WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	RoActemra [1]
Manufacturer of Prequalified Product:	Name and address of the manufacturer of the biological active substance: Genentech, Inc. 1000 New Horizons Way Vacaville, CA 95688 United States Genentech Inc. 1 Antibody Way Oceanside, CA 92056 United States Samsung Biologics Co Ltd 300, Songdo bio-daero, Yeonsu-gu Incheon, 21987 Republic of Korea Name and address of the manufacturer of the drug product: Genentech Inc. 4625 NE Brookwood Parkway, Hillsboro, OR 97124, United States Chugai Pharma Manufacturing Co., Ltd. 16-3 Kiyohara Kogyodanchi Utsunomiya-city, Tochigi, 321-3231 Japan Name and address of the manufacturer(s) responsible for batch release: Roche Pharma AG Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
Active Pharmaceutical Ingredient (API):	Tocilizumab

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Pharmaco-therapeutic group (ATC Codes):	Antineoplastic and immunomodulating agents, Interleukin inhibitors (L04AC07)
WHO recommended therapeutic indication:	Treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation

1. Introduction

RoActemra (tocilizumab) is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of different diseases including inflammatory diseases, osteoporosis and neoplasias.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely the "European Medicines Agency" (EMA http://www.ema.europa.eu/ema/) in line with the "WHO Guidelines on submission of documentation for the procedure for prequalification of biotherapeutic products or their corresponding similar biotherapeutic products approved by stringent regulatory authorities"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR

2. Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant provided data to demonstrate the maintenance of the required 2°C - 8°C temperature conditions during shipment when different active and passive shipping containers are exposed at extreme environmental conditions. Furthermore, the Applicant provided evidence that the shipment set up can be successfully performed for all shipments and will meet the required criteria. The data are considered in compliance with WHO requirements.

The Applicant confirmed the performance of 100% temperature monitoring for all shipments. Calibrated monitoring devices are used to assess the incoming material. Potential temperature excursions during the

2 https://extranet.who.int/pqweb/sites/default/files/documents/03_Prequalification_general_AbridgedPathway.pdf

transport are revealed and the product quality impact is assessed against the stability data of the affected product.

The Applicant confirmed also that information and training required for handling the temperature monitoring device at the packing/sending and receiving sites will be provided.

In case of delays in transportation the first priority is to ensure the proper storage and handling of the material. Established and documented procedures are in place to limit the time of exposure of pharmaceuticals to uncontrolled temperatures as much as possible.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the Applicant provides details, among others, on the criteria to define the complaint criticality, root cause investigation process and impact assessment on other batches and/or products, established timelines for effective recall system, definition of quality issues/recalls that implies notification to Authorities and timelines for notification to National Medicines Regulatory Authorities and WHO, description of the recall arrangements and actions to put in place at the distribution level, as well as description of the periodical mock-recall.

The Applicant also provided the quality agreement provisions for complaints notified to a 3rd party customer that has to recall the prequalified product.

Conclusion: The quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: The pharmacovigilance part of the dossier is accepted.

[3] https://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1)

Risk Management Plan Addendum for WHO Prequalification Pilot

Actemra/RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion

Based on : EU RMP Version 27.1

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
COVID-19	coronavirus disease 2019
EEA	European Economic Area
EMA	European Medicines Agency
LMIC	Lower Middle Income Countries
NAPs	Nationally Approved Product
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
TCZ	tocilizumab
WHO	World Health Organization

1. INTRODUCTION

1.1. INDICATION(S) AND DOSAGE(S) IN THE EUROPEAN ECONOMIC AREA (EEA)

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass directed against the soluble interleukin-6 receptor (sIL-6R) and membrane-bound (m)IL-6R. TCZ is available as either intravenous (IV) or subcutaneous (SC) formulations. TCZ IV was initially approved in the European Union (as RoActemra®) on 16 January 2009 for the treatment of rheumatoid arthritis and has since been approved in over 80 countries for the treatment of systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA) and chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS). Of note, TCZ is registered as RoActemra® in EU and Mexico, and as Actemra® in all other countries.

