Part VI: Summary of the risk management plan

Summary of risk management plan for Kyntheum® (brodalumab)

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

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

This summary of the RMP for Kyntheum® 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 Kyntheum®'s RMP.

I. The medicine and what it is used for

Kyntheum® is authorised for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy (see SmPC for the full indication). It contains brodalumab as the active substance and it is given by subcutaneous route of administration.

Further information about the evaluation of Kyntheum's benefits can be found in Kyntheum'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/kyntheum.

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

Important risks of Kyntheum®, together with measures to minimise such risks and the proposed studies for learning more about Kyntheum®'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 Kyntheum® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kyntheum® 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 Kyntheum®. 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	Infections
Important potential risks	SIB MACE Malignancy
Missing information	Risks during pregnancy and lactation Use in geriatric patients Use in patients after recent vaccination

II.B Summary of important risks

Important identified risk - Infections	
Evidence for linking the risk to the medicine	In the clinical trials, patients were more likely to develop infections while taking brodalumab. Most infections were mild or moderate and could be easily managed.
Risk factors and risk groups	Concomitant treatment with immunosuppressants such as methotrexate or corticosteroids may increase the risk of infections.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects SmPC Section 5.2, Pharmacokinetic properties PIL Section 2, What you need to know before you use brodalumab PIL Section 4, Possible side effects
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The BRodalumab Assessment of Hazards: A Multi-national Safety (BRAHMS) study in electronic healthcare databases See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk – Suicidal thoughts and behaviour (thoughts about wanting to kill or harm yourself or attempting to kill or harm yourself)	
Evidence for linking the risk to the medicine	Patients with psoriasis are known to be at an increased risk of suicidal thoughts and behaviour compared with the general population. This is partially because risk factors for suicidality, such as anxiety and depression, are more common in patients with psoriasis than in those without psoriasis. Some patients in clinical trials for brodalumab experienced suicidal thoughts and behaviour, including a small number who committed suicide. Many of these patients had a history of depression and/or suicidal thoughts or behaviour. A causal relationship between brodalumab treatment and suicidal thoughts and behaviour has not been established. Doctors should inform patients receiving brodalumab to tell their doctor if they experience new or worsening depression, suicidal thoughts, or mood changes.
Risk factors and risk groups	History of suicidality is a well-recognised predictor of subsequent suicide thoughts or behaviour and was demonstrated in the psoriasis programme, where subjects with a known history of suicidality who reported an event of suicide thoughts or behaviour had a 30-fold higher rate of suicide thoughts or behaviour compared with subjects with no history of suicidality (5.05 per 100 subject-years versus 0.16 per 100 subject-years, respectively).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 5.2, Pharmacokinetic properties PIL Section 2, What you need to know before you use brodalumab
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The BRodalumab Assessment of Hazards: A Multi-national Safety (BRAHMS) study in electronic healthcare databases A meta-analysis of future randomised controlled clinical trials data, for which information regarding SIB has been collected with the C-SSRS questionnaires. See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk – Major adverse cardiac events (MACE) (serious heart problems)	
Evidence for linking the risk to the medicine	Patients with psoriasis are often at increased risk of serious heart problems because they are more likely to have known risk factors, including increased levels of fat and sugar in the blood, obesity, and high blood pressure. It is not yet known if brodalumab increases further the likelihood of heart or circulation problems in patients with psoriasis.
Risk factors and risk groups	Subjects for whom a major cardiac event was reported had one or more of the following major cardiovascular risk factors and additional confounding diseases: obesity, diabetes, tobacco use, increased blood pressure, abnormal amount of lipids in the blood (dyslipidemia), previous cardiac medical history e.g. arrythmia and hearth failure.
Risk minimisation measures	No specific measures are required for patients receiving brodalumab; standard of care is adequate.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The BRodalumab Assessment of Hazards: A Multi-national Safety (BRAHMS) study in electronic healthcare databases 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	Brodalumab is a targeted immunomodulatory agent but is not considered a general immunosuppressant. Humans with genetic mutation (changes in genetic information) of IL-17F or IL-17RA are not reported to have an enhanced malignancy risk. The potential for carcinogenic risk of brodalumab is considered low and the evidence from non-clinical and clinical experience support that there is no increased risk of malignancy.
Risk factors and risk groups	A recent meta-analysis of epidemiologic studies assessing the association between psoriasis and malignancy found that there is a modest suggestion of an elevated risk of solid malignancies with psoriasis; however, it is possible that alcohol and tobacco consumption may account for at least some of this increased risk. Although there is no clear elevated risk of melanoma with psoriasis, non-melanoma skin cancer is elevated and may be due in part to PUVA therapy, as well as use of systemic immunosuppressants cyclosporine and methotrexate.
Risk minimisation measures	No specific measures are required for patients receiving brodalumab; standard of care is adequate.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: The BRodalumab Assessment of Hazards: A Multi-national Safety (BRAHMS) study in electronic healthcare databases See section II.C of this summary for an overview of the post-authorisation development plan.

Important missing information – Risks during pregnancy and breast feeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special Warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy, and lactation PIL Section 2, What you need to know before you use brodalumab.

Important missing information – Use in geriatric patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 5.2, Pharmacokinetic properties PIL None

Important missing information – Use in patients after recent vaccination	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction PIL Section 2, What you need to know before you use brodalumab

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 Kyntheum®.

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

II.C.2.1

Study short name:

The BRodalumab Assessment of Hazards: A Multi-national Safety (BRAHMS) study

Purpose of the study

The study aims to evaluate potential excess risks associated with the use of brodalumab in the treatment of psoriasis with regards to suicidal behaviour, serious infections, MACE, and malignancies.

II.C.2.2

Study short name:

Meta-analysis of future randomised controlled clinical trials

Purpose of the study

This meta-analysis aims to evaluate potential excess risks associated with the use of brodalumab in the treatment of psoriasis with regards to suicidal ideation and behaviour.