Ilumetri®

Tildrakizumab

100 mg and 200 mg solution for injection in pre-filled syringe

100 mg and 200 mg solution for injection in pre-filled pen

Summary of Risk Management Plan (RMP)

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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 Ilumetri® 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 Ilumetri® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Almirall AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ilumetri®.

Part VI: Summary of the risk management plan

Summary of risk management plan for tildrakizumab 100 mg solution for injection in pre-filled syringe (Ilumetri)

This is a summary of the risk management plan (RMP) for Ilumetri 100 mg Solution for injection. The RMP details important risks of Ilumetri, how these risks can be minimised, and how more information will be obtained about Ilumetri's risks and uncertainties (missing information).

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

This summary of the RMP for Ilumetri should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Ilumetri's RMP.

I. The medicine and what it is used for

Ilumetri is authorised for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy (see SmPC for the full indication). It contains tildrakizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Ilumetri's benefits can be found in Ilumetri's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

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

- 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 sizes — 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*.

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

II.A List of important risks and missing information

Important risks of Ilumetri 100 mg Solution for injection 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 Ilumetri. 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).

Table 1. Part VI: List of important risks and missing information

Important identified risks	None
Important potential risks	Hypersensitivity Serious infections Malignancies Major adverse cardiac events Suicidal ideation behaviour (SIB) Inflammatory Bowel Disease (IBD)
Missing information	Safety in pregnant and lactating women Long-term safety Use after recent vaccination with live bacterial or live viral vaccines Use in immunosuppressed patients Use in patients with severe hepatic impairment Use in patients with severe renal impairment

II.B Summary of important risks

Table 2. Part VI: Important potential risks

Important potential risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Treatment with monoclonal antibodies may lead to the development of serious anaphylactic or anaphylactoid hypersensitivity reactions, therefore hypersensitivity is considered as a potential risk in the RMP. The classification of hypersensitivity as a potential risk is based on evidence from literature the safety profile described for similar mAbs used for Psoriasis and form the tildrakizumab clinical development programme

Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.3 • PL Sec. 2 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • Post Authorisation Safety Study (PASS) in European Psoriasis Registries See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Serious infections	
Evidence for linking the risk to the medicine	The classification of serious infections as a potential risk is based on evidence from the clinical development programme and the safety profile described for similar MABs that acts in the same pathways used for Psoriasis. Animal studies do not suggest that tildrakizumab produces a detrimental effect on the immune system. Tildrakizumab has an immunomodulatory mode of action, therefore serious infection is considered a potential risk in the RMP and will be monitored in the post-marketing setting.
Risk factors and risk groups	Patients with concomitant chronic debilitating conditions (such as haematological or lymphoreticular malignancies, organ transplanted patients, severe stages of rheumatoid arthritis or systemic lupus erythematosus) who require concomitant immunosuppressive therapies such as steroids at immunosuppressive doses, methotrexate, immunosuppressant or tumour necrosis factor α (TNFα) antagonists (Fica, 2014). A recent systemic review showed that there may be a small increased risk of overall infection related to the short-term use of TNFα antagonists in the treatment of psoriasis, the majority of infections were non-serious (97.6%) and were upper respiratory tract infections (Dommasch, 2011). It is well-recognised that serious infections including atypical infections like TB have been reported with the use of TNF-alpha inhibitors in psoriasis (Dommasch, 2011).
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.3 and 4.4 • PL Sec. 2 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study

	See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	The classification of malignancies as a potential risk is based on the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis and evidence from the clinical development programme. Animal studies for tildrakizumab have shown no increase in carcinogenic risk. Tildrakizumab has however an immunomodulatory mode of action, therefore malignancies is considered as a potential risk in the RMP and will be further assessed in the post-marketing setting.
Risk factors and risk groups	Cancer risk seems to be higher in patients with severe psoriasis (Beyaert, 2013). Patients with long standing psoriasis seem to be at an increased risk for colon, bladder and kidney cancer (Brauchli, 2009). Patients receiving high dose PUVA and methotrexate for psoriasis are at an increased risk of skin cancer. In a US prospective PUVA follow-up study of patients with severe psoriasis, more than 25% of patients exposed to high doses of PUVA developed squamous cell cancer (SCC): the relative risk of SCC for patients exposed to high dose PUVA was 5.9 (95% CI 4.0-8.7) compared to those exposed to low dose PUVA. High dose methotrexate was determined to be an independent risk factor for developing SCC with a relative risk of 2.1(95% CI 1.4-2.8) compared to low or no exposure to methotrexate (Stern, 1994).
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 5.3 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Major adverse cardiac events (MACE)	
Evidence for linking the risk to the medicine	Psoriasis patients have an increased risk of cardiovascular events due to overlapping mechanisms of systemic inflammation; therefore MACE is considered a potential risk in the RMP and will be further assessed in the post-marketing setting. The classification of MACE as a potential risk is based on evidence from the clinical development programme, the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis.