On 6 December 2021, European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended extending the indication of TCZ to include the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation. The recommended posology for treatment of COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation, one additional infusion of TCZ 8 mg/kg may be administered if clinical signs or symptoms worsen or do not improve after the first dose. The interval between the two infusions should be at least 8 hours.

Only the COVID-19 indication for the IV formulation is invited for the WHO prequalification programme. Detailed information relevant to the COVID-19 indication in the European Economic Area (EEA) are provided in the Stringent Regulatory Authority (SRA)-approved EU Risk Management Plan (RMP) version 27.1 and in the Summary of Product Characteristics (SmPC).

1.2. SUMMARY OF SAFETY CONCERNS

A summary of the important identified and potential risks with use of TCZ IV in the COVID-19 indication (treatment of adults with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation) as per EU RMP version 27.1 is presented in Table 1 below. A summary of risk minimization activities and pharmacovigilance activities by safety concern is presented in Table 2.

Table 1 Summary of Safety Concerns for use of TCZ IV in COVID-19 indication (as per EU RMP v27.1)

Summary of Safety Concerns for COVID-19 indication	
Important identified risks	• Neutropenia • Hepatotoxicity
Important potential risks	• Serious infection* • Complications of diverticulitis* • Thrombocytopenia and the potential risk of bleeding • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

COVID-19 = coronavirus disease 2019; TCZ = tocilizumab.

* The safety concerns “serious infection” and “complications of diverticulitis” are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

Table 2 Summary table of the Safety Concerns, Pharmacovigilance Activities and Risk Minimization Measures for use of TCZ IV in COVID-19 indication (as per EU RMP v27.1)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Neutropenia	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations **Patient Information Leaflet** Section 2 What you need to know before you are given RoActemraSection 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** *In COVID-19 patients, neutrophil counts should be monitored according to current standard clinical practices.* **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions, i.e. for events of special interest will collect neutrophil data in cases of serious infection **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication
Hepatotoxicity	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 What you need to know before you are given RoActemra Section 4 Possible side effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: *In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices.* **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 for COVID-19 indication	
Serious infections*	**Routine risk communication:** **SmPC** Section 4.3 Contraindications *- Active, severe infections with the exception of COVID-19 (see Section 4.4)* Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet:** Section 2. What you need to know before you are given RoActemra Section 4 Possible serious 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. No Additional Risk Minimization Measure for COVID-19 indication.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication

Safety concern	Risk minimization measures	Pharmacovigilance activities
Complications of Diverticulitis*	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet:** Section 2 What you need to know before you are given RoActemra 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. No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication
Thrombocytopenia and the potential risk of bleeding	**Routine risk communication:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** *In COVID-19 patients, platelet counts should be monitored according to current standard clinical practices.* **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication

Safety concern	Risk minimization measures	Pharmacovigilance activities
	No Additional Risk Minimization Measure for COVID-19 indication	
Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 What you need to know before you are given RoActemra 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 No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication
Malignancies	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use 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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication

Safety concern	Risk minimization measures	Pharmacovigilance activities
Demyelinating Disorders	**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 No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication
Immunogenicity	**Routine risk communication:** **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collect and analyze anti-TCZ antibodies in patients who experience hypersensitivity reactions that led to study withdrawal in ongoing clinical trials and investigate the risk of developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted. This is specific to the ongoing clinical trials and does not apply to spontaneous post-marketing cases **Additional pharmacovigilance activities:** None

IV=intravenous; SC=subcutaneous; sJIA = systemic juvenile idiopathic arthritis; SmPC=Summary of Product Characteristics; TCZ=tocilizumab.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

1.3. ACKNOWLEDGEMENT FROM APPLICANT

Roche acknowledges that the healthcare settings and infrastructure may vary between countries and that following prequalification, the adequacy of safety concerns, PV activities, risk minimization measures and traceability of the product at a national level, will be evaluated. Roche will implement sufficient pharmacovigilance, risk minimization measures, and product traceability following product prequalification even if differences, compared to SRAs, in health care settings and/or infrastructure, are found at a national level.

