EUROPEAN UNION RISK MANAGEMENT PLAN

AMGEVITA® (adalimumab biosimilar)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	7.1
Date:	04 March 2024
Supersedes:	Version 6.0, dated 07 May 2021

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	7.1
Data lock point of this RMP:	31 December 2022
Date of final sign-off:	04 March 2024
Rationale for submitting an updated RMP:	• To update the RMP to align with the proposed new AMGEVITA formulations • To align the safety concerns with the reference product (Humira®) RMP

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	• Proposed dosages updated • High concentration formulation (HCF) added to the Pharmaceutical form(s) and strength(s) section	09 January 2024, Version 7.0
	• The proposed dosage introduction was updated to reflect that the dosing text is based on the 100 mg/ml presentation of AMGEVITA.	04 March 2024, Version 7.1
Part II: Safety Specification		
SIII: Clinical Trial Exposure	Clinical trial exposure data was updated with data from completed Studies 20200497 and 20200286	09 January 2024, Version 7.0
SIV: Populations Not Studied in Clinical Trials		
SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program	The criterion of 'Patients with immune-compromised conditions' was removed as missing information to align with the reference product RMP	09 January 2024, Version 7.0
SV: Postauthorization Experience	Postmarketing exposure data was updated to the data lock point of 31 December 2022	09 January 2024, Version 7.0
SVII: Identified and Potential Risks	• The missing information of 'Patients with immune-compromised conditions' was removed to align with the reference product RMP • The missing information of 'Long-term safety data in the treatment of adults and children with uveitis' was reclassified as 'Long-term safety data in the treatment of children with uveitis	09 January 2024, Version 7.0
SVIII: Summary of the Safety Concerns	Updated to align with the changes above	09 January 2024, Version 7.0
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)		
III.2: Additional Pharmacovigilance Activities	Study objectives for Study 20160264 were updated to align with the protocol	09 January 2024, Version 7.0

Part/Module/Annex	Major Change(s)	Version Number and Date
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies) (continued)		
III.3: Summary Table of Additional Pharmacovigilance Activities	• Updated to align with the changes above • Updated the milestones and status for Study 20160264	09 January 2024, Version 7.0
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Updated to align with the changes in Module SVII.	09 January 2024, Version 7.0
Part VI: Summary of the Risk Management Plan	Updated to align with the changes above	09 January 2024, Version 7.0
Part VII: Annexes		
Annex 2: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Study objectives and milestones for Study 20160264 were updated to align with the protocol	09 January 2024, Version 7.0

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	6.0
Approved with procedure:	EMEA/H/C/004212/IB/0027/G
Date of approval (opinion date):	21 July 2021
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm, MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
6-MP	6-mercaptopurine
adalimumab (EU)	Humira® (adalimumab) that is approved in and sourced from the EU
adalimumab (US)	Humira® (adalimumab) that is approved in and sourced from the US
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZA	azathioprine
BCG	Bacillus Calmette-Guérin
BSRBR-RA	British Society for Rheumatology Biologics Register for Rheumatoid Arthritis
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CRP	C-reactive protein
CVA	cerebrovascular accident
DMARDs	disease-modifying anti-rheumatic drugs
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HBV	hepatitis B virus
HCF	high concentration formulation
HCP	healthcare professional
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
HSTCL	hepatosplenic T-cell lymphoma
INN	International Nonproprietary Name
MAH	marketing authorization holder
MRI	magnetic resonance imaging
nbDMARD	non-biologic disease-modifying antirheumatic drug
NMSC	non-melanoma skin cancer
NYHA	New York Heart Association

Term/Abbreviation	Explanation
OLE	open-label extension
PI	Product Information
PL	package leaflet
PML	progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PUVA	psoralen plus ultraviolet A
PY	patient year
QPPV	Qualified Person for Pharmacovigilance
RA	rheumatoid arthritis
RMP	Risk Management Plan
RPLS	reversible posterior leukoencephalopathy syndrome
SC	subcutaneous(ly)
SmPC	summary of product characteristics
TB	tuberculosis
TNF	tumor necrosis factor
TNFα/TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
USPI	United States prescribing information

Note to Reviewers: AMGEVITA (adalimumab) was developed as a biosimilar to Humira® (adalimumab). Humira® (adalimumab) that is approved in and sourced from the United States (US) is referred to as "Humira® (US)." Humira® (adalimumab) that is approved in and sourced from the European Union (EU) is referred to as "Humira® (EU)." In all other contexts in this document it is referred to as Humira®. The biosimilar to Humira® is referred to as AMGEVITA in this document.