Risk factors and risk groups	Patients with psoriasis are at increased risk of myocardial infarction (MI) and stroke (Armstrong, 2013) and of MACE (Parisi, 2015) and this risk appears to increase with severity of disease (Armstrong, 2013; Parisi, 2015; Mehta, 2011). The increased cardiovascular risk observed in psoriasis may result from a number of often related risk factors including: smoking, obesity, hypertension and alcohol misuse. In addition, the use of dyslipidaemic therapies, such as corticosteroids, acitretin and ciclosporin and an associated unfavourable lipid profile with high triglycerides and low HDL cholesterol may contribute. Psoriasis itself is an independent risk factor for MACE (Mehta, 2011) and the overall increased risk may be related to a combination of these factors in the patient (Mrowietz, 2006).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Suicidal ideation behaviour (SIB)	
Evidence for linking the risk to the medicine	The classification of SIB as a potential risk is based on the safety profile described for similar mAbs that acts in the same pathways used for Psoriasis and on evidence from the clinical development programme. Psoriasis patients have an increased risk of depression and suicidal ideation. SIB events have been observed with monoclonal antibodies used in psoriasis, therefore SIB is considered as a potential risk in the RMP and will be closely monitored in the post-marketing setting.
Risk factors and risk groups	Patients with psoriasis have an increased prevalence of the psychiatric disorders anxiety and depressive disorders (30% and 60% respectively). About 10% of psoriasis patients consider the possibility of suicide (Gupta, 1998). Patients with psoriasis are at a higher risk of depression, suicidal ideation, suicide attempt and completed suicide (Gupta, 1998; Kurd, 2010; Koo, 2017).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Inflammatory Bowel Disease (IBD)	
Evidence for linking the risk to the medicine	IBD events have been observed with other monoclonal antibodies (known as IL-17 inhibitors) used in psoriasis, therefore IBD is considered as a potential risk in the RMP and will be closely monitored in the post-marketing setting.
Risk factors and risk groups	IBD is considered a potential co-morbidity in patients with psoriasis. Patients with Crohn's Disease (CD) have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population (Gulliver, 2008; Christophers, 2001; Vlachos, 2016).
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Safety in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.6 and 5.3 • PL Sec. 2 • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Pregnancy safety related studies (US). • PASS in European Psoriasis Registries

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • Pack size • Prescription only medicine
Additional pharmacovigilance activities	Additional pharmacovigilance activities • Review of safety data from long-term (4 years) extension studies • PASS in European Psoriasis Registries • US Observational Study See Sec. II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use after recent vaccination with live bacterial or live viral vaccines	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.4 and 4.5 • PL Sec. 2 • Pack size • Prescription only medicine

Missing information: Use in immunosuppressed patients	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.5 • PL Sec. 2 • Pack size • Prescription only medicine

Missing information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.2 and Sec 5.2 • Pack size • Prescription only medicine

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC Sec. 4.2 and Sec 5.2 • Pack size • Prescription only medicine

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 Ilumetri 100 mg Solution for injection.

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

1. **P010 study:** A 64-Week, Phase 3, Randomized, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis.

   Purpose of the study: To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years.

2. **P011 study**: A 52-Week, Phase 3, Randomized, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to–Severe Chronic Plaque Psoriasis.

   Purpose of the study: To assess the long-term safety profile and tolerability of tildrakizumab for up to 4 years.

3. **PASS in European Psoriasis Registries (M-14745-40):** An observational cohort study to assess the long-term safety of tildrakizumab compared to other biological therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy in a real world clinical setting.

   Purpose of the study: To address whether the use of tildrakizumab is associated with an increased risk of events of special interest (Malignancies, MACEs, serious infections SIB, Hypersensitivity and IBD) for biologic therapies for psoriasis in new users of tildrakizumab compared to “other biologics” and to “non-biologic systemic therapies” as well study pregnancy related outcomes in patients exposed to tildrakizumab.

4. **Tildrakizumab Post-authorization observational study 3357-4 (US):** An observational study to assess the long-term safety of tildrakizumab compared to other therapies used in the treatment of adults with moderate to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care.

   Purpose of the study: To assess the long-term risk of malignancy, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

5. **Pregnancy safety related study 3357-2:** A prospective observational study to assess the maternal, foetal and infant outcomes of women exposed to tildrakizumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis.

   Purpose of the study: To assess the incidence of major congenital malformations, spontaneous abortions, stillbirths, elective terminations and small for gestational age and other adverse pregnancy outcomes in pregnant women exposed to tildrakizumab in the

course of routine clinical care compared to an unexposed control population of psoriasis patients that are exposed to other biologics approved for treatment of psoriasis.

6. **Pregnancy safety related study 3357-3:** A retrospective study 3357-3 to assess the association between some maternal, foetal and infant outcomes with exposure to tildrakizumab compared to the population receiving other therapies used in the treatment of adults with moderate to severe plaque psoriasis.

   Purpose of the study: To evaluate the association of tildrakizumab exposure with major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths and infant infections compared to other biologic therapies used in the treatment of adults with moderate to severe plaque psoriasis.

Annex 1. Reference List:

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