Summary of Risk Management Plan for Taltz (Ixekizumab)

This summary of the RMP for Taltz 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 are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Taltz RMP.

I - The Medicine and What It is Used for

Taltz is authorised for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

Taltz, alone or in combination with methotrexate, is also authorised for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies (see SmPC for the full indication). It contains ixekizumab as the active substance and it is given by subcutaneous injection.

Taltz is authorised for the treatment of adult patients with active radiographic axSpA/AS.

Taltz is authorised for the treatment of adult patients with active nonradiographic axSpA with objective signs of inflammation.

Taltz is authorised for the treatment of children from the age of 6 years and adolescents with moderate-to-severe plaque psoriasis who are candidates for systemic therapy. Further information about the evaluation of Taltz's benefits can be found in Taltz'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/taltz

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Taltz, together with measures to minimise such risks and the proposed studies for learning more about Taltz'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 providers
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (for example, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of Important Risks and Missing Information

Important risks of Taltz are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely. 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 Taltz. 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 (for example, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Inflammatory bowel disease (Crohn’s disease and ulcerative colitis) Serious infections
Important potential risks	MACE[a] Malignancies[a]
Missing information	Long-term safety in adults (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years) Long-term safety in paediatrics Use in patients with active infections Immune response to live vaccinations

Abbreviation: MACE = major adverse cerebro-cardiovascular events.

[a] In adult population.

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk: Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis)	
Evidence for linking the risk to the medicine	Crohn's disease and ulcerative colitis are long-term conditions that can flare up periodically. Some patients receiving ixekizumab may develop or experience a flare-up of Crohn's disease or ulcerative colitis during treatment.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Ixekizumab works by modulating the immune system for the treatment of psoriasis, PsA, and axSpA. This may also reduce the body's ability to fight certain infections. In clinical trials, more patients on ixekizumab than on placebo experienced nonserious infections such as upper airway infection, thrush, conjunctivitis ("pink eye"), and fungal skin infections. Neutropaenia has been commonly observed in patients receiving ixekizumab, raising the concern for possible increased risk of serious infection. For the majority of cases, neutropaenia was transient in nature and did not result in treatment discontinuation or hospitalisation. The majority of infection events were mild to moderate, with only a small proportion of patients (3%) experiencing a severe infection in clinical trials.

Summary of Important Risks

Important Identified Risk: Serious Infections	
Risk factors and risk groups	No risk groups or specific risk factors have been identified from the psoriasis, PsA, or axSpA clinical development programmes. Due to the mechanism of action and potential effect on decreasing immune response by anti-TNF or anti-IL 17 classes of medicines, patients with evidence of untreated latent (inactive) TB or certain viral infections such as chronic HBV may be at greater risk of reactivation or exacerbation of their underlying disease. It is reasonable to assume that this additional risk in patients with evidence of untreated latent TB or certain viral infections such as chronic HBV would apply to ixekizumab as well, even though this has not been observed in the clinical development programme.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care See Section II.C of this summary for an overview of the post-authorisation development plan.

Summary of Important Risks

Important Potential Risk: MACE[a]	
Evidence for linking the risk to the medicine	Current evidence is mixed regarding contributions of IL-17A to the atherosclerotic plaque instability. Sustained IL-17 levels are present in the target population and may be linked to the pathology of atherosclerosis; however, the role played by IL-17 and T helper-17 cells in atherosclerosis is still controversial. Several studies in mice suggest a contribution of the IL-17 pathway to vascular inflammation (Dart et al. 2010; Kotla et al. 2013; Lim et al. 2014), yet other studies in animal models suggest a stabilising effect on the atherosclerotic plaque related to an inhibitory effect on endothelial vascular cells adhesion molecules (VCAM-1) (Taleb et al. 2009) and to a stimulatory effect on fibrillar collagen synthesis by smooth muscle cells (Gisterå et al. 2013).
Risk factors and risk groups	No specific risk factors for MACE in relation to treatment with ixekizumab have been identified.
Risk Minimisation measures	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Malignancy[a]	
Evidence for linking the risk to the medicine	There are theoretical considerations which could link the pharmacologic mode of action of ixekizumab to the development of tumours; however, the current clinical and nonclinical data do not suggest that ixekizumab causes malignant tumours or promotes tumour growth.
Risk factors and risk groups	No specific risk factors for malignancy in relation to treatment with ixekizumab have been identified.
Risk Minimisation measures	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT See Section II.C of this summary for an overview of the post-authorisation development plan.

