Summary of Risk Management Plan (RMP)

for

Anzupgo® (delgocitinib)

20 mg/g Cream

MA no. 69330

Based on EU RMP V0.3 and Swiss addendum V0.1

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 Anzupgo 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 Anzupgo 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 Anzupgo.

Summary of risk management plan for Anzupgo

This is a summary of the risk management plan (RMP) for Anzupgo cream 20 mg/g. The RMP details important risks of Anzupgo, how these risks can be minimised, and how more information will be obtained about Anzupgo's risks and uncertainties (missing information).
Anzupgo cream's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Anzupgo cream should be used.
This summary of the RMP for Anzupgo cream 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 Anzupgo cream's RMP.

I. The medicine and what it is used for

Anzupgo cream is authorised for the treatment of moderate to severe chronic hand eczema in adults for whom topical corticosteroids are inadequate or inappropriate (see SmPC for the full indication). It contains delgocitinib as the active substance and it is given by topical application.
Further information about the evaluation of Anzupgo cream's benefits can be found in the Anzupgo cream's EPAR, including in its plain-language summary, available on the EMA website.

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

Important risks of Anzupgo cream, together with measures to minimise such risks and the studies for learning more about Anzupgo cream'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 regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Anzupgo cream 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 Anzupgo cream. 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	• Non-melanoma skin cancer at long term use • Serious infections • All-cause mortality • Malignancies excluding NMSCs • Major adverse cardiovascular events (MACE) • Thromboembolic events
Missing information	None

II.B Summary of important risks

Important potential risk: Non-melanoma skin cancer at long term use	
Evidence for linking the risk to the medicine	NMSC is considered a class-effect of systemic JAK inhibitors and included as an important potential risk of another topical JAK inhibitor due to their theoretical potential to influence cancer immune surveillance. Topical application of Anzupgo cream has a minimal systemic exposure that does not overlap with the systemic exposure of an oral dose of Anzupgo regarded as sub-therapeutic. In the Anzupgo cream clinical programme, 2 NMSCs have been reported in patients treated with Anzupgo cream 20 mg/g, both occurring on location distant to application sites. The 2 NMSCs reported on Anzupgo cream were both basal cell carcinoma, one from Trial 1403, located on the left ear of a 76-year-old male with 57 days of Anzupgo cream exposure, and the other from Trial 1528, located on lower leg of a 59-year-old male with 29 days of Anzupgo treatment. Both subjects had risk factors (age and

Important potential risk: Non-melanoma skin cancer at long term use	
	sun exposure). No causal relationship to Anzupgo cream has been established given the clinical information and latency period of both events. No other events were reported in completed or ongoing clinical trials. Cumulative post-marketing safety data for Anzupgo ointment, CORECTIM®, approved in Japan for the treatment of AD since 2020, include no confirmed reports of skin cancer. Based on current non-clinical and clinical data, there is no evidence pointing to an increased risk of NMSC in CHE patients treated with Anzupgo cream 20 mg/g for up to 52 weeks. However, since there is uncertainty in the effect of local immunosuppression in the pathogenesis of NMSCs and NMSCs develop over extended periods of time, further long-term data is needed.
Risk factors and risk groups	Cumulative exposure to UV radiation, both from sun exposure and/or tanning beds, is considered a primary risk factor for NMSC pathogenesis. Immunosuppressed states, history of NMSC or premalignant skin conditions including HPV infections, exposure to ionizing radiation and carcinogenic chemicals, advanced age, fair skin, and genetic predisposition are also risk factors for NMSC. There are no available data on the risk of NMSC in patients with CHE but there are reports showing increased risk of NMSC, particularly of squamous cell carcinoma, in atopic dermatitis patients. It is proposed that the filaggrin abnormalities in AD patients increases susceptibility of keratinocytes to UV-induced damage. Increased cell turnover due to the chronic inflammatory state may also explain the association of cancer and AD. CHE and AD are different disease entities, but an immunological process of CHE is shared with AD and about a third of CHE patients have a history of AD.
Risk minimisation measures	Routine risk minimisation measures: Text related to a recommendation for periodic skin examination is included in the SmPC, Section 4.4 Special warnings and precautions for use. Additional risk minimisation measures: None

Important potential risk: Non-melanoma skin cancer at long term use	
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Enhanced safety surveillance of NMSC events reported in the post-marketing setting. Additional pharmacovigilance activities: Anzupgo cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS. See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Serious infection	
Evidence for linking the risk to the medicine	Serious infections are considered a class-effect of systemic JAK inhibitors and are included as a warning and precaution in the USPI and SmPC for oral JAK inhibitors and the USPI of another topical JAK inhibitor.
Risk factors and risk groups	No specific risk factors for serious infections have been identified through the Anzupgo cream clinical programme or are available in the literature for patients with CHE.
Risk minimisation measures	Routine risk minimisation measures: Serious infections seen with oral JAK inhibitors is included in the Information for Healthcare Professionals, Section 'Warnings and precautions'. Additional risk minimisation measures: None
Pharmacovigilance activities	Additional routine pharmacovigilance activities: Activity 1 - Safety concern included in routine signal detection. Activity 2 - Safety concern included in Switzerland-specific annex to the EU PSUR Additional pharmacovigilance activities: None

