Swiss Summary of the Risk Management Plan (RMP)

Remicade®

(Infliximab)

Active substance(s): Infliximab

Product(s) concerned: REMICADE®

Based on EU-RMP V21.1 (December 2023)

Version 2.0 (April 2024)

Marketing Authorisation Holder: MSD Merck Sharp & Dohme AG, Lucerne

Disclaimer:

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 Remicade® 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 Remicade® in Switzerland is the «Arzneimittelinformation/ Information sur le médicament» (see www.swissmedic.ch) approved and authorized by Swissmedic. MSD Merck Sharp and Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Remicade®.

Summary of Risk Management Plan for REMICADE® (Infliximab)

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

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

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

I. The Medicine and What it is Used For

REMICADE is authorized for the treatment of rheumatoid arthritis, Crohn's disease (adult and pediatric), ulcerative colitis (adult and pediatric), ankylosing spondylitis, psoriatic arthritis, and psoriasis (see SmPC for the full indication). It contains infliximab as the active substance, and it is given by the intravenous route of administration.

Further information about the evaluation of REMICADE's benefits can be found in REMICADE's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

Measures to minimize the risks identified for medicinal products can include:

- Specific information, such as warnings, precautions, and advice on correct use included in the PL addressed to patients and the SmPC addressed to healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - ie, the amount of medicine included in a single pack which is chosen to ensure that the medicine is used correctly;
- The medicine's legal status - ie, the way a medicine is supplied to the patient (eg, with or without a prescription).

Together, these measures constitute routine risk minimization measures.

In the case of REMICADE, these measures are supplemented with the additional risk minimization measures mentioned under relevant important risks (see section II.B, below).

In addition to risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including in Periodic Safety Update Reports (PSURs) 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 REMICADE 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 REMICADE. 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).

List of Important Risks and Missing Information	
Important identified risks	Serious infection/sepsis Bacille Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE Demyelinating disorders Malignancy
Important potential risks	Colon carcinoma/dysplasia (in pediatric ulcerative colitis)
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Serious Infection/Sepsis	
Evidence for linking the risk to the medicine	REMICADE acts by inhibiting the activity of TNFα and reduces the immune response and inflammation in the body. Patients may therefore get infections more easily when receiving treatment with REMICADE. These infections may be serious and may, in rare cases, be life threatening. Serious infections/sepsis, including opportunistic infections, TB, and hepatitis B reactivation, have been reported in patients treated with REMICADE in clinical trials and in the postmarketing setting. These findings are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF. Serious infection/sepsis is considered an important identified risk because the impact of this risk on the individual patient can be potentially significant and the risk needs to be carefully weighed against the benefit conferred by the use of the medicine. REMICADE is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and opportunistic infections (section 4.3 of the SmPC).
Risk factors and risk groups	**Serious Infection/Sepsis** Because REMICADE suppresses the activity of TNFα, which mediates inflammation and regulates immune responses, patients treated with REMICADE are more susceptible to serious infections. Elderly patients In clinical trials, the incidence of serious infection in REMICADE-treated patients 65 years of age and older was greater than that seen in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general. Children In clinical trials, more children who received REMICADE developed infections than adults who received REMICADE. **Opportunistic Infections** The risk of developing opportunistic infections increases dramatically with progressive impairment of the immune system. Patients with chronic infection or a history of recurrent infection, including those who use other immunosuppressive medications, such as methotrexate, are at a greater risk of developing an opportunistic infection during REMICADE therapy.

Important Identified Risk: Serious Infection/Sepsis	
	Patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, and blastomycosis are widespread, are also at increased risk of developing an opportunistic infection during REMICADE therapy. **Tuberculosis** The most common risk factors for the development of TB include conditions that weaken the immune system, such as advanced age, human immunodeficiency virus (HIV) infection, alcohol abuse, malignancy, use of corticosteroids or other immunosuppressive therapy, connective tissue disease, renal failure, diabetes, and pregnancy. Other risk factors for the development of TB include contact with a person(s) with active TB infection and having been born in, or lived in, or traveled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (eg, hospitals and nursing homes) or high-density institutions (eg, prisons). **Hepatitis B Reactivation** Approximately 14% to 50% of immunosuppressed patients who are chronic carriers of HBV will experience acute reactivations during the natural history of their disease. Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (eg, chemotherapy, corticosteroids, methotrexate, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.3 (Contraindications) • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card