Summary of Important Risks

Important Missing Information: Long-term Safety in Adults (Such as Events with a Low Frequency and/or Long Latency)	
Risk minimisation measures	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-B005 See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Missing Information: Use in Very Elderly (≥75 Years)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study I1F-MC-RHBT See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Missing Information: Long-term Safety in Paediatrics	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Additional risk minimisation measures: None proposed

Summary of Important Risks

Important Missing Information: Long-term Safety in Paediatrics	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Missing Information: Use in Patients with Active Infections	
Risk minimisation measures	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.3 states that ixekizumab should not be used in patients with clinically important active infections (e.g. active tuberculosis). • SmPC Section 4.4 advises not to give to patients with active tuberculosis. Other routine risk minimisation measures beyond the Product Information: None
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: None
Important Missing Information: Immune Response to Live Vaccines	
	Routine risk communication: • SmPC Section 4.4 • SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises that Taltz should not be used with live vaccines, that no data are available on the response to live vaccines and that insufficient data are available on the response to inactive vaccines. • SmPC Section 5.1 provides information on a study with 2 inactive vaccines in healthy subjects who demonstrated no safety concerns, but immunisation data were considered too limited to conclude that there was an adequate immune response to these inactive vaccines. Other routine risk minimisation measures beyond the Product Information: None

Summary of Important Risks

Important Missing Information: Immune Response to Live Vaccines	
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: None

Abbreviations: axSpA = axial spondyloarthritis; HBV = hepatitis B virus; IL = interleukin; MACE = major adverse cerebro-cardiovascular events; PsA = psoriatic arthritis; SmPC = summary of product characteristics; TB = tuberculosis; TNF = tumour necrosis factor.

[a] In adult population.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Taltz.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study Short Name and Title: [Trial alias pending] An Observational Study to Assess the Utilization and Safety of Ixekizumab Among Pediatric Patients Treated in the Course of Routine Clinical Care

Rationale and Study Objectives: Ixekizumab, a humanised IgG subclass 4 monoclonal antibody that neutralises IL-17A, is under review for the treatment of plaque psoriasis in children ages 6 years and above. Data from clinical trials demonstrate that ixekizumab is effective and generally well-tolerated; however, long-term safety pertaining to the important risks of inflammatory bowel disease and serious infections among pediatric patients treated in clinical practice is not fully characterized.

The objectives of this study are:

- To monitor the uptake of ixekizumab in a real-world pediatric population
- To characterize the demographics and clinical characteristics of pediatric patients receiving ixekizumab
- To provide additional information about the long-term safety pertaining to serious infections and inflammatory bowel disease

Study Short Name and Title: I1F-MC-RHBT– A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care

Purpose of the study: Ixekizumab is an IL-17A antagonist approved for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis. Data from clinical trials demonstrate that ixekizumab is effective and generally well tolerated; however, the long-term safety profile among patients treated in routine clinical practice is not fully characterised.

The objectives of this study are:

- To monitor the frequency and nature of infections, hypersensitivity (allergic) reactions, inflammatory bowel disease, “heart attack” (myocardial infarction) and stroke, and cancers in clinical practice
- To provide additional information on the long-term safety (effects which are infrequent, and/or take a long time to develop) in routine clinical practice
- To watch the frequency and nature of side effects in the very elderly in routine clinical practice
- To look for any new side effects
- To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real-world setting

Study Short Name and Title: I1F-MC-B005 – Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab

Purpose of the study: Ixekizumab, a humanised IgG subclass 4 monoclonal antibody that neutralises IL-17A, is currently intended for systemic treatment of individuals with moderate-to-severe chronic plaque psoriasis and PsA. Pregnant women were not included in the ixekizumab clinical development programme; however, it is recognised that IgG does cross the placenta and is central to foetal immunity, with transport increasing as the pregnancy progresses. Given that disease onset in the indicated psoriasis population commonly occurs prior to age 35 years, when many women become pregnant, characterisation of risks to pregnant mothers and their infants is sought.

The objectives of this study are:

- To understand the utilisation of ixekizumab among pregnant mothers with psoriasis, PsA, and other newly approved indications
- To look for any harmful effects of ixekizumab on pregnant mothers and their babies
- To look for any new side effects