PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

ABRILADA (ADALIMUMAB)

Marketing Authorization Numbers:

67832 (pre-filled syringe)

67831 (pre-filled pen)

67830 (vial)

Solution for injection in pre-filled syringe, 40 mg/0.8 mL

Solution for injection in pre-filled pen, 40 mg/0.8 mL

Solution for injection (vial), 40 mg/0.8 mL

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AxSpA	Axial Spondyloarthritis
BCG	Bacillus Calmette-Guérin
CD	Crohn's Disease
EPAR	European Public Assessment Report
EU	European Union
GBS	Guillain-Barré Syndrome
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HS	Hidradenitis Suppurativa
HSTCL	Hepatosplenic T-Cell Lymphoma
IBD	Inflammatory Bowel Disease
JIA	Juvenile Idiopathic Arthritis
MCC	Merkel Cell Carcinoma
MS	Multiple Sclerosis
ON	Optic Neuritis
pedCD	Paediatric Crohn's Disease
pedERA	Paediatric Enthesitis-Related Arthritis
pedPs	Paediatric Psoriasis
pedUV	Paediatric Uveitis
PL	Package Leaflet
PML	Progressive multifocal leukoencephalopathy
Ps	Psoriasis
PsA	Psoriatic Arthritis
PSC	Primary Sclerosing Cholangitis
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RPLS	Reversible posterior leukoencephalopathy syndrome
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
TB	Tuberculosis
UC	Ulcerative Colitis
UTI	Urinary Tract Infections
UV	Ultraviolet

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OVERVIEW

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 for Abrilada 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 Abrilada in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Abrilada.

In the following summary, Abrilada is referenced with the trade name Amsparity, as approved in the EU.

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SUMMARY OF RISK MANAGEMENT PLAN FOR ADALIMUMAB[1]

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

Amsparity's SmPC and its PL give essential information to HCPs and patients on how adalimumab should be used.

This summary of the RMP for Amsparity 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 EPAR.

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

I. The Medicine and What It Is Used For

Amsparity is being developed as a biosimilar to the Innovator's product Humira (adalimumab). Humira was developed and is currently marketed by AbbVie. Humira is authorised in adults for indications RA, PsA, AxSpA, CD, Ps, UC and HS. Humira is authorised in paediatric patients for the treatment of JIA, pedERA, pedCD, pedPs, HS, Uveitis, and UC. Adalimumab is the active substance, and it is given by the SC route of administration. Indications for Amsparity are all indications approved for Humira.

Further information about the evaluation of Amsparity benefits can be found in Amsparity's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's link to product's EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of adalimumab, together with measures to minimise such risks and the proposed studies for learning more about adalimumab'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 to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

[1] Changes are considered important if they relate to the following: new safety concerns or important changes/removal to a known safety concerns, major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies), any 'additional risk minimisation measure' which is added or removed, routine risk minimisation activities recommending specific clinical measures to address the risk.

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

In the case of Amsparity, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

Patient reminder cards for the following important risks:

- Serious infections
- Tuberculosis
- Demyelinating disorders (including MS, GBS, and ON)
- Bacillus Calmette-Guérin disease following live BCG vaccination in infants with *in utero* exposure to Amsparity

In addition to these measures, information about adverse events is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

II.A. List of Important Risks and Missing Information

Important risks of adalimumab are risks that need special risk management activities to further investigate or minimise 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 adalimumab. 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).

Table 1. List of important risks and missing information

Important identified risks	• Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including MS, GBS and ON) • Bacillus Calmette-Guérin disease following live BCG vaccination in infants with *in utero* exposure to Amsparity
Important potential risks	• Progressive multifocal leukoencephalopathy • Reversible posterior leukoencephalopathy syndrome • Adenocarcinoma of colon in ulcerative colitis patients
Missing information	• Patients with Immune Compromised conditions • 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 JIA • Long term safety information in the treatment of children with uveitis • Long-term safety information in the treatment of children from 6 years to less than 18 years with UC

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II.B. Summary of Important Risks

Table 2. Important Identified Risk: Serious infections

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), registries and from the Innovator's post-marketing data.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of co-morbidities, 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 (eg, pneumonia, influenza, and TB), bacteraemia, UTIs, salmonellosis, hepatitis, and nosocomial infections. While taking adalimumab, the risk for infection might increase, particularly if you are over 65 years of age, taking immunosuppressive treatment (eg, 6-MP, AZA), a heavy smoker, or have a history of decreased lung function. Infections may be serious and, in rare cases, life threatening.
Risk minimisation measures	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 3. Important Identified Risk: Tuberculosis (TB)