PART I. PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Adalimumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Immunosuppressants, Tumor Necrosis Factor alpha (TNFα) inhibitors (L04AB04)
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	AMGEVITA
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Immunosuppressants: TNFα inhibitors
Summary of mode of action	AMGEVITA binds specifically to tumor necrosis factor (TNF) and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. AMGEVITA also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.
Important information about its composition	AMGEVITA is a recombinant immunoglobulin G1 human monoclonal antibody expressed in Chinese hamster ovary cells.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.

Table 1. Product Overview

Indication(s) in the EEA Current:	Rheumatoid arthritis AMGEVITA in combination with methotrexate, is indicated for: • the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate. • the treatment of severe, active, and progressive rheumatoid arthritis in adults not previously treated with methotrexate. AMGEVITA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. AMGEVITA reduces the rate of progression of joint damage as measured by x-ray and improves physical function, when given in combination with methotrexate. Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis* AMGEVITA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. AMGEVITA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. AMGEVITA has not been studied in patients aged less than 2 years. *Enthesitis-related arthritis* AMGEVITA is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Axial spondyloarthritis *Ankylosing spondylitis (AS)* AMGEVITA is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. *Axial spondyloarthritis without radiographic evidence of AS* AMGEVITA is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Table 1. Product Overview

Indication(s) in the EEA (continued)	
Current (continued):	Psoriatic arthritis AMGEVITA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. AMGEVITA reduces the rate of progression of peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease and improves physical function. Psoriasis AMGEVITA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy. Paediatric plaque psoriasis AMGEVITA is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Hidradenitis suppurativa (HS) AMGEVITA is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. Crohn’s disease AMGEVITA is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Paediatric Crohn's disease AMGEVITA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Table 1. Product Overview

Indication(s) in the EEA (continued)	
Current (continued):	Ulcerative colitis AMGEVITA is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric ulcerative colitis AMGEVITA is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Uveitis AMGEVITA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. Paediatric Uveitis AMGEVITA is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.
Proposed (if applicable)	Not applicable.
Dosage in the EEA	
Current:	• Rheumatoid arthritis – 40 mg administered every other week as a single dose via subcutaneous (SC) injection. Methotrexate should be continued during treatment with AMGEVITA. – In monotherapy, some patients who experience a decrease in their response to AMGEVITA 40 mg every other week may benefit from an increase in dosage to 40 mg AMGEVITA every week or 80 mg every other week.

Table 1. Product Overview

Dosage in the EEA (continued) Current (continued):	• Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis from 2 years of age* – Dose of AMGEVITA based on body weight and administered via SC injection: Patient Weight: Dosing Regimen 10 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week *Enthesitis-related arthritis (from 6 years of age)* – Dose of AMGEVITA based on body weight and administered via SC injection: Patient Weight: Dosing Regimen 15 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week • Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, and psoriatic arthritis – 40 mg administered every other week as a single dose via SC injection. • Psoriasis – Initial dose of 80 mg administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose. • Paediatric plaque psoriasis (from 4 to 17 years of age) – Dose of AMGEVITA based on body weight and administered via SC injection: Patient Weight: Dosing Regimen 15 kg to < 30 kg: Initial dose of 20 mg, followed by 20 mg given every other week starting 1 week after the initial dose ≥ 30 kg: Initial dose of 40 mg, followed by 40 mg given every other week starting 1 week after the initial dose • Hidradenitis suppurativa – 160 mg initially at day 1 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at day 15 (given as two 40 mg injections in 1 day). – Two weeks later (day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in 1 day). • Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg) – 80 mg at week 0 followed by 40 mg every other week starting at week 1 via SC injection.

