Summary of Risk Management Plan (RMP)

for

Adtralza®

(Tralokinumab)

Solution for injection

MA no. 68229

Marketing Authorisation Holder: LEO Pharmaceutical Products Sarath Ltd.

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Disclaimer:
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Adtralza® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Adtralza® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. LEO Pharmaceutical Products Sarath Ltd. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Adtralza®.

Summary of risk management plan for Adtralza® (tralokinumab)

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

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

This summary of the RMP for Adtralza® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Adtralza® is authorised for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy (see SmPC for the full indication). It contains tralokinumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Adtralza®'s benefits can be found in Adtralza®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/adtralza.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Adtralza®, together with measures to minimise such risks and the proposed studies for learning more about Adtralza®'s risks, are outlined below.

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 authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Adtralza® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Adtralza® 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 Adtralza®. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Conjunctivitis Malignancy
Missing information	Use in pregnant and lactating women Long-term safety

II.B Summary of important risks

Important potential risk: Conjunctivitis	
Evidence for linking the risk to the medicine	The incidence of conjunctivitis was higher with tralokinumab than with placebo in the clinical development programme. However, this risk remains to be further characterised over longer term and it cannot be ruled out that conjunctivitis of longer duration can affect the benefit:risk profile, although this is not supported by currently available data. Therefore, conjunctivitis is considered an important potential risk.
Risk factors and risk groups	Patients with AD have an increased risk of ocular comorbidities including conjunctivitis compared with the general population, and the incidence of ocular complications increases with AD severity. Also, a medical history of allergic conjunctivitis increases the risk of developing conjunctivitis. In the clinical development program for tralokinumab more than half of the subjects with conjunctivitis AESI in the initial treatment period had a past or current history of allergic conjunctivitis.
Risk minimisation measures	Routine risk minimisation measures: Communicate to physicians and patients that conjunctivitis is common adverse reaction, and that patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. Relevant text is provided in the following sections of the SmPC: • Section 4.4 (Special warnings and precautions for use) • Section 4.8 (Undesirable effects) Relevant text is provided in the following sections of the PIL: • Section 2 (What you need to know before you use tralokinumab) • Section 4 (Possible side effects) Additional risk minimisation measures: None

Important potential risk: Conjunctivitis	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Tralokinumab is an immunomodulatory monoclonal antibody but is not considered a general immunosuppressant. There is a general belief that immunomodulatory monoclonal antibodies can theoretically contribute to tumour progression over time similar to immunosuppressive agents, and malignancy is often considered an important potential risk for immunomodulatory biologics. Based on current non-clinical and clinical data there is no evidence of an increased risk of malignancy in patients treated with tralokinumab for up to 1 year, but since tumours develop over time further long-term data is needed.
Risk factors and risk groups	Atopic dermatitis could in itself be associated with an increased risk of cancer as immune dysregulation is an inherent part of the disease. Known risk factors for cancer development such as smoking, alcohol, stress, and sleep deprivation have also been hypothesised to be risk factors for exacerbation of adult AD. Despite these hypotheses, there is little empirical evidence of an association between AD and most types of cancer. Conflicting findings have been reported regarding the risk of lymphoma and non-melanoma skin cancer (NMSC); a few studies have reported a lack of or a negative association between AD and NMSC, whereas slightly elevated risks have also been reported for NMSC collectively, and specifically for squamous cell carcinoma.
Risk minimisation measures	No specific measures are required for patients receiving tralokinumab; standard care is adequate.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND. See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: Communicate to physicians and patients that there is a limited amount of data from the use of tralokinumab in pregnant women; therefore, as a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy. Communicate to physicians and patients that it is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion, so a decision must be made whether to discontinue breast-feeding or to discontinue tralokinumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Relevant text is provided in the following section of the SmPC: • Section 4.6 (Fertility, pregnancy and lactation) Relevant text is provided in the following section of the PIL: • Section 2 (What you need to know before you use tralokinumab) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Observational PASS of tralokinumab use in pregnancy. Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data. See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: Communicate to physicians and patients that the long-term safety of tralokinumab was assessed in the 2 monotherapy studies up to 52 weeks and in 1 combination study with TCS up to 32 weeks. The safety profile of tralokinumab through week 52 and week 32 respectively was consistent with the safety profile observed up to week 16. Relevant text is provided in the following section of the SmPC: • Section 4.8 (Undesirable effects) – text below the list of adverse reactions Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS investigating long-term safety with tralokinumab. A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND. See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Adtralza®.

II.C.2 Other studies in post-authorisation development plan

One PASS is currently planned and one PASS is ongoing; details are included below.

Study short name:

Observational PASS of tralokinumab use in pregnancy.

Post-authorisation safety study of tralokinumab use in pregnancy: An observational study based on electronic health care data.

Purpose of the study:

No experimental data indicate reproductive toxicity of tralokinumab, but the available evidence is currently insufficient to draw conclusions about the safety of using tralokinumab during pregnancy. The study will investigate whether maternal exposure to tralokinumab during pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortion, or stillbirths.

Study short name:

PASS investigating long-term safety with tralokinumab.

A phase 3 open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials – ECZTEND.

Purpose of the study:

To enable collection of long-term tralokinumab safety data for up to 5 years.