Important potential risk: All-cause mortality	
Evidence for linking the risk to the medicine	All-cause mortality is considered a class-effect of systemic JAK inhibitors and is included as a warning and precaution in the USPI and SmPC for oral JAK inhibitors and the USPI of another topical JAK inhibitor.
Risk factors and risk groups	No specific risk factors have been identified based on the Anzupgo cream 20 mg/g clinical programme.
Risk minimisation measures	Routine risk minimisation measures: Higher all-cause mortality rate seen with oral JAK inhibitors in patients with rheumatoid arthritis patients aged 50 years and older with at least one cardiovascular risk factor is included in the Information for Healthcare Professionals, Section 'Warnings and precautions'. Additional risk minimisation measures: None
Pharmacovigilance activities	Additional routine pharmacovigilance activities: Activity 1 - Safety concern included in routine signal detection. Activity 2 - Safety concern included in Switzerland-specific annex to the EU PSUR Additional pharmacovigilance activities: None

Important potential risk: Malignancies (excluding NMSC)	
Evidence for linking the risk to the medicine	Malignancies are considered a class-effect of systemic JAK inhibitors as these events have been observed in patients treated with oral JAK inhibitors for inflammatory conditions.
Risk factors and risk groups	Individual risk factors have been identified for the few reported malignancies in the Anzupgo cream clinical development program.
Risk minimisation measures	Routine risk minimisation measures: Increased risk of malignancies (excluding NMSCs), including lymphomas, seen with oral JAK inhibitors for the treatment of inflammatory diseases with an increased risk in smokers and ex-smokers is included in the Information for Healthcare Professionals, Section 'Warnings and precautions'. Additional risk minimisation measures:

	None
Pharmacovigilance activities	Additional routine pharmacovigilance activities: Activity 1 - Safety concern included in routine signal detection. Activity 2 - Safety concern included in Switzerland-specific annex to the EU PSUR Additional pharmacovigilance activities: None

Important potential risk: Major adverse cardiovascular events (MACE)	
Evidence for linking the risk to the medicine	Cardiovascular safety is considered a class-effect of systemic JAK inhibitors and is included a warning and precaution in the USPI and SmPC for oral JAK inhibitors and the USPI of another topical JAK inhibitor.
Risk factors and risk groups	No specific risk factors for major adverse cardiovascular events have been identified through the Anzupgo cream clinical programme.
Risk minimisation measures	Routine risk minimisation measures: Higher rate of major adverse cardiovascular events seen with oral JAK inhibitors in rheumatoid arthritis patients aged 50 years and older with at least one cardiovascular risk factor is included in the Information for Healthcare Professionals, Section 'Warnings and precautions'. Additional risk minimisation measures: None
Pharmacovigilance activities	Additional routine pharmacovigilance activities: Activity 1 - Safety concern included in routine signal detection. Activity 2 - Safety concern included in Switzerland-specific annex to the EU PSUR Additional pharmacovigilance activities: None

Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Thromboembolic events are considered a class-effect of systemic JAK inhibitors as these events have been observed in subjects that are already at higher risk for thromboembolic events. They are included as a warning and precaution in the USPI and SmPC for oral JAK inhibitors and the USPI of another topical JAK inhibitor.
Risk factors and risk groups	No specific risk factors for thromboembolic events have been identified through the Anzupgo cream clinical programme.
Risk minimisation measures	Routine risk minimisation measures: Thrombosis, including deep vein thrombosis and pulmonary embolism, seen with oral JAK inhibitors in rheumatoid arthritis patients aged 50 years and older with at least one cardiovascular risk factor, is included in the Information for Healthcare Professionals, Section 'Warnings and precautions'. Additional risk minimisation measures: None
Pharmacovigilance activities	Additional routine pharmacovigilance activities: Activity 1 - Safety concern included in routine signal detection. Activity 2 - Safety concern included in Switzerland-specific annex to the EU PSUR Additional pharmacovigilance activities: None

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 Anzupgo cream.

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

Study name: Anzupgo cream 20 mg/g in moderate to severe CHE and risk of NMSC: a nationwide registry based long-term PASS.

Purpose of the study: There is no indication of skin malignancy (including NMSC) developing in relation to use of Anzupgo cream 20 mg/g, but NMSC is considered a potential risk for JAK

inhibitors. The study will investigate whether the use of Anzupgo cream 20 mg/g in patients with moderate to severe CHE is associated with a higher risk of developing NMSC compared to patients with moderate to severe CHE never exposed to Anzupgo cream 20 mg/g.