Table 1. Product Overview

<table>
<tr><td>Dosage in the EEA (continued)

Current (continued):</td><td>

Crohn’s disease

80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg at week 2 (given as two 40 mg injections in 1 day), can be used with the awareness that the risk for adverse events is higher during induction.
After induction treatment, the recommended dose is 40 mg every other week via SC injection.

Paediatric Crohn’s disease (from 6 to 17 years of age)

Dose of AMGEVITA based on body weight and administered via SC injection:

<table>
<tr><th>Patient Weight</th><th>Induction Dose</th><th>Maintenance Dose Starting at Week 4</th></tr>
<tr><td>< 40 kg</td><td>• 40 mg at week 0 and 20 mg at week 2
In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:
• 80 mg at week 0 and 40 mg at week 2</td><td>20 mg every other week</td></tr>
<tr><td>≥ 40 kg</td><td>• 80 mg at week 0 and 40 mg at week 2
In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used:
• 160 mg at week 0 and 80 mg at week 2</td><td>40 mg every other week</td></tr>
</table>

Ulcerative colitis

160 mg at week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days) and 80 mg at week 2 (given as two 40 mg injections in 1 day).
After induction treatment, the recommended dose is 40 mg every other week via SC injection.

</td></tr>
</table>

Table 1. Product Overview

Dosage in the EEA (continued)

Current (continued):

- Paediatric ulcerative colitis (from 6 to 17 years of age)
  - Dose of AMGEVITA based on body weight and administered via SC injection:

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	• 80 mg at week 0 (given as two 40 mg injections in one day) and • 40 mg at week 2 (given as one 40 mg injection)	40 mg every other week
≥ 40 kg	• 160 mg at week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and • 80 mg at week 2 (given as two 40 mg injections in one day)	80 mg every other week

* Paediatric patients who turn 18 years of age while on AMGEVITA should continue their prescribed maintenance dose.

- Uveitis
  - Initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose.
  - There is limited experience in the initiation of treatment with AMGEVITA alone. Treatment with AMGEVITA can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting 2 weeks after initiating treatment with AMGEVITA.
- Paediatric uveitis
  - Dose of AMGEVITA based on body weight and administered via SC injection:

Patient Weight	Dosing Regimen
< 30 kg	20 mg every other week in combination with methotrexate
≥ 30 kg	40 mg every other week in combination with methotrexate

  - When AMGEVITA therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy.

Table 1. Product Overview

<table>
<tr><td>Dosage in the EEA (continued)

Proposed (if applicable):</td><td>The following updates to the dosages are proposed for the following indications. Dosing text is based on the 100 mg/ml presentations of AMGEVITA. There are small modifications in the 50 mg/ml presentations:
• Hidradenitis suppurativa (adult patients)
– 160 mg initially at day 1 (given as two 80 mg injections in 1 day or as one 80 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at day 15.
– Two weeks later (day 29) continue with a dose of 40 mg every week or 80 mg every other week.
• Crohn’s disease (adult patients)
– 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as two 80 mg injections in 1 day or as one 80 mg injection per day for 2 consecutive days), followed by 80 mg at week 2 , can be used with the awareness that the risk for adverse events is higher during induction.
– After induction treatment, the recommended dose is 40 mg every other week via SC injection.
• Ulcerative colitis (adult patients)
– 160 mg at week 0 (given as two 80 mg injections in 1 day or as one 80 mg injection per day for 2 consecutive days) and 80 mg at week 2 .
– After induction treatment, the recommended dose is 40 mg every other week via SC injection.
• Pediatric ulcerative colitis (from 6 to 17 years of age)
<table><tr><th>Patient Weight</th><th>Induction Dose</th><th>Maintenance Dose Starting at Week 4*</th></tr><tr><td>< 40 kg</td><td>• 80 mg at week 0 (given as one 80 mg injections in one day) and
• 40 mg at week 2 (given as one 40 mg injection)</td><td>40 mg every other week</td></tr><tr><td>≥ 40 kg</td><td>• 160 mg at week 0 (given as two 80 mg injections in one day or one 80 mg injection per day for two consecutive days) and
• 80 mg at week 2 (given as one 80 mg injections in one day)</td><td>80 mg every other week</td></tr></table>* Paediatric patients who turn 18 years of age while on AMGEVITA should continue their prescribed maintenance dose</td></tr>
</table>

