune disorders are contraindications for HDM SLIT TABLET, as documented in the current CCSI.

Review of all cases of autoimmune disorders did not reveal any significant new safety information for HDM SLIT TABLET. Nevertheless, this safety concern will still be watched as part of regular pharmacovigilance practices.

Lead Member State assessment comment:

Cases of autoimmune disorders will continue to be closely monitored, and this is endorsed. However, the MAH is requested to present and discuss all new reported cases of autoimmune disorders AID in the future PSURs.

UPDATE ON MISSING INFORMATION

2.3.2.5. PREGNANT AND LACTATING WOMEN

Post marketing experience: The search of all cases received and registered in the Database has been performed using the SMQ "Pregnancy and neonatal topics".

Interval period: **Eight non-serious cases of exposure during pregnancy have been retrieved during the interval period**. Among them, **one case 202300830 reported adverse event oral pruritus**. **No case of exposure during lactation** has been retrieved during the interval period.

Cumulative period: Nineteen cases (201602185, 201701024, 201800008, 201800289, 201800295, 201801399, 201901100, 201901986, 201902049, 202000974, 202200470, 202300830, 202301076, 202301682, 202301683, 2024-AER-01022, 2024-AER-02997, 2025-AER-00416, 2025-AER- 02131) have been retrieved since the first marketing of HDM SLIT TABLET.

To Note: The tabular cumulative overview of all cases of exposure during pregnancy is presented by the MAH in the PSUR report from page 94 up to page 97.

MAH Discussion: Cumulatively, **nineteen cases of drug exposure during pregnancy** and breast-feeding during treatment with HDM SLIT TABLET have been reported. **One case was serious**.

The action taken with HDM SLIT TABLET was the following: Drug continued by eight patients and Action taken with HDM SLIT TABLET was unknown for nine cases and Drug discontinued by two patients. The patient's ages ranged from 29 to 41. Patient's age was unknown in eight cases.

MAH Conclusion: About 20 to 30% of women with confirmed pregnancies bleed during the first 20 weeks of pregnancy; half of these women spontaneously abort. Thus, incidence of spontaneous abortion is about 10 to 15% in confirmed pregnancies. Incidence in all pregnancies is probably higher because some very early abortions are mistaken for a late menstrual period. The cumulative analysis of all cases of pregnancy and breast-feeding reported in the Database concludes that no specific risk for pregnant and lactating patient to develop pregnancy complications or for babies to develop adverse reaction could be identified. Up to date, there is no safety signal with the use of HDM SLIT TABLET in pregnant and lactating women.

Lead Member State assessment comment:

MAH Stallergenes SAS

Taking into consideration the review of the risks presented by the MAH, no further action is considered warranted at this stage.

2.4. Characterisation of risks

Lead Member State assessment comment:

The MAHs have presented the characterisation of risks for dermatophagoides pteronyssinus / dermatophagoides farina based upon cumulative data available through the DLP on 22 September 2025.

The characterisation and discussion on important identified and potential risks described in the PSURs are acknowledged.

The safety concerns remain unchanged.

3. Benefit evaluation

Lead Member State assessment comment:

The benefit evaluation made by the MAHs is acknowledged.

During the reporting period no new relevant information on efficacy and effectiveness was identified for dermatophagoides pteronyssinus / dermatophagoides farina.

There are no new data on efficacy that alters previous assessments, and which are described in the approved product information.

4. Benefit-risk balance

4.1. MAH ALK-Abelló-A/S

No new data on the efficacy and effectiveness were received during the current reporting interval.

During the reporting period, two phase III clinical trials were completed: MT-11 and MT-12. The clinical trial in Chinese subjects: MT-16 was prematurely terminated due to the impact of the coronavirus pandemic. One clinical trial MT-21 was ongoing, during the reporting interval.

During the reporting period, four non-interventional studies were completed: Torii500; NI-MT-04 (summary was included in the previous PSUR); and MITI5001 or closed: NI-MT-06. Additionally, three non-interventional studies were ongoing: NI-MT-08; NI-MT-09 and NI-X-05.