2. SUMMARY OF THE METHODOLOGICAL CONCEPTS THAT WILL BE EMPLOYED AT A NATIONAL LEVEL FOR COUNTRY SPECIFIC RMPS

2.1. SAFETY CONCERNS

Based on assessment of data collected for more than 15 years since first market authorization in Japan for Castleman's disease, and with an overall post-marketing exposure of over 3 million patients (until 10 October 2021; data lock point of the most recent TCZ PBRER), the safety profile of TCZ IV is well characterized and a favorable benefit-risk profile is well established in the approved indications.

Furthermore, the overall safety profile observed in COVID-19 patients treated with TCZ was consistent and comparable with that observed in placebo-treated patients, both in the overall pooled Safety-Evaluable Population from the Roche-sponsored Phase III COVID-19 studies, and in the subgroup receiving systemic corticosteroids at baseline. No new safety signals with the use of TCZ in patients with COVID-19 were identified in any of the studies or in the Roche Global Safety Database for TCZ. Roche continues to monitor both the Roche Global Safety Database and the published literature closely for any new reports.

Before a product enters into a new market in a country, on the basis of either the Core RMP or the EU RMP (depending on the country specific requirements), the Local Safety Responsible at the Roche Affiliate for the new market country, is responsible for the preparation and implementation of a local RMP. This could be performed, as applicable, in collaboration with other Affiliate functions (e.g. Medical; Local Drug Regulatory Affairs) in order to get a full understanding of the local settings. Based on this, it will be determined whether the information included in the core or EU RMP (e.g. description of safety concerns; PV activities) is applicable to the local market, and whether there are any potential different or new safety concerns for the country in scope. This step includes the assessment of several specific country factors that are variable across countries that could include the current practices where the product is intended for use, such as local healthcare settings, local medical practice and infrastructures, epidemiology, local label. Ultimately, this could result in a local adaptation of the RMP (e.g. including revision and/or description of local specific safety concerns) depending on specific national needs, feasibility and local regulations.

In case there is no Roche Affiliate in a certain country, the tasks/steps described above are conducted by a designated representative in the respective country or by a Roche affiliate in another country with in-depth knowledge of the country of intended new launch.

Roche global PV system includes Signal Detection and Management processes which identify, assess and address any potential safety issue in a timely and effective manner to ensure that Roche products' risk profiles are continuously monitored. Signal detection activities are performed at local levels by Local Safety Responsibles based on safety data collected at local level (e.g., ICSR), as well as by the global drug safety staff in the context of the globally collected data. For each product, a Signal Detection Plan is in place which outlines the Events to Monitor, Adverse Events of Special Interest, standard routine signal detection activities, and product specific signal detection activities. The outcome of the PV activities performed globally and locally could lead to a re-evaluation of the adequacy of the safety information described in the local RMP, a potential further revision and local adaptation (which is primarily managed at local level by the Local Safety Responsibles). In addition, the safety profile of medicines approved in individual countries is also monitored by national Health Authorities, which can request the local affiliates to modify the local RMP and the PV measures in place to address any new identified safety concerns or situations.

2.2. PHARMACOVIGILANCE ACTIVITIES

Roche's global PV system employs a robust and comprehensive process to ensure signal detection, validation, prioritization, and assessment. The process ensures appropriate escalation to the company governance body, in addition to the prompt communication of safety concerns to regulatory authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), investigators, treating physicians, and the public throughout the product lifecycle.

Roche proactively identifies and evaluates potential safety issues from reported adverse events (AEs) and other available safety data and assesses the potential impact of these data on the risk profile of Roche medicinal products. Established routine pharmacovigilance and signal generation activities are used to capture and review safety information, including cases entered onto the Roche Global Safety Database and information retrieved from other sources, including from regulatory authorities.

Signal generation strategies are employed to systematically review safety data, including: Customized Periodic Listings; Standardized periodic case review; Systematic, regular literature searches of internationally recognized biomedical databases; Signal Detection, Assessment and Management Using Disproportionality Analysis; Trending analysis for potential product defects.

Safety data (e.g. AE reports) collected at a national level from the use of TCZ will also be integrated in the global PV system described above to monitor its safe use and to

ensure a positive benefit-risk profile based on local practices or specificities of the areas where the product is intended for use. This is achieved via Affiliates' drug safety units in local territories that ensure that safety data relating to the use of Roche drugs are systematically collected to high standards of medical quality, enabling the evaluation of causal relationship, identification of changes of frequency, or a modification of the treated population, as well as managed in accordance with medical ethics, current local regulations and industry requirements. This also includes assessment of any additional PV activities required to address local specificities that may change the benefit/risk profile defined within local settings. Local specificities considered could include epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social, economic and other.