Table 1. Product Overview

Pharmaceutical form(s) and strength(s)	
Current (if applicable):	AMGEVITA is supplied as a clear and colourless to slightly yellow sterile, single-use solution for SC injection in a pre-filled syringe or pre-filled pen (SureClick®) containing 40 mg/0.8 mL drug product. AMGEVITA is also supplied as a 20 mg/0.4 mL pre-filled syringe.
Proposed (if applicable):	AMGEVITA is a clear and colourless to slightly yellow solution and is supplied as a single-use solution for SC injection in a pre-filled syringe or pre-filled pen (SureClick®). <u>50 mg/ml Formulation</u> • AMGEVITA 20 mg solution for injection in pre-filled syringe: Each single dose pre-filled syringe contains 20 mg of adalimumab in 0.4 ml solution (50 mg/ml). • AMGEVITA 40 mg solution for injection in pre-filled syringe: Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 ml solution (50 mg/ml). • AMGEVITA 40 mg solution for injection in pre-filled pen: Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 ml solution (50 mg/ml). <u>100 mg/ml Formulation (High Concentration Formulation)</u> • AMGEVITA 20 mg/0.2 ml solution for injection in pre-filled syringe: Each single dose pre-filled syringe contains 20 mg of adalimumab in 0.2 ml solution (100 mg/ml). • AMGEVITA 40 mg/0.4 ml solution for injection in pre-filled syringe: Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.4 ml solution (100 mg/ml). • AMGEVITA 80 mg/0.8 ml solution for injection in pre-filled syringe: Each single dose pre-filled syringe contains 80 mg of adalimumab in 0.8 ml solution (100 mg/ml). • AMGEVITA 40 mg/0.4 ml solution for injection in pre-filled pen: Each single dose pre-filled pen contains 40 mg of adalimumab in 0.4 ml solution (100 mg/ml). • AMGEVITA 80 mg/0.8 ml solution for injection in pre-filled pen: Each single dose pre-filled pen contains 80 mg of adalimumab in 0.8 ml solution (100 mg/ml).
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

As per the Guideline on Good Pharmacovigilance Practices Module V – Risk management systems (EMA/838713/2011 Rev 2) Part II Module SI may be omitted from the EU RMP for new applications for similar biological products.

Part II: Module SII - Nonclinical Part of the Safety Specification

AMGEVITA is a biosimilar to Humira® (adalimumab). Analytical studies and in vitro pharmacotoxicological studies have been conducted to support biosimilarity. Comparability of AMGEVITA to Humira®, the reference medicinal product, was established through physicochemical and biological characterization studies, as recommended in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