The following three signals: `Rash`, `Dizziness` and `Malaise` were assessed as new risks and closed, during the reporting interval. One additional signal of `Oral mucosal discolouration` was refuted after evaluation, as well.

The important identified risks for the SQ-HDM-SLIT product is ´Eosinophilic oesophagitis`.

In Canada, educational material to parents/guardians of children 5-11 years old has been implemented, to ensure recognition of early signs of potential systemic allergic reactions so appropriate treatment can be initiated promptly and the impact of the reaction can be reduced.

In India, the competent authorities have imposed a phase IV post-marketing surveillance study to further assess the safety.

Based on data and actions received in the period covered by this report, the benefit-risk profile of HDM SLIT-tablet remains positive.

4.2. MAH Stallergenes SAS

No new data on the efficacy and effectiveness were received during the current reporting interval.

One NIS was completed during the reference period and one Post-Authorisation Safety Study (PASS) with HDM SLIT TABLET HDM tablets was ongoing during the reference period. Additionally, during the reporting period, one investigator-initiated study IIS in Australia was completed and one investigator-initiated study Investigator-initiated study IIS in Australia was ongoing.

The important identified risk for the HDM-SLIT product is ´Severe laryngopharyngeal reactions´ and ´Pregnant and lactating women` is considered as missing information. `Anaphylactic reactions including

anaphylactic shock´ as well as ´Eosinophilic oesophagitis´ are considered as Important identified risk (class effect) and as Important potential risk (class effect) is considered `Autoimmune disorders`-

There were no signals new, ongoing or closed during the current reporting period.

In Europe, a safety variation has been submitted and approved during the reporting period: to remove mannitol in the section excipients with known effect.

In New Zeeland, a safety variation has been submitted and approved during the reporting period for extension of indication to the paediatric population (5-12).

In Australia, a safety variation has been submitted and approved during the reporting period with minor editorial changes in accordance with 9D of the ACT for changes in the Product Information (PI).

In South Korea, a safety variation has been submitted and approved during the reporting period: with update of Actair leaflet following alignment to Australian leaflet and a post-marketing surveillance

The benefit-risk balance of HDM-SLIT tablet remains unchanged and is considered positive.

Lead Member State assessment comment:

Based on the data provided by the MAHs the benefit-risk balance of the product dermatophagoides pteronyssinus / dermatophagoides farina remains unchanged. There have been no significant changes in the benefit profile in the reporting interval.

The proven and observed benefit of treatment of moderate to severe HDM-induced rhinitis, allergic rhinitis or rhinoconjunctivitis and/or intermittent allergic asthma in patients of 12-years and older, clearly outweighs the risk associated with the product.

In conclusion, the benefit-risk profile remains unchanged and is consider positive.

Appendix: Overview of the nationally authorised products for which PSURs were submitted in the context of this EU single assessment