Roche confirms that, the company Affiliate or company representative will establish contact with the appropriate PV contact/function within the national PV centre (e.g. Ministry of Health) or National Regulatory Authority. In countries where a local PV point is not present, Roche Affiliate or representative responsible for that particular country will confirm who the appropriate contact is to establish contact for PV questions between the company and the National Regulatory Authority or other National Health Agency/Organization.

Overall, TCZ is expected to be used for the COVID-19 indication in hospital settings with certain standards (such as being able to appropriately assess dosing, administration and manage any adverse events), which are expected to follow PV standards.

Additional PV and risk minimization activities, once approved by the European Medicines Agency (EMA) or other national competent authority, are considered PV commitments. The overview of adherence to Risk Management Plan (RMP) commitments is monitored by two components as outlined below.

The RMP Implementation Coordinator monitors the local implementation of additional PV and/or risk minimization activities for their assigned countries (or territories) and tracks these in the relevant specific company system. This provides oversight of adherence to Roche defined submission timelines for additional risk minimization activities. This data is integrated with the product approval and marketing status and a compliance assessment is performed and documented, providing the basis for compliance metrics generated on a monthly timeframe.

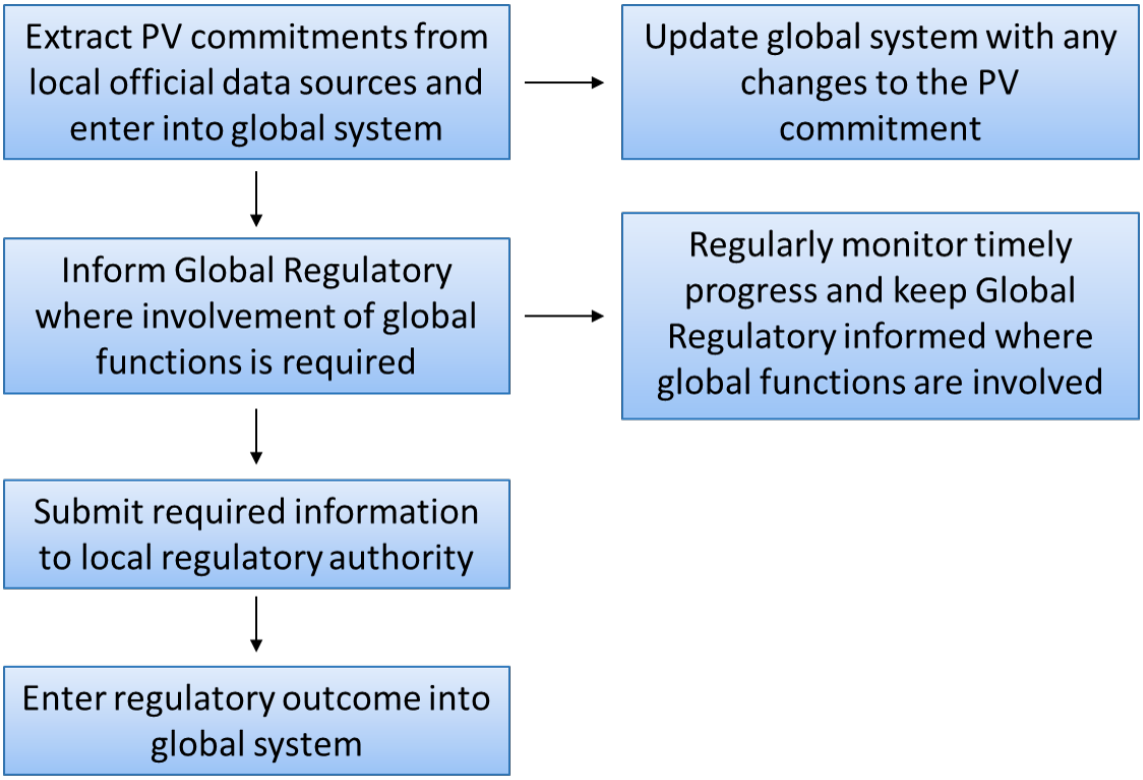
All PV commitments are tracked using the relevant system which provides oversight of adherence to Regulatory Authority agreed submission timelines. The process for tracking PV commitments for Nationally Approved Products (NAPs) in EEA countries and all non-EU country specific requirements is shown in Figure 1.