Comparative toxicology studies were performed for detection of any meaningful toxicological differences between AMGEVITA and Humira® (US) in terms of nonclinical safety and toxicokinetics. Humira® that is approved in and sourced from the US (Humira® US) is similar and comparable to Humira® that is approved in and sourced from the EU (Humira® EU) based on the pharmacokinetic similarity that was demonstrated in the phase 1, healthy volunteer Study 20110217. AMGEVITA comparative toxicology to Humira® US studies included a nonterminal study in male cynomolgus monkeys (Study 114832) and a 1-month, terminal repeat-dose study in male and female monkeys (Study 115674). In repeat-dose toxicology studies performed in the cynomolgus monkey, the toxicokinetic profile and expected lymphoid changes due to AMGEVITA were similar to that of Humira® US and no unexpected toxicity was observed. Thus, the nonclinical safety data for Humira® are expected to be relevant for the AMGEVITA risk assessment. The difference in formulation (excipients) between AMGEVITA and Humira® (Section 2.2.2 of Module 2.6.6 Toxicology Written Summary) did not affect AMGEVITA's toxicity profile. Table 2 provides a summary of nonclinical safety findings from AMGEVITA nonclinical studies and the reference medicinal product Humira® nonclinical studies (Scientific Discussion: EMEA-H-481-II-06-AR).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from AMGEVITA studies		
Toxicity Single and repeat dose toxicity 2-week and 1-month repeat-dose toxicity studies in the cynomolgus monkey at 32 mg/kg or 157 mg/kg dosed SC once weekly (Study 114832 and Study 115674) Effects on immune system	Single-dose and repeat-dose toxicokinetic profiles were similar for AMGEVITA and Humira® (US) which is comparable to Humira® (EU). In the 1-month terminal repeat-dose study in male and female monkeys, the expected lymphoid changes for AMGEVITA and Humira® (US) were similar and were characterized by decreased size and number of germinal centers in axillary lymph node, mesenteric lymph node, and tonsil. In the spleen, decreased $CD21^{+}$ B lymphocytes were observed by immunohistochemical staining and by flow cytometry. The lymphoid findings were generally consistent with those observed following treatment of monkeys with adalimumab for 1 or 9 months.	AMGEVITA is a medicinal product which is biosimilar to Humira®. Humira® has been in clinical use as a marketed medicinal product for over 10 years. The pharmacological effects of AMGEVITA on immune system changes in the lymphoid reticular system are similar to those observed for Humira® and are assumed to be relevant for humans. Please note that the 157 mg/kg AMGEVITA dose administered to monkeys in Study 115674 is 275-fold higher by dose and 166-fold higher by exposure (area under the curve) compared to the typical human dose of 40 mg given to a 70 kg person. These changes are consistent with reduced immune surveillance, which may be related to increased incidence of infectious disease. Serious infections and malignancies have been listed as important identified risks for AMGEVITA in Module SVII.3 of the RMP.
Developmental and Reproductive Toxicity; Genotoxicity; Carcinogenicity; Safety pharmacology; Cardiotoxicity; and Drug interactions	In line with the EU guidance on Biosimilar products (Committee for Medicinal Products for Human Use [CHMP] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev 1]) these comparative studies have not been performed for AMGEVITA.	As a biosimilar medicinal product, the observed effects of Humira® are expected for AMGEVITA.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Humira® studies		
Single and repeat dose toxicity		
Single intravenous doses in mice and rats and repeat dose toxicity studies of 4 weeks (32-157 mg/kg bw) and 39 weeks (32-215 mg/kg bw) duration in cynomolgus monkeys. Effects on the immune system	A single dose of Adalimumab appears to be well tolerated up to a dose of almost 2000 times higher than the single human dose. In repeat doses, changes in the lymphoreticular system were noted. Overall, no major toxicological concerns were identified in cynomolgus monkeys (European Medicines Agency European Public Assessment Report: Scientific Discussion, 2006).	Changes in the lymphoid reticular system are consistent with reduced immune surveillance, which may be related to increased incidence of infectious disease. Serious infections and malignancies have been listed as important identified risks for AMGEVITA in Module SVII.3 of the RMP.
Genotoxicity	For Humira®, genotoxicity studies were not performed as they are not applicable for biotechnology-derived pharmaceuticals	Not applicable.
Carcinogenicity	For Humira®, carcinogenicity studies were not conducted because of the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralizing antibodies in rodents (Humira® summary of product characteristics [SmPC], October 2022).	In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. With the current knowledge, a possible risk for the development of lymphomas, leukemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded (Humira® SmPC, October 2022). Malignancies has been listed as an important identified risk for AMGEVITA in Module SVII.3 of the RMP.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Humira® studies (continued)		
Reproductive/ developmental toxicity	In an embryo-foetal/perinatal developmental toxicity study of Humira® conducted in monkeys at doses up to 100 mg/kg, there was no indication of maternal toxicity, embryotoxicity, or teratogenicity. Nonclinical data on fertility or postnatal toxicity of Humira® are not available because of the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralizing antibodies in rodents (Humira® SmPC, October 2022).	A large number (approximately 2100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes did not indicate an increase in the rate of malformation in the newborn. In a prospective cohort registry, there were no distinct differences between adalimumab-treated (n = 257) and untreated women (n = 120) for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies were reported. Due to its inhibition of TNF-α, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Adalimumab should only be used during pregnancy if clearly needed. Therefore, women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Humira® treatment. Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines (eg, Bacillus Calmette-Guérin [BCG] vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy (Humira® SmPC, October 2022). Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, Humira® can be used during breastfeeding (Humira® SmPC, October 2022).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Humira® studies (continued)		
General Safety Pharmacology (Cardiovascular and Respiratory function)	There were no effects of Humira® on cardiovascular and respiratory functions in animal studies.	In a clinical trial with another TNF-antagonist, worsening of congestive heart failure (CHF) and increased mortality due to CHF have been observed. Cases of worsening CHF have also been reported in patients receiving Humira®. Humira® should be used with caution in patients with mild heart failure (New York Heart Association [NYHA] class I/II). Humira® is contraindicated in moderate to severe heart failure (NYHA class III/IV) (Humira® SmPC, October 2022).
Local tolerance	In rabbits, no local intolerance was seen after administration of the formulation intended for marketing. Moreover, no effects at the injection sites (after both intravenous or SC) were seen in various studies in monkeys (European Medicines Agency European Public Assessment Report: Scientific Discussion, 2006).	Based on animal studies no local intolerability of Humira® is expected in humans.