Product Name (in authorisation country)	MRP/DCP Authorisation Number	National Authorisation Number	MAH of product in the Member State	Member State where product is authorised
АКТАИР	DE/H/4913/002	20210315	Stallergenes	Republic of Bulgaria
ACTAIR	DE/H/4913/001	PL 04534/0013	Stallergenes	United Kingdom (Northern Ireland)
ACTAIR	DE/H/4913/003	140789	Stallergenes	Republic of Austria
ACARIZAX	DE/H/1947/001	PEI.H.11754.01.1	Alk-Abello A/S	Federal Republic of Germany
ACARIZAX	DE/H/1950/001		Alk-Abello A/S	Romania
Aitmyte	DE/H/4913/001	20-13437	Stallergenes	Kingdom of Norway
Actair	DE/H/4913/002	86402	Stallergenes	Kingdom of Spain
ACTAIR	DE/H/4913/001	59/133/20-C	Stallergenes	Czech Republic
ORYLMYTE	DE/H/4913/002	HR-H-839244660	Stallergenes	Republic of Croatia
Actair	DE/H/4913/003	86405	Stallergenes	Kingdom of Spain
ACTAIR	DE/H/4913/003		Stallergenes	Romania
Aitmyte	DE/H/4913/003	20-13439	Stallergenes	Kingdom of Norway
Aitaro	DE/H/1950/001	PEI.H.11820.01.1	Alk-Abello A/S	Federal Republic of Germany
ACARIZAX	DE/H/1950/001		Alk-Abello A/S	Republic of Slovenia
ORYLMYTE	DE/H/4913/003	2021080159	Stallergenes	Grand Duchy of Luxembourg
ACARIZAX	DE/H/1947/001	59/558/15-C	Alk-Abello A/S	Czech Republic
ACTAIR	DE/H/4913/002	140790	Stallergenes	Republic of Austria
ACTAIR	DE/H/4913/002	14056/2021/01	Stallergenes	Romania
ACTAIR	DE/H/4913/003	PA2113/002/003	Stallergenes	Ireland
АКТАИР	DE/H/4913/003	20210316	Stallergenes	Republic of Bulgaria
ORYLMYTE	DE/H/4913/002	BE588195	Stallergenes	Kingdom of Belgium
Aitmyte	DE/H/4913/001	64344	Stallergenes	Kingdom of Denmark
ORYLMYTE	DE/H/4913/001		Stallergenes	Italian Republic
ACARIZAX	DE/H/1947/001	59/0472/15-S	Alk-Abello A/S	Slovak Republic
ORYLMYTE	DE/H/4913/001		Stallergenes	French Republic
ACARIZAX	DE/H/1947/001	32830	Alk-Abello A/S	Republic of Finland
Actair	DE/H/4913/003	RVG 126704	Stallergenes	Kingdom of the Netherlands

Product Name (in authorisation country)	MRP/DCP Authorisation Number	National Authorisation Number	MAH of product in the Member State	Member State where product is authorised
Aitmyte	DE/H/4913/002	64903	Stallergenes	Kingdom of Denmark
Actair	DE/H/4913/002	H/21/02865/003	Stallergenes	Republic of Slovenia
ACTAIR	DE/H/4913/001	PA2113/002/001	Stallergenes	Ireland
ORYLMYTE	DE/H/4913/002	2021080158	Stallergenes	Grand Duchy of Luxembourg
ACTAIR	DE/H/4913/003		Stallergenes	Portuguese Republic
ACTAIR	DE/H/4913/002	PL 04534/0014	Stallergenes	United Kingdom (Northern Ireland)
ACTAIR	DE/H/4913/003	59/0210/21-S	Stallergenes	Slovak Republic
ACTAIR	DE/H/4913/001	59/0208/21-S	Stallergenes	Slovak Republic
ORYLMYTE	DE/H/4913/001	BE588204	Stallergenes	Kingdom of Belgium
Acarizax	DE/H/1950/001		Alk-Abello A/S	Kingdom of Belgium
Actair	DE/H/4913/001	86403	Stallergenes	Kingdom of Spain
ACTAIR	DE/H/4913/002	27087	Stallergenes	Republic of Poland
АКТАИР	DE/H/4913/001	20210314	Stallergenes	Republic of Bulgaria
ACARIZAX	DE/H/1950/001	81213	Alk-Abello A/S	Kingdom of Spain
Actair	DE/H/4913/001		Stallergenes	Republic of Slovenia
ACTAIR	DE/H/4913/002	59/134/20-C	Stallergenes	Czech Republic
ORYLMYTE	DE/H/4913/002	PEI.H.12040.02.1	Stallergenes	Federal Republic of Germany
ACTAIR	DE/H/4913/001		Stallergenes	Romania
ACTAIR	DE/H/4913/001		Stallergenes	Portuguese Republic
Acarizax	DE/H/1950/001	2020020052	Alk-Abello A/S	Grand Duchy of Luxembourg
Actair	DE/H/4913/003		Stallergenes	Republic of Slovenia
Acarizax	DE/H/1947/001	55024	Alk-Abello A/S	Kingdom of Denmark
ACARIZAX	DE/H/1947/001	52085	Alk-Abello A/S	Kingdom of Sweden
ACARIZAX	DE/H/1947/001	22945	Alk-Abello A/S	Republic of Poland
Actair	DE/H/4913/002	RVG 126703	Stallergenes	Kingdom of the Netherlands
ACTAIR	DE/H/4913/003	59/135/20-C	Stallergenes	Czech Republic
ORYLMYTE	DE/H/4913/003	PEI.H.12040.03.1	Stallergenes	Federal Republic of Germany
Aitmyte	DE/H/4913/001	60614	Stallergenes	Kingdom of Sweden

