CIMZIA®

SUMMARY OF RISK MANAGEMENT PLAN

Version 1.0

Active substance(s) (INN or common name):	CERTOLIZUMAB PEGOL
Product(s) concerned (brand name(s)):	Cimzia®
Marketing authorization holder:	UCB Pharma-AG
Version number :	1.0 (summary of EU RMP v19.1, dated 27-May-2021)
Date of final sign off :	31-Jan-2023

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.
The RMP summary of Cimzia® is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Cimzia® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. UCB-Pharma-AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Cimzia®.

Date: 31 January 2023 20230131rmp summary-v1.0-pxl-ch

Contents

PART I: THE MEDICINE AND WHAT IT IS USED FOR

Active substance(s)	Certolizumab pegol (CZP)
Pharmacotherapeutic group(s)	Tumor necrosis factor alpha (TNFα) inhibitor (L04AB05)
Brief description of the product	Biologic (monoclonal antibody)
	Specificity for human TNFα
	Certolizumab pegol is a recombinant, humanized antibody Fab′ fragment against TNFα expressed in *Escherichia coli* and conjugated to polyethylene glycol
Pharmaceutical form(s) and strength(s)	Current: Solution for injection 200mg in prefilled syringe (content 1mL) of CZP Solution for injection 200mg in prefilled pen (content 1mL) [also called AutoClicks, auto injector] of CZP Solution for injection 200mg in dose-dispenser cartridge (content 1mL) of CZP
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	No
Is/will the product be subject to additional monitoring in Switzerland ?	No

This is a summary of the RMP for Cimzia® (CZP). The RMP details important risks of Cimzia, how these risks can be minimized, and how more information will be obtained about Cimzia's risks and uncertainties (missing information).
The Summary of Product Characteristics (SmPC) and package leaflet of Cimzia give essential information to HCPs and patients on how Cimzia should be used.
This summary of the RMP for Cimzia 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 data will be included in updates of the Cimzia RMP.

Cimzia is authorized for RA; axSpA including AS and axSpA without radiographic evidence of ankylosing spondylitis, PsA, and plaque PSO (see SmPC for the full indication). It contains CZP

as the active substance and it is given by solution for injection 200mg in prefilled syringe, solution for injection 200mg in prefilled pen, and solution for injection 200mg in dose-dispenser cartridge.
Further information about the evaluation of Cimzia's benefits can be found in Cimzia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Cimzia | European Medicines Agency (europa.eu)

PART II: RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

Important risks of Cimzia, together with measures to minimize such risks and the proposed studies for learning more about Cimzia's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be as follows:

- 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 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 Cimzia, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate actions can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

1.1 List of important risks and missing information

Important risks of Cimzia 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 Cimzia. 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 Error! No text of specified style in document.**–1:List of important risks and missing information**

Important identified risks	Serious infections and opportunistic infections, including tuberculosis, and hepatitis B virus reactivation Moderate-to-severe congestive heart failure (New York Heart Association class III/IV) Hypersensitivity reactions Malignancies including lymphoma, leukemia, Merkel cell carcinoma, hepatosplenic T-cell lymphoma, and melanoma Demyelinating-like disorders
Important potential risks	None
Missing information	Pregnancy Live vaccines

1.2 Summary of important risks

Table Error! No text of specified style in document.**–2:Summary of important identified risks**

Important identified risks	
Serious infections and opportunistic infections, including tuberculosis, and hepatitis B virus reactivation	
Evidence for linking the risk to the medicine	It is well documented that tumor necrosis factor (TNF) antagonists increase the rate of serious infections (Curtis et al, 2007). Tumor necrosis factor is known to be essential for host defenses against *Mycobacterium tuberculosis*. Based on the class mechanism of action, the possibility exists that anti-TNF agents increase the risk of viral replication, including reactivation of the dormant state.
Risk factors and risk groups	Rheumatoid arthritis (RA): Factors associated with infection in RA patients include increasing age, extra-articular manifestations of RA, leukopenia, and comorbidities (chronic lung disease, alcoholism, organic brain disease, and diabetes mellitus) (Doran et al, 2002). In addition, several treatments have been associated with an increased risk of infection, including disease-modifying antirheumatic drugs, corticosteroids, and TNF inhibitors (Galloway et al, 2011; Smitten et al, 2008). A review of the association between tuberculosis infection in RA patients found that the use of TNF inhibitors was associated with a higher tuberculosis risk (Ai et al, 2015). Psoriatic arthritis (PsA): An increased risk of infection was associated with biologic use and female patients in an observational cohort study among patients with PsA versus patients with psoriasis (PSO) without arthritis