Depending on requirements, which differ from country to country, Roche Affiliates establish contacts with National Regulatory Authorities, and the RMPs are submitted to

the National Regulatory Authorities responsible for their assessment and approval as applicable. In countries without a National Regulatory Authority, the local Affiliates determine the local adaptation and implementation of the core or EU RMP based on local needs, following the assessment described in Section 2.1. In some situations, a "reference" National Regulatory Authority (e.g. of a neighbouring country), can assess and approve the RMP for a country where no National Regulatory Authority is present.

A Periodic Safety Update Report (PSUR) including an evaluation of all safety data collected globally during the reporting period is prepared annually (for TCZ the data-lock point is 10 April). PSURs are submitted in the EU on a three yearly basis in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal (next EU PSUR is planned for the reporting interval 11 April 2019 to 10 April 2022). PSURs will be submitted in accordance with the national requirements.

Figure 1 Tracking PV Commitments for Nationally Approved Products within the EEA Countries and All Non-EU Country Specific Commitments



Note: The actions described in Figure 1 are all fulfilled by the appropriate local regulatory manager who has responsibility for the product in question.

2.3. RISK MINIMIZATION MEASURES

The EU RMP for TCZ describes routine and additional risk minimization activities as well as additional pharmacovigilance activities (e.g. post-authorization safety studies). There are no additional risk minimization measures for the COVID-19 indication in the EU RMP v27.1. A description of the safety concerns, along with associated risk minimization activities and pharmacovigilance activities relevant to the use of TCZ IV in the COVID-19 indication, are provided below.

Table 3 Risk Minimization Measures for use of TCZ IV in COVID-19 indication

Safety concern	Risk minimization measures	Pharmacovigilance activities	Applicability in LMICS
Neutropenia	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations **Patient Information Leaflet** Section 2 What you need to know before you are given RoActemra Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** *In COVID-19 patients, neutrophil counts should be monitored according to current standard clinical practices.* **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions, i.e. for events of special interest will collect neutrophil data in cases of serious infection **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of neutropenia. Guided questionnaire for adverse events of special interest also collect neutrophil data in cases of serious infection. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and managing neutropenia. Optimal diagnosis and management of neutropenia also depends on the availability of adequate laboratory testing facilities.

Safety concern	Risk minimization measures	Pharmacovigilance activities	Applicability in LMICS
Hepatotoxicity	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration (IV formulation) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 What you need to know before you are given RoActemra Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** *In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices.* **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of hepatotoxicity. *Applicability in LMICs* • Hepatotoxicity may also occur independently as a complication of COVID-19. • Physicians working in hospitalized settings have experience in recognizing and managing hepatotoxicity. Optimal diagnosis and management of hepatotoxicity also depends on the availability of adequate laboratory testing facilities.

Safety concern	Risk minimization measures	Pharmacovigilance activities	Applicability in LMICS
Serious infections*	**Routine risk communication:** **SmPC** Section 4.3 Contraindications *- Active, severe infections with the exception of COVID-19 (see Section 4.4)* Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet:** Section 2. What you need to know before you are given RoActemra Section 4 Possible serious 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. No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of Infections. Guided questionnaire for adverse events of special interest also collect neutrophil data in cases of serious infection. *Applicability in LMICs* • While clinical trial data do not suggest increased rates of serious infections in patients receiving 1 or 2 doses of ACTEMRA as COVID-19 treatment, the number of patients enrolled from LMICs in Roche sponsored clinical trials was limited (6 patients treated with TCZ in Study ML42528 [EMPACTA]). • Serious infections may also occur independently as complications of COVID-19. • Physicians working in hospitalized settings have experience in recognizing and treating the most common secondary infections in a patient's geographical region, including those in immunocompromised patients. • Diagnosis and treatment of secondary infections would be based on standard of care established in the HCPs region.