Important Identified Risk: Serious Infection/Sepsis	
	• DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Bacille Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE	
Evidence for linking the risk to the medicine	REMICADE crosses the placenta. REMICADE acts by inhibiting the activity of TNFα and reduces the immune response. If REMICADE is given during pregnancy, it may cause some rare side-effects in the baby for up to 12 months after birth such as specific types of infection after the baby receives a live vaccine or has low white blood cell count. Cases of BCG breakthrough infection and agranulocytosis have been reported in postmarketing reports in babies whose mothers used REMICADE while pregnant. These findings are consistent with published medical literature. BCG breakthrough infection and agranulocytosis in infants with in utero exposure to REMICADE is considered an important identified risk because the impact of this risk on an infant exposed to REMICADE in utero is significant.
Risk factors and risk groups	Infants exposed to REMICADE in utero and who receive BCG vaccine within 12 months after birth are at risk for developing disseminated BCG infection. Infants exposed in utero to REMICADE are also at increased risk of developing agranulocytosis.
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) • SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • SmPC section 4.6 (Fertility, pregnancy and lactation) • SmPC section 4.8 (Undesirable effects) • PL section 2 • PL section 4 Additional risk minimization measures: • Patient reminder card (BCG only)

	• DHPC (BCG only)

Important Identified Risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis, and Guillain-Barré syndrome are rare side effects of REMICADE. In clinical trials, demyelinating disorders have been reported in patients treated with REMICADE. Reports have been noted in the postmarketing setting and are consistent with published medical literature and experience with other medicines that also act by inhibiting TNF. Demyelinating disorders are considered an important identified risk because of the consistency of evidence across multiple sources, including data from other products in the same class.
Risk factors and risk groups	Multiple Sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk to develop MS than the general population. Whites, particularly of northern European descent, are also more likely to develop MS. Several studies have suggested an association between smoking and MS. Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS.
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 • PL section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Malignancy	
Evidence for linking the risk to the medicine	TNF blockers, including REMICADE, decrease the activity of the immune system. This may increase the risk of cancer. Certain cancers have been seen more commonly in TNFα treated patients than expected. Although this has not been seen with all cancer types, it is possible that REMICADE may have some effect on other cancers. Malignancies, including the subtypes of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukemia, melanoma, Merkel cell carcinoma, cervical cancer, Kaposi's sarcoma, and pediatric malignancy, have been reported in clinical trials with REMICADE, the postmarketing setting, published medical literature, or epidemiological studies. Some children and teenage patients who have received TNF blockers such as REMICADE have developed cancers, including unusual types such as HSTCL, which sometimes resulted in death. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine, or 6-mercaptopurine.
Risk factors and risk groups	Because disease severity, cumulative disease activity, and disease duration may also contribute to an increased risk of malignancy in patients with immune-mediated diseases, it is difficult to distinguish the individual contribution of immunosuppressive medications, including those like REMICADE that inhibit TNFα, from other risk factors for the development of malignancy. This is further complicated by the fact that patients with severe disease are more likely to have been treated with one or more immunosuppressive medications. A risk for the development of malignancies other than the types noted specifically above in patients treated with TNF blockers cannot be excluded.
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 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	Colorectal cancer is known to occur at a higher rate in patients with chronic ulcerative colitis than in the general population. Tumor necrosis factor blocking agents, including REMICADE, decrease the activity of the immune system and as a result, there may be an increased risk of intestinal cancer if abnormal growth in the intestine develops in patients with ulcerative colitis who are treated with REMICADE. Therefore, colon carcinoma/dysplasia (in pediatric ulcerative colitis) is considered an important potential risk that needs to be carefully weighed against the benefit conferred by use of the medication.
Risk factors and risk groups	Patients with long-standing ulcerative colitis or primary sclerosing cholangitis, or who had a prior history of dysplasia or colon carcinoma are at a higher risk for developing colon cancer or dysplasia. Other risk factors for development of colorectal dysplasia and cancer in patients with ulcerative colitis include extent of disease, family history of colorectal cancer, young age at diagnosis, and the presence of backwash ileitis (ileal inflammation in the context of ulcerative colitis).
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • DEVELOP registry (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization 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 REMICADE.

II.C.2. Other Studies in Postauthorization Development Plan

Study	Purpose of the Study
DEVELOP (consists of 3 protocols: C0168Z02, REMICADEPIB4002, and REMICADEPIB4003)	To obtain long-term safety and clinical status information on pediatric patients (under 17 years of age) with inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis, or indeterminate colitis) who were treated with REMICADE and/or other medical therapies for inflammatory bowel disease. Data from the 3 studies will be pooled, analyzed, and presented in the DEVELOP report. To address the safety concerns of: Serious infection/sepsis Demyelinating disorders Malignancy Colon carcinoma/dysplasia (in pediatric ulcerative colitis)