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Swiss Summary of the Risk Management Plan (RMP) for Amgevita® (Adalimumab)

RMP Summary: Version 2, March 2023
EU RMP: Version 6.0, 07 May 2021

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 Amgevita® 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 Amgevita® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Amgevita®.

The medicine and what it is used for

AMGEVITA is authorized for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic-arthritis, ankylosing spondylitis (Morbus Bechterew), Crohn's disease, paediatric Crohn's disease, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, , ulcerative colitis, uveitis (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of AMGEVITA's benefits can be found in AMGEVITA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/AMGEVITA.

Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

- 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 authorized pack size — the amount of medicine in a pack is chosen so 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 minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In the case of AMGEVITA, these measures are supplemented with additional risk minimization measures mentioned under relevant risks, below.
In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment 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 AMGEVITA is not yet available, it is listed under 'missing information' below.

List of Important Risks and Missing Information

Important risks of Amgevita 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 Amgevita. 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).

Summary of safety concerns

List of important risks and missing information

Important Identified Risk	Serious infections Tuberculosis Malignancies Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis) Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to AMGEVITA
Important Potential Risk	Progressive multifocal leukoencephalopathy Reversible posterior leukoencephalopathy syndrome Colon cancer 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 Crohn's disease Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis Long-term safety data in the treatment of adults and children with uveitis Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Summary of Important risks

Important identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, December 2018 and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Patients with autoimmune disease have an inherently higher risk of infections. Other risk factors including advanced age, disease activity, comorbidities (eg, diabetes, chronic obstructive pulmonary disease) and baseline corticosteroid use significantly increase the risk of serious infectious events (Doran et al, Arthritis Rheum, 2002;46:2287-2293).
Risk minimization measures	Routine risk minimization measures: · SmPC Section where dose interruption is discussed · SmPC Section where close monitoring for infections and discontinuation of AMGEVITA is discussed · PL Section where symptoms of infection, interruption of treatment with AMGEVITA, and advice not to take AMGEVITA with medicines containing anakinra or abatacept is discussed · PL Section where symptoms of infection are discussed Additional risk minimization measures: · Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: · (ABP 501) 20160264 study See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Tuberculosis	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, December 2018 and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Patients with autoimmune disease have an inherently higher risk of infections. Other risk factors including advanced age, disease activity, comorbidities (eg, diabetes, chronic obstructive pulmonary disease) and baseline corticosteroid use significantly increase the risk of serious infectious events (Doran et al, Arthritis Rheum, 2002;46:2287-2293).
Risk minimization measures	Routine risk minimization measures: · SmPC Section where dose interruption is discussed · SmPC Section where close monitoring for tuberculosis, treatment of latent tuberculosis before initiation of AMGEVITA, and discontinuation of AMGEVITA is discussed · PL Section where symptoms of tuberculosis, interruption of AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept is discussed Additional risk minimization measures: · Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: · (ABP 501) 20160264 study See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medical product Humira®. Evidence sources: Literature reports (Burmester et al, Arthritis Res Ther, 2014;16:R24:5-11; Burmester et al, Ann Rheum Dis, 2013;72:517-524); Humira® SmPC, December 2018; Humira® USPI, January 2019; and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Established risk factors for non-Hodgkin's lymphoma are infection and immune dysregulation, immunosuppressed populations (those who had organ transplant, immunosuppressive medical treatment, and human immunodeficiency virus [HIV]/acquired immune deficiency syndrome [AIDS]) and among individuals with certain auto-immune diseases (ie, rheumatoid arthritis, systemic lupus erythematosis, psoriasis, Sjogren's syndrome, and celiac disease, etc) (Zhang et al, Exp Opin Med Diagnost, 2011;5(6):539-550). Risk factors for Hodgkin's lymphoma include genetic predisposition, Epstein-Barr virus infection, HIV infection and immune diseases (Mani and Jaffe, Clin Lymphoma Myeloma, 2009;9(3):206-216). Some events of hepatosplenic T-cell lymphoma reported with Humira® have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease (Humira® SmPC, December 2018). Established risk factors for hepatosplenic T-cell lymphoma are similar to lymphoma and include infection and immune