Safety concern	Risk minimization measures	Pharmacovigilance activities	Applicability in LMICS
			• Chronic infections have a higher prevalence in LMICs than in wealthy countries. Hence, the chance of a patient experiencing manifestation of a chronic infection may be greater in LMICs, but also the level of knowledge and experience among HCPs recognizing and managing the condition. • Screening and management of chronic infection should be available in LMICs given its high prevalence, as well as availability of agents for treatment of these infections.
Complications of Diverticulitis*	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet:** Section 2 What you need to know before you are given RoActemra Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of complications of diverticulitis. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and treating diverticulitis. • Diagnosis and treatment of diverticulitis also depends on the availability of adequate laboratory and imaging services as well as suitable antibiotics, IV fluids, pain medications, and the availability of surgical support.

Safety concern	Risk minimization measures	Pharmacovigilance activities	Applicability in LMICS
	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 for COVID-19 indication		
Thrombocytopenia and the potential risk of bleeding	**Routine risk communication:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** *In COVID-19 patients, platelet counts should be monitored according to current standard clinical practices.* **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of thrombocytopenia and the potential risk of bleeding. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and managing thrombocytopenia. • Optimal diagnosis and management of thrombocytopenia also depends on the availability of adequate laboratory testing facilities.

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**	**Applicability in LMICS**
Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	**Routine risk communication:** **<u>SmPC</u>** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **<u>Patient Information Leaflet</u>** Section 2 What you need to know before you are given RoActemra 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 No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of elevated lipid levels and potential risk of cardiovascular/cerebrovascular events. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and managing elevated lipids and potential cardiovascular and cerebrovascular events. • Optimal diagnosis and management of elevated lipids and potential cardiovascular and cerebrovascular events also depends on the availability of adequate diagnostic services.

Malignancies	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use 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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of malignancies. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and managing malignancies. • Optimal diagnosis and management of malignancies depends on the availability of diagnostic and pathology services.
Demyelinating Disorders	**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 No Additional Risk Minimization Measure for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** No Additional PV activities for COVID-19 indication	Product information provides clear instructions on prevention, recognition and management of demyelinating disorders *Applicability in LMICs* Physicians working in hospitalized settings have experience in recognizing and managing demyelinating disorders.

Immunogenicity	**Routine risk communication:** **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 for COVID-19 indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collect and analyze anti-TCZ antibodies in patients who experience hypersensitivity reactions that led to study withdrawal in ongoing clinical trials and investigate the risk of developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted. This is specific to the ongoing clinical trials and does not apply to spontaneous post-marketing cases **Additional pharmacovigilance activities:** None	Product information provides clear instructions on prevention, recognition and management of immunogenicity. *Applicability in LMICs* • Physicians working in hospitalized settings have experience in recognizing and managing effects resulting from immunogenicity. • Optimal diagnosis and management of immunogenicity depends on the availability of appropriate laboratory services.

IV=intravenous; SC=subcutaneous; LMICs=lower middle income countries; sJIA = systemic juvenile idiopathic arthritis; SmPC=Summary of Product Characteristics; TCZ=tocilizumab.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

TCZ IV is expected to be used in hospitalized settings with certain standards (such as being able to appropriately assess dosing, administration and manage any adverse events). In general, physicians with the necessary expertise to treat patients with severe COVID-19 should also have appropriate expertise to manage the key risks associated with TCZ treatment. Furthermore, hospitals with the diagnostic and treatment resources needed to diagnose and manage patients with severe COVID-19 in lower middle income countries (LMICs) should also have the basic diagnostic and treatment resources that are needed to manage the key risks associated with TCZ therapy.

Core or EU RMPs are generally adopted at local level as the main reference for risk minimization activities, which can be further adapted depending on several variables across countries (and approved by local regulatory authorities if applicable) as well as revised to add additional risk minimization activity, if required.

Before a new market entry, the Local Safety Responsibles and/or RMP Implementation Coordinators at Affiliates assess the adequacy of the safety concerns, PV activities and risk minimization activities described in the core or EU RMP, approved by SRAs, and whether a revision is required depending on local settings in order to address potential specific national needs (see also Section 2.1). This evaluation for local adaptation, can be performed with the involvement from different functions, as applicable, at Affiliates (e.g. Medical; Local Drug Regulatory Affairs) to get a comprehensive understanding of the country settings.

