Part VI: Summary of the risk management plan

Summary of Risk Management Plan for ORALAIR®

This is a summary of the risk management plan (RMP) for ORALAIR®. The RMP details important risks of ORALAIR® how these risks can be minimised, and how more information will be obtained about ORALAIR®'s risks and uncertainties (missing information).

ORALAIR®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ORALAIR® should be used.

Important new concerns or changes to the current ones will be included in updates of ORALAIR®'s RMP.

I. The medicine and what it is used for

ORALAIR® is authorised in treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen. (See SmPC for the full indication). It contains Grass pollen allergen extract from: Cocksfoot (Dactylis glomerata L.), Sweet vernal grass (Anthoxanthum odoratum L.), Rye grass (Lolium perenne L.), Meadow grass (Poa pratensis L.) and Timothy (Phleum pratense L.) 100 IR* or 300 IR* per sublingual tablet.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ORALAIR®, together with measures to minimise such risks and the proposed studies for learning more about ORALAIR®'s risks, are outlined in the next sections.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.
If important information that may affect the safe use of ORALAIR® is not yet available, it is listed under 'missing information' outlined in the next section.

A. List of important risks and missing information

Important risks of ORALAIR® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ORALAIR®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 22: List of important risks and missing information

Important Identified risks	Severe laryngopharyngeal disorders Anaphylactic reaction Eosinophilic esophagitis
Important potential risk	Anaphylactic shock Autoimmune disorders
Missing information	Pregnant and lactating women Elderly patients (older than 65 years)

B. Summary of important risks

Table 23: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any - Important identified risk: Severe laryngopharyngeal disorders

Important Identified risk: Severe laryngopharyngeal disorders	
Evidence for linking the risk to the Medicine	Clinical data, post marketing surveillance
Risk factors and risk groups	Pollen season
Risk minimization measures	Routine risk minimization measures: Labelled in the PIL: - Section 2: "Talk to your doctor or pharmacist before taking ORALAIR if you experience severe allergic symptoms, such as difficulty in swallowing or breathing, changes in your voice, hypotension (low blood pressure) or a feeling of a lump in the throat. Stop the treatment and contact your doctor immediately." - Section 4: "During treatment with ORALAIR, you will be exposed to substances that may cause application site reactions and/or symptoms which may affect the whole body. You may expect application site reactions (such as itching of the mouth and throat irritation). These reactions usually occur at the beginning of therapy, are temporary and generally diminish over time."

Table 24: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any - Important identified risk: Anaphylactic reaction

Important Identified risk: Anaphylactic reaction	
Evidence for linking the risk to the Medicine	Clinical data, post marketing surveillance
Risk factors and risk groups	Administration during the height of the pollen season as well as poorly controlled asthma have been identified as risk factors for severe AIT induced anaphylactic reaction. A high degree of hypersensitivity, use of beta blockers, change in health status or reaction to previous AIT were also identified as risk factor to develop anaphylactic reaction to AIT [*Cox et al.2011*] season.
Risk minimization measures	Routine risk minimization measures: Labelled in the PIL in: Section 2 of the PIL: - "Talk to your doctor or pharmacist before taking ORALAIR if you experience severe allergic symptoms, such as difficulty in swallowing or breathing, changes in your voice, hypotension (low blood pressure) or a feeling of a lump in the throat. Stop the treatment and contact your doctor immediately." - "Talk to your doctor or pharmacist before taking ORALAIR if you have previously had a severe allergic reaction to a drug with allergen extracts." Section 4: - "During treatment with ORALAIR, you will be exposed to substances that may cause application site reactions and/or symptoms which may affect the whole body." - "Systemic allergic reaction"

Table 25: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any - Important identified risk: Eosinophilic esophagitis