	dysregulation. The supportive evidences include elevated incidence rates in immunosuppressed populations (those who had organ transplant, immunosuppressive medical treatment, and HIV/AIDS) and among individuals with certain auto-immune diseases (ie, rheumatoid arthritis, systemic lupus erythematosis, psoriasis, Sjogren's syndrome, celiac disease, etc) (Zhang et al, Exp Opin Med Diagnost, 2011;5(6):539-550). Risk of leukemia may be higher in patients who are predisposed to this event, such as patients with a hematologic disorder (eg, severe congenital neutropenia) or an inherited disease (eg, Bloom syndrome and Fanconi's anemia), patients who have had myelodysplastic syndrome for at least 3 months, or those who have been exposed to leukemogenic agents, often as a component of therapy for an unrelated neoplasm (Lowenberg et al, N Engl J Med, 1999;341:1051-1062). The risk of non-melanoma skin cancer and melanoma may be higher in patients who are predisposed to this event. Significant risk factors for non-melanoma skin cancer include excessive, chronic sun exposure, indoor tanning, fair complexion, prior exposure to ionizing radiation, exposure to chemical carcinogens such as arsenic, and genetic determinants (Tung and Vidimos, Non melanoma skin cancer, Curr clin med: Expert Consult-Online, 2007; Miller and Weinstock, J Am Acad Dermatol, 1994;30:774-778). The strongest risk factors for melanoma are a family history of melanoma, multiple benign or atypical nevi, and a previous melanoma. Immunosuppression, sun sensitivity, and exposure to ultraviolet radiation are additional risk factors. Each of these risk factors corresponds to a genetic predisposition or an environmental stressor that contributes to the genesis of melanoma (Miller and Mihm, N Eng J Med, 2006;355:51-65). The risk of Merkel cell carcinoma may be higher in patients who are predisposed to this event, such as those with prior infection with Merkel cell polyomavirus, exposure to ultraviolet light (such as extended exposure to the sun, tanning beds, or in patients who received treatment for psoriasis), lighter skin tone, increasing age, men, patients with other cancers, and those with compromised immune systems (HIV infection, organ transplants) (American Cancer Society, http://www.cancer.org/cancer/skincancermerkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-riskfactors, 2015; Becker, Ann Oncol, 2010;21(7):vii81-85; Agelli and Clegg, J Am Acad Dermatol, 2003;49(5):832-841). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	Routine risk minimization measures: · SmPC Section where examination for the presence of non-melanoma skin cancer prior to and during treatment with AMGEVITA is discussed · PL Section where appearance of new skin lesions or change in the appearance of existing lesions during or after AMGEVITA therapy is discussed Additional risk minimization measures: · Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: · (ABP 501) 20160264 study See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medical product Humira®. Evidence sources: Literature report (Burmester et al, Ann Rheum Dis, 2013;72:517–524) and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Multiple sclerosis arises from a combination of genetic susceptibility and environmental exposures acting from gestation to early adulthood. Vitamin D deficiency, season of birth, Epstein-Barr virus infection, and smoking behavior are strongly implicated and able to influence genetic predisposition to multiple sclerosis (Disanto et al, CNS Neurol Disord Drug Targets, 2012;11(5):545-555). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	Routine risk minimization measures: · SmPC Section where neurologic evaluation in patients with non-infectious intermediate uveitis to assess for pre-existing or developing central demyelinating disorders is described · PL Sections where symptoms of demyelinating disease are described Additional risk minimization measures: · Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: · (ABP 501) 20160264 study See Section II.C of this summary for an overview of the postauthorization development plan

Important identified risk: BCG Disease Following Live BCG Vaccination in Infants With In Utero Exposure to AMGEVITA	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, December 2018 and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Infants exposed to AMGEVITA in utero and administered live BCG vaccination within 5 months of the mother's last AMGEVITA injection during pregnancy.
Risk minimization measures	Routine risk minimization measures: · SmPC Sections where guidance that administration of live vaccines (eg, BCG vaccine) to infants exposed to AMGEVITA in utero is not recommended for 5 months following the mother's last AMGEVITA injection during pregnancy is provided · PL Section 2 Additional risk minimization measures: · Patient Reminder Card

