Summary of risk management plan for KEVZARA (Sarilumab)

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

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

This summary of the RMP for KEVZARA 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 KEVZARA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

KEVZARA in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active RA in adult patients who have responded inadequately to, or who are intolerant to one or more Disease Modifying Anti-Rheumatic Drug (DMARDs). KEVZARA can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see SmPC for the full indication). It contains sarilumab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of KEVZARA's benefits can be found in KEVZARA's EPAR, including in its plain-language summary, available on the European medicines agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/kevzara

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of KEVZARA, together with measures to minimize such risks and the proposed studies for learning more about KEVZARA's risks, are outlined in the next sections.

Measures to minimize 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 HCPs;
- Important advice on the medicine's packaging;

- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of KEVZARA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (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 KEVZARA are risks that need special risk management activities to further investigate or minimize 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 KEVZARA. 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 (eg, on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risks	Serious infections
	Neutropenia
	Gastrointestinal perforations
Important potential risks	Thrombocytopenia and potential risk of bleeding
	Clinically evident hepatic injury
	Lipid abnormalities and increased risk of major cardiovascular events
	Malignancy
Missing information	None

II.B Summary of important risks

Table 2 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Serious infections

Serious infections	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Consistent with the mechanism of action, sarilumab administration is associated with an increase in the rate of infections, including serious infections.
Risk factors and risk groups	Known risk factors for infections include increased age, medical history of diabetes or chronic obstructive pulmonary disease, smoking, use of concomitant immunosuppressant (eg, MTX).[a]
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.2, 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** Patient Alert Card
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

a Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford) [Internet]. 2013;52(1):53–61. Available from: http://dx.doi.org/10.1093/rheumatology/kes305

EU: European Union; HCP: Healthcare Professional; MTX: Methotrexate; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 3 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Neutropenia

Neutropenia	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased neutrophil count, consistent with its mechanism of action. Neutropenia was not associated with increased incidence of infection.
Risk factors and risk groups	Subgroup analyses on the placebo-controlled population (Pool 1) and sarilumab + DMARD long-term safety population (Pool 2) were conducted for ANC <1.0 Giga/L according to age, gender, race, ethnicity, BMI, weight, geographic region, RA duration of disease, RA functional class, prior biologic use, baseline steroid use MTX dose, concomitant DMARD use (ie, MTX or non-MTX), and baseline ANC <5.99 Giga/L. As anticipated due to the mean decrease in ANC in patients on sarilumab, a numerically higher incidence of ANC <1.0 Giga/L was observed in patients with baseline ANC <5.99 Giga/L in both the placebo-controlled population and sarilumab + DMARD long-term safety population. A numerically higher incidence of ANC <1.0 Giga/L was also observed in patients with weight <60 kg. Weight has been observed as a

Neutropenia	
	covariate on the pharmacokinetics of sarilumab with higher drug exposure at lower body weight.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.2, 4.4, 4.8 and 5.1 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** Patient Alert Card

ANC: Absolute Neutrophil Count; BMI: Body Mass Index; DMARD: Disease Modifying Anti-Rheumatic Drug; HCP: Healthcare Professional; IL-6: Interleukin-6; MTX: Methotrexate; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 4 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Gastrointestinal perforations

Gastrointestinal perforations	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Gastrointestinal perforations were primarily reported as complications of diverticulitis, including lower GI perforation and abscess and were generally confounded by the use of concomitant steroids or NSAIDs.
Risk factors and risk groups	Age, history of diverticulitis, use of glucocorticoids, and/or prescription NSAIDs, concomitant NSAID or steroid use.[a]
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** Patient Alert Card
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

a Gout T, Ostor AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Clin Rheumatol. 2011 Nov;30(11):1471-4.

EU: European Union; GI: Gastrointestinal; HCP: Healthcare Professional; NSAID: Nonsteroidal Anti-Inflammatory Drug; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 5 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Thrombocytopenia and potential risk of bleeding

Thrombocytopenia and potential risk of bleeding	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormality of decreased platelet count, consistent with its mechanism of action.