Table Error! No text of specified style in document.**–2:Summary of important identified risks**

Important identified risks	
	(Haddad et al, 2016), while analysis of randomized controlled trials found no increased risk associated with TNF antagonists (Dommasch et al, 2011). Axial spondyloarthritis (axSpA): Biologic use was not identified as a significant risk factor for serious infections in analysis of randomized controlled trials (Fouque-Aubert et al, 2010) and a longitudinal observational cohort study (Wallis et al, 2015), while disease-modifying antirheumatic drug use has been associated with an increased risk of infection (Wallis et al, 2015). PSO: Increasing age, diabetes mellitus, smoking, and significant infection history were each associated with an increased risk of serious infections (Kalb et al, 2015). Individuals with a history of excessive alcohol use are at risk of hepatobiliary conditions. No additional risk groups or risk factors have been identified besides the classical risk groups for hepatitis A virus, hepatitis B virus, and hepatitis C virus transmission and the concomitant use with disease-modifying antirheumatic drugs other than methotrexate.
Risk minimization measures	**Routine risk minimization measures:** Summary of Product Characteristics (SmPC) Section 4.2 (Posology) SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) SmPC Section 4.6 (Fertility, Pregnancy and Lactation) SmPC Section 4.8 (Undesirable Effects) Package leaflet (PL) Section 2 (What You Need to Know Before You Use Cimzia) PL Section 4 (Possible Side Effects) Available by prescription only **Additional risk minimization measures:** Educational program (Patient Reminder Card)
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections:** Targeted follow-up with reporters with tuberculosis questionnaire **Additional pharmacovigilance activities:** **None**
Moderate-to-severe congestive heart failure (New York Heart Association class III/IV)	
Evidence for linking the risk to the medicine	Tumor necrosis factor has been implicated in multiple deleterious effects on the myocardium, including left ventricular dysfunction and remodeling, and increased cardiac myocyte apoptosis.
Risk factors and risk groups	Traditional cardiovascular disease risk factors are hypertension, dyslipidemia, smoking, obesity, and physical inactivity.

Table Error! No text of specified style in document.**–2:Summary of important identified risks**

Important identified risks	
	RA: A recent study found that oral glucocorticoids were associated with a dose-related gradient of heart failure risk, with an elevated risk among patients exposed to ≥5mg vs. no exposure (Solomon et al, 2013). PsA: Severity of disease has been demonstrated to be a risk factor for cardiovascular disease among PsA patients (Gladman et al, 2009). PSO: The prevalence of cardiovascular risk factors among PSO patients and controls was studied in the Clinical Practice Research Datalink database (Parisi et al, 2015). Psoriasis patients had a greater prevalence of cardiovascular disease risk factors including inflammatory arthritis, chronic kidney disease, hypertension, hyperlipidemia, depression, smoking, body mass index, and Index of Multiple Deprivation score relative to controls (Parisi et al, 2015). In addition, several studies have reported a greater risk of congestive heart failure among patients with severe PSO (Khalid et al, 2014; Yang et al, 2011).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) for congestive heart failure SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Cimzia) PL Section 4 (Possible side effects) Available by prescription only **Additional risk minimization measures:** Educational program (Patient Reminder Card)
Additional pharmacovigilance activities	None
Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Hypersensitivity to active substance or to any of the excipients is noted to be contraindicated in the SmPC.
Risk factors and risk groups	Risk groups include patients who have hypersensitivity to the active substance or to any of the excipients.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Cimzia) PL Section 4 (Possible side effects) Available by prescription only

Table Error! No text of specified style in document.**–2:Summary of important identified risks**