Important Potential Risk: Progressive Multifocal Leukoencephalopathy	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medical product Humira®. Evidence sources: Published literature (Burmester et al, Ann Rheum Dis, 2013;72:517-524) and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Progressive multifocal leukoencephalopathy has been most commonly observed among patients infected with HIV, those with malignancies, and in organ transplant recipients. Progressive multifocal leukoencephalopathy has also been reported rarely in patients with inflammatory autoimmune disorders including rheumatoid arthritis and other rheumatic conditions, particularly in those using cytotoxic and biologic therapies including rituximab, natalizumab, efalizumab, and less commonly tumor necrosis factor inhibitors (Bharat et al, Arthritis Care Res, 2012;64(4):612-615). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	No risk minimization measures

Important Potential Risk: Reversible Posterior Leukoencephalopathy Syndrome	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medical product Humira®. Evidence sources: Case reports and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.
Risk factors and risk groups	Posterior leukoencephalopathy syndrome is often associated with an abrupt increase in blood pressure and is usually seen in patients with eclampsia, renal disease, and hypertensive encephalopathy. It is also seen in the patients treated with cytotoxic and immunosuppressive drugs such as cyclosporin, tacrolimus, and interferon alfa (Garg, Postgrad Med J, 2001;77(903):24-28). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	No risk minimization measures

Important Potential Risk: Adenocarcinoma of colon in ulcerative colitis patients	
Evidence for linking the risk to the medicine	This important potential risk is included per the reference medical product Humira®. Evidence source: Humira® SmPC, January 2021.
Risk factors and risk groups	Risk factors for colon cancer in ulcerative colitis patients include a long history of Crohn's disease, often (but not exclusively) over 20 years predating cancer development; a relatively young age of intestinal cancer diagnosis in Crohn's disease; and, the appearance of other histopathological types, including mucinous adenocarcinoma. Most cancers occur in the distal colorectum, often in the presence of extensive inflammatory disease (Freeman, World J Gastroenterol, 2008;14(12):1810-1811). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section where regular screening for the presence of colonic dysplasia prior to and during treatment with AMGEVITA is discussed Additional risk minimization measures: • None

Missing Information: Patients With Immune-compromised Conditions	
Risk minimization measures	Routine risk minimization measures: • relevant SmPC Section Additional risk minimization measures: • None

Missing Information: Long-term Safety Information in the Treatment of Children, Aged From 6 Years to Less Than 18 Years With Crohn's Disease	
Risk minimization measures	Routine risk minimization measures: • relevant SmPC Section Additional risk minimization measures: • None

Missing Information: Episodic Treatment in Psoriasis, Ulcerative Colitis, and Juvenile Idiopathic Arthritis	
Risk minimization measures	No risk minimization measures

Missing Information: Long-term Safety Data in the Treatment of Adults and Children With Uveitis	
Risk minimization measures	Routine risk minimization measures: · SmPC Section where where recommendation for yearly evaluation of benefit-risk is included Additional risk minimization measures: · None

Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimization measures	No risk minimization measures

Post-authorisation development plan

Studies which are a condition of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of AMGEVITA.