Important Identified risk: Eosinophilic esophagitis	
Evidence for linking the risk to the Medicine	Post marketing surveillance and scientific literature articles.
Risk factors and risk groups	Eosinophilic esophagitis (EoE) is a disorder which affects all ages, from infancy through adulthood. It typically affects atopic individuals and is a chronic allergic Disorder [*Muir, and al., 2019*]. In EoE, large numbers of white blood cells called eosinophils are found in the inner lining of the esophagus. Eosinophils can release substances into surrounding tissues that cause inflammation. Normally there are no eosinophils in the esophagus. This inflammatory process leads to symptoms, which include heartburn, regurgitation, and esophageal stenosis (with dysphagia being more frequent in eosinophilic esophagitis in young adults and children), are similar to those of gastroesophageal refluxdisease [*Gomez-Aldana, and al., 2019*]) .The aetiologies of EoE are not fully identified, but an association between EoE and food allergies is recognised, suggesting that food antigens may represent a possible cause [*Philpott et al., 2014*]. 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 [*Fogg et al., 2003*]. It is noteworthy that most patients developing EoE have underlying allergic disease suggesting a strong allergic component of this disease.
Risk minimization measures	Routine risk minimization measures: Labelled in the PIL in: - Section 2: "You experience persistent heartburn or difficulty swallowing. You should contact your doctor - Section 4: "Additional oesophageal inflammation has been reported"

Table 26: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any - Important potential risk: Anaphylactic shock

Important potential risk: Anaphylactic shock	
Evidence for linking the risk to the Medicine	Post marketing surveillance
Risk factors and risk groups	Same as anaphylactic reaction
Risk minimization measures	Routine risk minimization measures: Labelled in the PIL in: Section 2: - "Talk to your doctor or pharmacist before taking ORALAIR if you experience severe allergic symptoms, such as difficulty in swallowing or breathing, changes in your voice, hypotension (low blood pressure) or a feeling of a lump in the throat. Stop the treatment and contact your doctor immediately." - "Talk to your doctor or pharmacist before taking ORALAIR if you have previously had a severe allergic reaction to a drug with allergen extracts."

	Section 4: - "During treatment with ORALAIR, you will be exposed to substances that may cause application site reactions and/or symptoms which may affect the whole body." - "Systemic allergic reaction"

Table 27: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any - Important potential risk: Autoimmune disorders

Important potential risk: Autoimmune disorders	
Evidence for linking the risk to the Medicine	Clinical data, post marketing surveillance and scientific literature articles.
Risk factors and risk groups	Auto immune disorders are more frequent in women that in men) Most autoimmune diseases affect younger and middle-aged people, and some illnesses begin specifically in childhood such as juvenile idiopathic arthritis or juvenile dermatomyositis, for example - A family history of autoimmune disease puts a child at higher risk. In fact, it's been estimated that about one-third of the risk of developing an autoimmune disease is tied to something in a child's genes. - Children of different races may be more prone to having certain autoimmune diseases. African-Americans, for instance, seem to be more likely than Caucasians to develop lupus (SLE) and scleroderma, but the opposite is true for type 1 diabetes and multiple sclerosis (MS). - Children with one autoimmune disease tend to run a higher risk of developing another. For example, kids with type 1 diabetes appear to be more susceptible to developing celiac disease or Addison's disease
Risk minimization measures	Routine risk minimization measures: Labelled in the PIL in Section 2: - "Do not take ORALAIR® if you have an illness which affects the immune system, you are taking medicines which suppress the immune system or if you have cancer" - "Talk to your doctor or pharmacist before taking ORALAIR if you have an autoimmune disease in remission." - "Talk to your doctor about personal or family history of any disease which could affect your immune system"

Table 28: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any – Missing information: Pregnant and lactating women

Missing information: Pregnant and lactating women	
Risk minimization measures	Routine risk minimization measures: Labelled in Section 2 of the PIL: "If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. There is no experience for the use of ORALAIR during pregnancy. Therefore, you should not start an immunotherapy if you are pregnant. If you become pregnant while taking this medicine, speak to your doctor about whether it is appropriate for you to continue the treatment."

Table 29: Important risks and missing information with corresponding risk minimisation activities and additional pharmacovigilance activities if any – Missing information: Elderly patients (older than 65 years)

Missing information: Elderly patients (older than 65 years)	
Risk minimization measures	No risk minimisation measures

C. Post-authorization development plan

1. Studies which are conditions of the Marketing Authorization

There are no studies which are condition of the marketing authorisation or specific obligation of ORALAIR®.

2. Other studies in post-authorization development plan

There are no studies required for Oralair®.