Product Name (in authorisation country)	MRP/DCP Authorisation Number	National Authorisation Number	MAH of product in the Member State	Member State where product is authorised
ACTAIR	DE/H/4913/003	27088	Stallergenes	Republic of Poland
ORYLMYTE	DE/H/4913/003		Stallergenes	Italian Republic
Aitmyte	DE/H/4913/003	64904	Stallergenes	Kingdom of Denmark
ORYLMYTE	DE/H/4913/003	HR-H-696635390	Stallergenes	Republic of Croatia
ACTAIR	DE/H/4913/003	PL 04534/0015	Stallergenes	United Kingdom (Northern Ireland)
ACTAIR	DE/H/4913/001	140791	Stallergenes	Republic of Austria
Acarizax	DE/H/1947/001	14-10408	Alk-Abello A/S	Kingdom of Norway
ACTAIR	DE/H/4913/002	59/0209/21-S	Stallergenes	Slovak Republic
ACTAIR	DE/H/4913/002	5826367	Stallergenes	Portuguese Republic
ACARIZAX	DE/H/1947/001		Alk-Abello A/S	French Republic
ACTAIR	DE/H/4913/001	27086	Stallergenes	Republic of Poland
Aitmyte	DE/H/4913/002	20-13438	Stallergenes	Kingdom of Norway
ACARIZAX	DE/H/1950/001		Alk-Abello A/S	Ireland
ACARIZAX	DE/H/1950/001		Alk-Abello A/S	Republic of Hungary
ACARIZAX	DE/H/1947/001	236641	Alk-Abello A/S	Republic of Austria
ACARIZAX	DE/H/1951/001	RVG 118889	Alk-Abello A/S	Kingdom of the Netherlands
ORYLMYTE	DE/H/4913/002	34009 302 360 2 4	Stallergenes	French Republic
ORYLMYTE	DE/H/4913/003		Stallergenes	French Republic
Actair	DE/H/4913/001	RVG 126694	Stallergenes	Kingdom of the Netherlands
ACARIZAX	DE/H/1950/001		Alk-Abello A/S	Republic of Croatia
ACTAIR	DE/H/4913/002	PA2113/002/002	Stallergenes	Ireland
ORYLMYTE	DE/H/4913/001	PEI.H.12040.01.1	Stallergenes	Federal Republic of Germany
AMITEND	DE/H/1951/001	PEI.H.11821.01.1	Alk-Abello A/S	Federal Republic of Germany
ACCARIZAX	DE/H/1947/001		Alk-Abello A/S	Italian Republic
ORYLMYTE	DE/H/4913/002	048824041	Stallergenes	Italian Republic
ORYLMYTE	DE/H/4913/001	HR-H-923307797	Stallergenes	Republic of Croatia
ORYLMYTE	DE/H/4913/001	2021080157	Stallergenes	Grand Duchy of Luxembourg
ORYLMYTE	DE/H/4913/003	BE588213	Stallergenes	Kingdom of Belgium

Product Name (in authorisation country)	MRP/DCP Authorisation Number	National Authorisation Number	MAH of product in the Member State	Member State where product is authorised
Aitmyte	DE/H/4913/003	60616	Stallergenes	Kingdom of Sweden