

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for AMGEVITA® (Adalimumab)

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

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

This summary of the RMP for AMGEVITA 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 ones will be included in updates of AMGEVITA's RMP.

I. The medicine and what it is used for

AMGEVITA is authorized for rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis - ankylosing spondylitis, axial spondyloarthritis - axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (including adolescents from 12 years of age), Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, and paediatric 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>.

II. 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 minimize 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.

II.A. 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).

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

II.B. 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, <i>Arthritis Rheum</i> , 2002;46:2287-2293).
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none">• SmPC Section 4.2 where dose interruption is discussed• SmPC Section 4.3• SmPC Section 4.4 where close monitoring for infections and discontinuation of AMGEVITA is discussed• SmPC Section 4.8• PL Section 2 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 4 where symptoms of infection are discussed <p>Additional risk minimization measures:</p> <ul style="list-style-type: none">• Patient Reminder Card
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">• (ABP 501) 20160264 study <p>See Section II.C of this summary for an overview of the postauthorization development plan</p>

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, <i>Arthritis Rheum</i> , 2002;46:2287-2293).
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • SmPC Section 4.2 where dose interruption is discussed • SmPC Section 4.3 • SmPC Section 4.4 where close monitoring for tuberculosis, treatment of latent tuberculosis before initiation of AMGEVITA, and discontinuation of AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where symptoms of tuberculosis, interruption of AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept is discussed • PL Section 4 <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Patient Reminder Card
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • (ABP 501) 20160264 study <p>See Section II.C of this summary for an overview of the postauthorization development plan</p>

Important Identified Risk: Malignancies	
Evidence for linking the risk to the medicine	<p>This important identified risk is included per the reference medical product Humira®. Evidence sources: Literature reports (Burmester et al, <i>Arthritis Res Ther</i>, 2014;16:R24:5-11; Burmester et al, <i>Ann Rheum Dis</i>, 2013;72:517-524); Humira® SmPC, December 2018; Humira® USPI, January 2019; and ABP 501 clinical studies of Rheumatoid Arthritis and Psoriasis.</p>
Risk factors and risk groups	<p>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 erythematosus, psoriasis, Sjogren's syndrome, and celiac disease, etc) (Zhang et al, <i>Exp Opin Med Diagnost</i>, 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, <i>Clin Lymphoma Myeloma</i>, 2009;9(3):206-216).</p> <p>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 erythematosus, psoriasis, Sjogren's syndrome, celiac disease, etc) (Zhang et al, <i>Exp Opin Med Diagnost</i>, 2011;5(6):539-550).</p> <p>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, <i>N Engl J Med</i>, 1999;341:1051-1062).</p> <p>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, <i>Curr clin med: Expert Consult-Online</i>, 2007; Miller and Weinstock, <i>J Am Acad Dermatol</i>, 1994;30:774-778).</p>

Important Identified Risk: Malignancies (continued)	
Risk factors and risk groups (continued)	<p>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, <i>N Eng J Med</i>, 2006;355:51-65).</p> <p>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/skincancer-merkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-risk-factors, 2015; Becker, <i>Ann Oncol</i>, 2010;21(7):vii81-85; Agelli and Clegg, <i>J Am Acad Dermatol</i>, 2003;49(5):832-841).</p> <p>No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.</p>
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • SmPC Section 4.4 where examination for the presence of non-melanoma skin cancer prior to and during treatment with AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where appearance of new skin lesions or change in the appearance of existing lesions during or after AMGEVITA therapy is discussed • PL Section 4 <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Patient Reminder Card
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • (ABP 501) 20160264 study <p>See Section II.C of this summary for an overview of the postauthorization development plan</p>

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, <i>Ann Rheum Dis</i> , 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, <i>CNS Neurol Disord Drug Targets</i> , 2012;11(5):545-555). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • SmPC Section 4.4 where neurologic evaluation in patients with non-infectious intermediate uveitis to assess for pre-existing or developing central demyelinating disorders is described • SmPC Section 4.8 • PL Sections 2 and 4 where symptoms of demyelinating disease are described <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Patient Reminder Card
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • (ABP 501) 20160264 study <p>See Section II.C of this summary for an overview of the postauthorization development plan</p>

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	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • SmPC Sections 4.4 and 4.6 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 <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • 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, <i>Ann Rheum Dis</i> , 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, <i>Arthritis Care Res</i> , 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, <i>Postgrad Med J</i> , 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: Colon Cancer 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, December 2018.
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, <i>World J Gastroenterol</i> , 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: <ul style="list-style-type: none"> SmPC Section 4.4 where regular screening for the presence of colonic dysplasia prior to and during treatment with AMGEVITA is discussed Additional risk minimization measures: <ul style="list-style-type: none"> Patient Reminder Card

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: <ul style="list-style-type: none"> SmPC Section 4.2 Additional risk minimization measures: <ul style="list-style-type: none"> None

Missing Information: Patients With Immune-compromised Conditions	
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> SmPC Section 4.4 Additional risk minimization measures: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> SmPC Section 4.2 where recommendation for yearly evaluation of benefit-risk is included Additional risk minimization measures: <ul style="list-style-type: none"> None

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 AMGEVITA.

II.C.2 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	<u>Primary objectives:</u> <ul style="list-style-type: none"> 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). <u>Secondary objective:</u> <ul style="list-style-type: none"> Evaluate incidence rates of other adverse events of interest (identified risks of adalimumab). <u>Safety concerns addressed include:</u> <ul style="list-style-type: none"> Serious infections Tuberculosis Malignancies Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)