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), registries and from the Innovator's post-marketing data.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of co-morbidities, 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 (eg, pneumonia, influenza, and TB), bacteraemia, UTIs, salmonellosis, hepatitis, and nosocomial infections.
Risk minimisation measures	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

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Table 4. Important Identified Risk: Malignancies

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), and from the Innovator's post-marketing data.
Risk factors and risk groups	Factors associated with an increased risk of NHL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), infection (eg, HIV, Epstein-Barr virus, H. pylori, HTLV-I, and hepatitis C), and age (over 60 years). Factors associated with an increased risk of HL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), viral infection (eg, HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older). 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]). 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. Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia 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 leukaemia. Factors associated with an increased risk of skin cancer include radiation (eg, sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (eg, antibiotics, hormones, antidepressants), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic. Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis. Factors associated with an increased risk of melanoma include UV radiation (eg, sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (eg, 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. Factors associated with an increased risk of MCC include advanced age, immunosuppression (eg, organ transplant, HIV), other cancers (eg, squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure.
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

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Table 5. Important Identified Risk: Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)

Evidence for linking the risk to the medicine	Data from Innovator clinical trials.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (eg, HLA-DR2 (HLA-DRBl *15), ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors. Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age. Subjects with intermediate uveitis have a high prevalence of demyelination.
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 6. Important Identified Risk: Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Evidence for linking the risk to the medicine	Data from Innovator clinical trials.
Risk factors and risk groups	Infants exposed to adalimumab in utero.
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings are precautions for use SmPC Section 4.6 Fertility, pregnancy, and lactation In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	There are none.

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Table 7. Important Potential Risk: Progressive multifocal leukoencephalopathy

Evidence for linking the risk to the medicine	Data from Innovator clinical trials and post-marketing data.
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS. 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. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, SLE, and other rheumatic diseases. The potential mechanism for PML is reactivation of polyomavirus JC in the brain that is believed to be started by severe immunosuppression as in HIV infection. There is no known association of PML with the use of adalimumab or other TNF inhibitors, however, because PML is rare and often fatal its appearance in patients on biologic medications including adalimumab is under observation.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 8. Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Evidence for linking the risk to the medicine	Data from Innovator clinical trials and post-marketing data.
Risk factors and risk groups	Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Co-morbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%). RPLS is a syndrome characterized by headache, confusion, seizures, and visual loss. This syndrome appears in patients who become severely immunosuppressed by drugs like those used for anti-rejection. Stopping the drug(s) makes the condition reverse. There is no known association of this event with adalimumab use; however, rare RPLS reports in patients using adalimumab have been received and although most have other causes, the reports are under observation for a possible association.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

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Table 9. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis patients

Evidence for linking the risk to the medicine	Data from Innovator clinical 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, co-morbid PSC, diet, and cigarette smoking. There is a known increased risk of adenocarcinoma of colon in UC patients that increases with degree of bowel inflammation as well as the duration of disease. Since early detection can limit morbidity from adenocarcinoma of colon, patients with UC, regardless of the therapy used, should receive routine screening (colonoscopy) more frequently than that recommended for the general population according to current practice guidelines. Since there may be an increased risk of cancer in patients receiving adalimumab, it is not known if this therapy further increases the risk of adenocarcinoma of colon in UC patients, thus, reports of this cancer are under observation in this patient group.
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use. 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 minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 10. Missing Information: Patients with Immune Compromised Conditions

Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use There is currently no information on subjects with a history of clinically significant drug or alcohol abuse listed in the SmPC. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 11. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Risk minimisation measures	Routine risk communication SmPC Section 4.2 Posology and method of administration Prescription only medicine Additional risk minimisation measures: There are none.

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Additional pharmacovigilance activities	There are none.

Table 12. Missing Information: Episodic treatment in Ps, UC and JIA

Risk minimisation measures	Routine risk communication Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 13. Missing Information: Long term safety information in the treatment of children with uveitis

Risk minimisation measures	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8, Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 14. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Risk minimisation measures	Routine risk communication Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of adalimumab.

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

There are none.

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