Important identified risks	
	Additional risk minimization measures: Educational program (Patient Reminder Card)
Additional pharmacovigilance activities	None
Malignancies including lymphoma, leukemia, Merkel cell carcinoma, hepatosplenic T-cell lymphoma, and melanoma	
Evidence for linking the risk to the medicine	Given the immunosuppressive effects, TNF inhibitors have been thought to be associated with an increased risk for some malignancies (eg, melanoma).
Risk factors and risk groups	RA: Among RA patients, biologic therapy has been associated with an increased incidence of skin cancers but not of solid tumor cancers or lymphoproliferative cancers (Mercer, 2017; Wolfe and Michaud, 2007). Haynes et al (2013) found that TNF-inhibitor treatment was not associated with a higher short-term incidence of malignancy, including lymphoma, relative to other commonly used treatment regimens for patients with RA. A recent analysis from the UK found that the addition of a TNF inhibitor to nonbiologic disease-modifying antirheumatic drug treatment for RA did not alter the risk of solid cancers (Mercer et al, 2015). The data from the RA certolizumab pegol development program did not identify specific subgroups that would be more at risk to develop cancer. axSpA: Merkel cell carcinoma is viewed as a class effect common to all TNF blockers given their immunosuppressive effect. The risk groups include elderly whites (Agelli et al, 2010). It presents most often in sun-exposed areas of the skin. PSO: Phototherapy is associated with an increased risk of skin carcinoma (Archier et al, 2012). Geography may also play a role in the risk of cutaneous cancers (Takeshita et al, 2017; Pouplard et al, 2013). Two retrospective cohort studies examined severity of disease and/or treatment in relation to cancer incidence and found a trend in the incidence of all cancers, lymphoma, melanoma, and nonmelanoma skin cancer associated with disease severity defined by treatment (Kimball et al, 2015; Lee et al, 2012).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 (Special Warnings and Precautions for Use) SmPC Section 4.8 (Undesirable Effects) PL Section 2 (What You Need to Know Before You Use Cimzia) PL Section 4 (Possible Side Effects) Available by prescription only **Additional risk minimization measures:** Educational program (Patient Reminder Card)

Table Error! No text of specified style in document.**–2:Summary of important identified risks**

Important identified risks	
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections:** Targeted follow-up with reporters with malignancy questionnaire **Additional pharmacovigilance activities:** None
Demyelinating-like disorders	
Evidence for linking the risk to the medicine	A signal evaluation for demyelinating disorders concluded that the characterization of this risk, as defined by increased frequency of reporting, subpopulation of special interest, and aggravated severity for demyelinating disorders remained unchanged. The risk "Demyelinating-like disorders" has been associated with the anti-TNF class.
Risk factors and risk groups	Not applicable.
Risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Cimzia) PL Section 4 (Possible side effects) Available by prescription only
Additional pharmacovigilance activities	None

axSpA=axial spondyloarthritis; PL=package leaflet; PsA=psoriatic arthritis; PSO=psoriasis; RA=rheumatoid arthritis; SmPC=summary of product characteristics; TNF=tumor necrosis factor

Table Error! No text of specified style in document.**–3:Summary of important potential risks**

Important potential risks
None

Table Error! No text of specified style in document.**–4:Summary of missing information**

Missing information	
Pregnancy	
Risk minimization measures	Summary of Product Characteristics (SmPC) Section 4.6 (Fertility, Pregnancy, and Lactation) Package leaflet (PL) Section 2 (What You Need to Know Before You Use Cimzia) Available by prescription only
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detections:** Targeted follow-up with reporters with pregnancy questionnaire **Additional pharmacovigilance activities:** Participation in a United States and Canada-based pregnancy registry, RA0023, conducted by the Organization of Teratology Information Specialists Research Group which includes a 5-year follow-up of infants
Live vaccines	
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4 (Special Warnings and Precautions for Use) SmPC Section 4.6 (Fertility, Pregnancy and Lactation) PL Section 2 (What You Need to Know Before You Use Cimzia) Available by prescription only **Additional risk minimization measures:** Educational program (Patient Reminder Card)
Additional pharmacovigilance activities	None

PL=package leaflet; SmPC=summary of product characteristics

1.3 Postauthorization development plan

1.3.1 Studies that are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Cimzia.

1.3.2 Other studies in post-authorization development plan

RA0023 (OTIS Autoimmune Disease in Pregnancy Project)

Study short name and title:

Cimzia Pregnancy Exposure Registry

Purpose of the study:

The purpose of the Cimzia Pregnancy Exposure Registry is to monitor planned and unplanned pregnancies exposed to Cimzia and to evaluate the possible teratogenic effect of this medication in the pregnancy outcome.