For this purpose, several key elements of the country settings are taken into account such as the local medical practice, including how familiar the healthcare professionals are with the product, local regulations, local technical language, target audience in the country, local healthcare system and infrastructure including the local healthcare delivery system of the product, and local label.

From the perspective of ensuring the risk minimization activities fit the local healthcare system and adherence to treatment behavior guideline, the RMP Implementation Coordinator verifies the adherence to the local requirements, and a Compliance officer ensures the adherence to additional monitoring requirements and non-promotional content. If needed, each risk minimization activity is then expected to be adapted to local needs to ensure it is tailored for the local market. This could include for instance addition to the local label of specific guidance for the HCPs or specific requirements to be in place as routine or additional risk minimization activities.

TCZ product information (e.g., Summary of Product Characteristics/package leaflet) provides healthcare professionals (HCPs) and patients with the essential information on how TCZ should be used and the relevant safety information. The product label is available on public websites such as EMA and FDA websites, and could also be available on local authority websites.

The TCZ label also includes instructions for it to be used under close supervision by an experienced HCP. Local company representatives in contact with local HCPs ensure this is appropriately communicated. If deemed necessary, additional locally developed documents,

e.g. checklists, can be used to inform and train HCPs about the correct use of TCZ and the risk minimization requirements.

Additional information, e.g. on the safe use of TCZ is also provided on the Roche website, accessible in all countries. When required, non-promotional product education material can be provided by Roche local staff on field to ensure HCPs are adequately informed and trained about the product. In addition, HCPs have the opportunity to directly contact responsible local affiliate for their country for inquiries.

Information on how Roche monitors whether the risk minimization activities are being implemented has been included within Section 2. The effectiveness of routine risk minimization activities at local level is generally monitored by the frequency (spontaneous reporting rates) and/or severity of an adverse reaction at local level in relation to patients' exposure via signal detection activities, which provides an overall measure of the level of risk control that has been achieved with any risk minimization activity in place.

For additional PV and/or risk minimization activities, effectiveness measures are also typically monitored by "Process indicators", i.e. measures of the extent of implementation (e.g. distribution records of risk minimization material), which are tracked and recorded by local affiliates via specific Roche internal systems. The actual success rate is calculated based on the success assessment criteria customized by each affiliate and determined in advance for the methods of distribution. In case the actual success rate is lower than the predefined target success rate, appropriate actions are taken as defined in the local implementation strategy or could be discussed directly with the local HA if applicable. In rare instances, a local HA can request a study to be conducted locally to assess the effectiveness of risk minimization activities. .

2.4. PRODUCT TRACEABILITY

Roche ensures traceability using an electronic system which covers the entire Roche supply chain for our finished products up to delivery to the first tier customers (i.e. first party outside of Roche). Traceability beyond this point is under the responsibility of the customer. This responsibility is emphasized under the Roche Quality Exhibit, which is an integral part of the purchasing agreement with the customer. Roche applies the same standardized procedure to all external customer deliveries globally and acknowledges the varying levels of infrastructure among them. In order to manage this we are supporting our first tier customers globally, e.g. with

- additional written guidance, for instance in performing Mock Recalls
- Roche-organized face to face trainings targeted to our customers as well as part of industry peer group initiatives (e.g. Rx360 educational stream)
- an established, focused global supply chain and affiliate quality organization. This includes sub-regional quality managers within the regions, who work closely with the local customers, e.g. by cutting out language barriers and being available for face to face interactions

Further, Roche is driving initiatives to simplify the distribution chain in order to reach the patient faster by reducing the number of intermediaries.

For AE reports, if either the name or batch number is missing from the initial reports, follow-up requests are initiated to request this information from the reporter. These follow-up attempts are documented, and if the reporter is unwilling or unable to provide the missing information, this is also documented within the case.

In addition, to ensure recording by the healthcare professionals of the name and batch number, the TCZ product information/label includes a warning that the name and batch number of the administered product should be clearly recorded in order to improve traceability of biological medicinal products.