Risk Management Plan Summary

Humira® (Adalimumab)

Marketing Authorization Numbers:
56221 (pre-filled syringe)
57862 (pre-filled pen)

Solution for Injection in pre-filled syringe
(20 mg/0.2 ml, 40 mg/0.4 ml, 80 mg/0.8 ml)

Solution for Injection in pre-filled pen
(40 mg/0.4 ml, 80 mg/0.8 ml)

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Marketing Authorization Holder:
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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 minimize them.

The RMP summary of Humira® 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 Humira® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AbbVie AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Humira®.

Summary of the Risk Management Plan for Humira

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

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

This summary of the RMP for Humira 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 are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Humira RMP.

I The Medicine and What it Is Used For

Humira is authorised for use in adults for the treatment of:
Rheumatoid Arthritis (RA);
Psoriatic Arthritis (PsA);
Axial Spondyloarthritis (Axial SpA);
Crohn's Disease (CD);
Psoriasis (Ps);
Ulcerative Colitis (UC);
Hidradenitis Suppurativa (HS);
Uveitis.
Humira is authorised for use in paediatrics for the treatment of:
Polyarticular Juvenile Idiopathic Arthritis (pJIA);
Paediatric Enthesitis-related Arthritis (pedERA);
Paediatric Crohn's Disease (pedCD);
Paediatric Psoriasis (pedPs);
Adolescent Hidradenitis Suppurativa (HS);
Paediatric Uveitis (pedUV);
Paediatric Ulcerative Colitis (pedUC).

See SmPC for the full indication. It contains adalimumab as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of Humira's benefits can be found in Humira's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124.

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

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

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 so to ensure that the medicine is used correctly; and
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Humira, 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 analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Humira are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Humira. 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 infections; • Tuberculosis (TB); • Malignancies; • Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON]); and • BCG disease following live BCG vaccination in infants with in utero exposure to Humira

Important potential risks	• Progressive multifocal leukoencephalopathy (PML); • Reversible posterior leukoencephalopathy syndrome (RPLS); and • Adenocarcinoma of colon in ulcerative colitis (UC) patients.
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; • Episodic treatment in Ps, UC, and juvenile idiopathic arthritis (JIA); • Long-term safety information in the treatment of children with uveitis; and • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC.

II.B Summary of Important Risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the company postmarketing safety database.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population ≥ 65 years.

	Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Humira: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the company postmarketing safety database.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Humira: • Patient Reminder Card.

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Data from adalimumab trials. No reports of this specific form of lymphoma were received from any clinical trial, open-label (OL) or controlled. Information from Company postmarketing safety database.
Risk factors and risk groups	A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01 – 13.9) (Beaugerie 2009). Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks may or may not be applicable to HSTCL which is rare (Kotlyar 2011, Parakkal 2011). Risk factors for leukemia depend on the type of leukemia. In general, factors associated with an increased risk of leukemia include smoking, exposure to certain chemicals such as benzene, exposure to radiation, past treatment with chemotherapy or radiation therapy, having certain inherited or genetic disorders, having certain blood disorders, and having a family history of leukemia (National Cancer Institute 2014). Factors associated with an increased risk of skin cancer include radiation (e.g., sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants, thiopurines [Peyrin-Biroulet 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic (National Cancer Institute 2011b). Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis (National Cancer Institute 2011b). Factors associated with an increased risk of melanoma include UV radiation (e.g., sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants), medical

	conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles (National Cancer Institute 2011b). Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g., organ transplant, HIV), other cancers (e.g., squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure (Becker 2010a).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Warning regarding lymphoma, HSTCL, leukaemia, NMSC, melanoma, MCC, and malignancies in the adult and paediatric population. Section 4.8: Information on incidence rates from clinical trials in lymphoma, NMSC, and melanoma. Information on incidence rates from postmarketing surveillance in HSTCL, leukaemia, and MCC. The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of AZA or 6-MP, and that the potential risk combination of AZA or 6-MP and Humira should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Humira: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Demyelinating disorders (including MS, GBS, and ON)	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (e.g., HLA-DR2 [HLA-DRB1*15], ethnic origin [being white], female sex, Epstein-Barr infection, smoking, latitude/vitamin D,

	and early exposure to environmental risk factors) (Ramagopalan 2010). Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age (Sejvar 2011). Subjects with intermediate uveitis have a high prevalence of demyelination (Burkholder 2012, Zein 2004, Llorenc 2012, Messenger 2015).
Risk minimization measures	Routine risk minimization measures: Text in SmPC Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in postmarketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of demyelinating disordersassociated with the use of Humira. • Patient Reminder Card.
Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Humira	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
Risk factors and risk groups	No epidemiological data available.
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: Section 4.4 of the SmPC has section on vaccinations that includes recommendations to avoid administration of live vaccines to infants exposed to adalimumab in utero for 5 months following the mother's last adalimumab injection during pregnancy. Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of live vaccines associated with the use of Humira and the risk of live vaccines in infants exposed to Humira in utero:

	• Patient Reminder Card.
Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the company postmarketing safety database.
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. A descriptive analysis of PML cases identified through claims found approximately 40% of patients were aged 40 to 49 years and 75% were male (Eng 2006). Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS (Weber 2008). Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukaemia (Carson 2009). Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases (Eng 2006, Carson 2009, Calabrese 2007, Bartt 2006, Govindappa 2007).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Important potential risk: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the company postmarketing safety database.
Risk factors and risk groups	Suspected etiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee 2008).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.

Important potential risk: Adenocarcinoma of colon in UC patients	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials.
Risk factors and risk groups	Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid PSC (Van Assche 2013), diet, and cigarette smoking (National Cancer Institute 2006).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry for pedCD patients (Study P11-292). See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Episodic treatment in Ps, UC, and JIA	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine.

	Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Treatment interruptions in registry studies will be evaluated.
Missing Information: Long-term safety information in the treatment of children with uveitis	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.2: Statement that the benefit and risk of continued longterm Humira treatment in this population should be evaluated on a yearly basis. Prescription only medicine.
	Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term uveitis data from the ongoing JIA registry (Study P10-262). See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term paediatric ulcerative colitis data from the ongoing extension study (Study M10-870). See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

Not applicable.

II.C.2 Other Studies in Post-Authorization Development Plan

Study short name: Study P10-023
Purpose of the study: a 10-year, post-marketing, observational, registry in adult patients with chronic plaque Ps.

Study short name: Study P10-262
Purpose of the study: a long-term, multi-center, longitudinal post-marketing, observational registry to assess long-term safety and effectiveness of Humira in children with moderately to severely active polyarticular or polyarticular course JIA.

Study short name: Study P11-292
Purpose of the study: a long-term non-interventional registry to assess safety and effectiveness of Humira in paediatric patients with moderately to severely active CD.

Study short name: Study P11-282
Purpose of the study: a long-term non-interventional registry to assess safety and effectiveness of Humira in patients with moderately to severely active UC.

Study short name: Study M10-870
Purpose of the study: a long-term, multi-center, open-label study to assess safety and tolerability of Humira in paediatric patients with UC.