Thrombocytopenia and potential risk of bleeding	
Risk factors and risk groups	Rarely does bleeding occur in patients with platelet counts >50 Giga/L. Purpura may occur in patients with platelet counts between 30-50 Giga/L. Platelet counts <5 Giga/L may result in spontaneous bleeding. [a]
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.2, 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** None

a Gauer RL, Braun MM. Thrombocytopenia. Am Fam Physician. 2012 Mar 15;85(6):612-22.
HCP: Healthcare Professional; IL-6: Interleukin-6; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 6 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Important potential risk: Clinically evident hepatic injury

Clinically evident hepatic injury	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with transient laboratory abnormalities of increased hepatic transaminases, consistent with its mechanism of action.
Risk factors and risk groups	A higher incidence of ALT >3xULN was seen in patients whose baseline ALT was >ULN in the placebo-controlled population and the sarilumab plus DMARD long-term safety population compared to patients whose baseline ALT values were not >ULN.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.2, 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** None

ALT: Alanine Aminotransferase; DMARD: Disease Modifying Anti-Rheumatic Drug; HCP: Healthcare Professional; IL-6: Interleukin-6; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics; ULN: Upper Limit of Normal.

Table 7 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Lipid abnormalities and increased risk of major cardiovascular events

Lipid abnormalities and increased risk of major cardiovascular events	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of clinical safety data observed with sarilumab during the clinical development program. Sarilumab administration was associated with laboratory abnormalities of increased lipids, consistent with its mechanism of action and may increase the risk of MACE.
Risk factors and risk groups	Rheumatoid arthritis is associated with increased CV morbidity and mortality, related not only to traditional CV risk factors (eg, age, gender,

Lipid abnormalities and increased risk of major cardiovascular events	
	diabetes, hyperlipidemia, and hypertension), but also to a chronic inflammatory state.[a] The results in a publication from a randomized, parallel-group, multicenter, non-inferiority, Phase 4 clinical trial to assess CV safety of TCZ (IL-6 inhibitor) were compared with etanercept in RA, showed that 83 MACE occurred over 4900 PYs in the TCZ arm versus 78 over 4891 PYs in the etanercept arm (HR 1.05; 95% CI 0.77, 1.43). [b]
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

a Amezaga Urruela M, Suarez-Almazor ME. Lipid paradox in rheumatoid arthritis: changes with rheumatoid arthritis therapies. Curr Rheumatol Rep. 2012 Oct;14(5):428-37.

b Giles JT, Sattar N, Gabriel S, Ridker PM, Gay S, Warne C, et al. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: A randomized controlled trial. Arthritis rheumatol [Internet]. 2020;72(1):31–40.

CV: Cardiovascular; IL-6: Interleukin-6; EU: European Union; HCP: Healthcare Professional; HR: Hazard Ratio; MACE: Major Adverse Cardiovascular Event; PY: Patient-Years; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics; TCZ: Tocilizumab.

Table 8 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Malignancy

Malignancy	
Evidence for linking the risk to the medicine	The important risk was defined based on in-depth review of the literature on IL-6, review and analysis of non-clinical findings, as well as of clinical safety data observed with sarilumab during the clinical development program. Due to the immunomodulatory effects of biologic DMARDs used in the treatment of RA, treatment may result in an increased risk of malignancies. Since a higher rate of malignancy was not observed in patients treated with sarilumab compared to the general population or patients with RA, this is considered an important potential risk.
Risk factors and risk groups	Age, duration/severity of RA and other risk factors based on type (eg, smoking history, family history).
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in sections 4.4 and 4.8 Prescription only medication. Treatment should be initiated by HCP experienced in diagnosis and treatment of RA. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Safety surveillance program using existing EU RA registries

DMARD: Disease Modifying Anti-Rheumatic Drug; EU: European Union; HCP: Healthcare Professional; IL-6: Interleukin-6; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of KEVZARA.

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

Table 9 - Other studies in post-authorization development plan

Safety surveillance program using existing EU RA registries (OBS15180 in Germany, 6R88-RA-1720 in Spain, OBS15220 in Sweden, 6R88-RA-1634 in United Kingdom) (Cat. 3)
Purpose of the study: To monitor the safety of sarilumab and evaluate the risk of selected outcomes of interest with long term use in patients with RA in real-world clinical practice.

EU: European Union; RA: Rheumatoid Arthritis.