PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ROACTEMRA (TOCILIZUMAB)

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

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

This summary of the RMP for RoActemra 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 RoActemra RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

RoActemra is authorized for rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis, and cytokine release syndrome (see SmPC for the full indication). It contains tocilizumab as the active substance and it is given by intravenous infusion or subcutaneous injection.

Further information about the evaluation of RoActemra benefits can be found in RoActemra 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 RoActemra, together with measures to minimize such risks and the proposed studies for learning more about RoActemra risks, are outlined below.

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 healthcare professionals;
- 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 (e.g., with or without prescription) can help to minimize its risks.

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

In the case of RoActemra, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 RoActemra is not yet available, it is listed under 'missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of RoActemra 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 RoActemra. 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	• Serious infection • Complications of diverticulitis • Serious hypersensitivity reactions • Neutropenia
Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with TCZ and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase by body weight. Healthcare professionals should exercise caution when considering the use of TCZ in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.
Risk minimization measures	**Routine risk measure:** **SmPC** **IV and SC formulation**: SmPC Section 4.3 Contraindications Active, severe infections (see section 4.4) SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Patient Information Leaflet:** **IV and SC Formulation** Section 2. What you need to know before you are given TCZ Section 4 Possible serious side effects: tell a doctor straightaway. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk: Complications of Diverticulitis	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.
Risk minimization measures	**Routine risk minimization measure:** **SmPC** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Patient Information Leaflet:** Section 2 Warnings and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.
Important identified Risk : Serious Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** **SmPC** SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Patient Information Leaflet** Warnings and precautions *(IV formulation):* Section 2 What you need to know before you are given TCZ. *(SC formulation)*: Section 2 What you need to know before you use TCZ Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure Rheumatoid Arthritis Dosing Guide pJIA and sJIA Dosing Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk: Neutropenia	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	None identified
Risk minimization measures	**Routine risk communication:** **SmPC** SmPC section 4.2 Posology and method of administration

	SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects/Laboratory evaluations **<u>Patient Information Leaflet</u>** Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR) See section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk : Thrombocytopenia and the potential risk of bleeding	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC section 4.2 Posology and method of administration (IV formulation) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:**

	Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR) See section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk: Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimization measures	**Routine risk communication:** **SmPC** SmPC section 4.2 Posology and method of administration (IV formulation) SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Patient Information Leaflet** (IV/SC formulation) Section 2 Warning and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) • WA28029 (ARTHUR) See section II.C of this summary for an overview of the post-

	authorization development plan.
Important Potential Risk : Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** **SmPC** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 Warnings and precautions **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk: Malignancies	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	None identified
Risk minimization measures	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use SmPC section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

	None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk: Demyelinating Disorders	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimization measures	**Routine risk communication:** SmPC section 4.4 Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • US claims database • EU registries (BSRBR, ARTIS, RABBIT, WA29358) See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk : Immunogenicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine No Additional Risk Minimization Measure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See section II.C of this summary for an overview of the post-authorization development plan.
IV=Intravenous; SC=Subcutaneous; SmPC=Summary of Product Characteristics; TCZ=Tocilizumab	

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 authorisation or specific obligation of RoActemra.

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

Study short name: WA22479 (British Society of Rheumatology Biologics Register [BSRBR])
Purpose of the study: Prospective observational cohort studies for safety data collection.

Study short name: WA22480 (ARTIS) registry study
Purpose of the study: To provide long term safety data from the use of TCZ in Sweden for RA patients.

Study short name: ML28664 (formerly tracked as GA28719) (RABBIT)
Purpose of the study: The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry

Study sort name: WA28029 (ARTHUR)
Purpose of the study: To investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients.

Study sort name: WA29358
Purpose of the study: To provide long term safety and efficacy data from the use of TCZ in pJIA patients.

Study sort name: GA28720 (OTIS) pregnancy registry
Purpose of the study: To monitor planned and unplanned pregnancies exposed to TCZ and to evaluate the possible teratogenic effect of this medication on pregnancy outcome.