Other studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
(ABP 501) 20160264 An observational study to evaluate long-term safety of AMGEVITA in patients with rheumatoid arthritis	Primary objectives: · Assess the long-term safety of AMGEVITA by evaluation of adverse events of special interest (identified risks of adalimumab) in Rheumatoid Arthritis patients exposed to AMGEVITA. · Compare the current estimated rates to historical comparators (only for: serious infections and tuberculosis). Secondary objective: · Evaluate incidence rates of other adverse events of interest (identified risks of adalimumab). Safety concerns addressed include: · Serious infections · Tuberculosis · Malignancies · Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Approval Date Procedure	Change
4.1	Date of RMP: 08 February 2019 EMEA/H/C/004212/ IB/0015/G Date of approval: 14 March 2019	*Safety Concerns* *Important Identified Risks:* *The following important identified risks were reclassified:* • *'Serious infections including diverticulitis and opportunistic infections, eg, invasive fungal infections, parasitic infections, legionellosis, and tuberculosis' was reclassified as 2 stand-alone important identified risks of 'Serious infections' and 'Tuberculosis'* • *'Malignancies' was reclassified and renamed as a single stand-alone important identified risk (previously classified under the multiple stand-alone important identified risks of 'Lymphoma,' 'Hepatosplenic T-cell lymphoma,' 'Leukemia,' 'Non-melanoma skin cancer,' 'Melanoma,' and 'Merkel cell carcinoma')* *The following important identified risk was added:* *□ BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA* *The following important identified risks were removed:* • *Reactivation of hepatitis B* • *Pancreatitis* • *Immune reactions – lupus-like reactions* • *Immune reactions – allergic reactions* • *Sarcoidosis* • *Congestive heart failure* • *Myocardial infarction* • *Cerebrovascular accident* • *Interstitial lung disease* • *Pulmonary embolism* • *Cutaneous vasculitis* • *Stevens-Johnson syndrome* • *Erythema multiforme* • *Worsening and new onset of psoriasis* • *Hematologic disorders* • *Intestinal perforation* • *Intestinal stricture in Crohn's disease* • *Liver failure and other liver events* ***Safety Concerns (continued)*** *Important Potential Risks:* *The following important potential risks were removed:* • *Other malignancies (except lymphoma, hepatosplenic* • *T-cell lymphoma, leukemia, non-melanoma skin* • *cancer, and melanoma) (this will be monitored under* • *the important identified risk of 'Malignancies')* • *Vasculitis (noncutaneous)* • *Amyotrophic lateral sclerosis* • *Infections in infants exposed to adalimumab in utero* • *Off-label use*

Version	Approval Date Procedure	Change
4.1 (continued)		Missing Information: The following missing information was reclassified: • 'Immune-compromised conditions either due to • underlying conditions (ie, diabetes, renal or liver • failure, human immunodeficiency virus infection, • alcohol or illicit drug abuse), or due to medications • (postcancer chemotherapy, anti-rejection drugs for • organ transplant) may have increased known risks of • infection or other unknown risks related to the • condition or to the concomitant medications' was • reclassified as 'Patients with immune-compromised • conditions.' • 'Remission-withdrawal-retreatment non-radiographic • axial spondyloarthritis/axial spondyloarthritis without • radiographic evidence of axial spondyloarthritis, and • episodic treatment in psoriasis, Crohn's disease, • ulcerative colitis, and polyarticular juvenile idiopathic • arthritis' was reclassified as 'Episodic treatment in • psoriasis, ulcerative colitis, and juvenile idiopathic • arthritis.' The following missing information was removed: • Use in pregnant and lactating women • Long-term safety data in the treatment of adults and • adolescents with hidradenitis suppurativa **Pharmacovigilance Plan** Specific Adverse Drug Reaction Follow-up Forms Removed: • Anaphylactic Reaction • Initial Pregnancy Questionnaire (Mother) • Initial Pregnancy Questionnaire (Father) • Lactation Questionnaire **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** • Annex 2: List of safety concerns addressed by Study 20160264 was updated to align with the current safety specification. • Annex 4: Specific adverse reaction follow-up questionnaires were removed • Annex 6: Details of Patient Reminder Card updated.

Version	Approval Date Procedure	Change
5.0	Date of RMP: 10 December 2020 Approval Date: 21 January 2021 Submitted within procedure: EMEA/H/C/004212/IB/0024	**Safety Concerns** Important Potential Risks: • The important potential risk of 'Colon cancer in ulcerative colitis patients' was renamed as 'Adenocarcinoma of colon in ulcerative colitis patients' to align with the reference medicinal product, Humira®. **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Additional Risk Minimization Measures: • Patient Reminder Card was removed for the important potential risk of 'Adenocarcinoma of colon in ulcerative colitis patients' to align with the reference medicinal product, Humira®. **Annexes** No change
6.0	Date of RMP: Version 6.0; 07 May 2021 To be confirmed by EMA	**Safety Concerns** Missing Information: • The missing informaton of 'Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis' was added to align with the reference medicinal product, Humira. **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** Annex 3: Protocol for Study 20160264 added **Other Changes** • Indication of paediatric ulcerative colitis was added to the RMP

This summary was generated in March 2023.