Part II: Module SIII - Clinical Trial Exposure

Total subject exposure by indication in AMGEVITA clinical studies is presented in Table 3. Subject exposure by age/sex group and by race/ethnicity are provided in Table 4 and Table 5, respectively.

Completed Trials

Table 3. Total Subject Exposure to AMGEVITA or Humira® in All Completed Clinical Trials by Product Indication (Safety Analysis Set)

Indication	Exposure to AMGEVITA n (subj-yrs)	Exposure to Humira® n (subj-yrs)
Global phase 1 study	437 (1.20)	136 (0.37)
Japan phase 1 study	91 (0.25)	88 (0.24)
Rheumatoid arthritis	264 (106.00)	262 (108.45)
Rheumatoid arthritis open-label extension	466 (573.33)	-
Psoriasis	437 (210.41)	598 (231.58)
Total	1466 (891.17)	1084 (340.64)

- = not applicable; n = number of subjects exposed to AMGEVITA or Humira®

Note: Subject-years of exposure is calculated as (the last dose date of investigational product - the first dose date of investigational product + 1)/365.25.

Subjects in psoriasis Study 20120263 who initially received Humira® and switched to AMGEVITA after week 16 re-randomization were counted to the Humira® exposure column for the first 16 weeks and were counted to the AMGEVITA exposure column after switching treatment.

Subjects in psoriasis Study 20200497 who were treated in the switching group were counted to the Humira® exposure column during the lead-in period and from week 16 to week 18; and were counted to the AMGEVITA exposure column from week 12 to week 14, and from week 20 to week 28.

Data from completed studies: global phase 1 Study 20110217 (last subject last visit: 26 October 2012); rheumatoid arthritis Study 20120262 (last subject last visit: 19 November 2014); psoriasis Study 20120263 (last subject last visit: 18 March 2015); Japan phase 1 Study 20120176 (last subject last visit: 04 December 2015); rheumatoid arthritis open-label extension Study 20130258 (last subject last visit: 11 April 2016); global phase 1 Study 20200286 (last subject last visit: 03 December 2021); psoriasis Study 20200497 (last subject last visit: 19 December 2022). Of the 466 subjects treated with AMGEVITA in rheumatoid arthritis open-label extension Study 20130258, 229 subjects were previously treated with AMGEVITA and 237 subjects were previously treated with Humira® in rheumatoid arthritis Study 20120262, thus the 229 subjects are not counted again in total subjects.

A study is considered completed if a clinical study report has been finalized and reports unblinded or open-label results.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source Dataset: ADSL, Program: t-cum-subj-exp.sas, Output: t-cum-subj-exp.rtf, Generated on: 10NOV2023 08:54

Table 4. Total Subject Exposure to AMGEVITA or Humira® in All Completed Clinical Trials by Age Group, Sex, and Product Indication (Safety Analysis Set)

Sex Indication	≥ 18 years to < 65 years Exposure to AMGEVITA n (subject-years)	≥ 65 years Exposure to AMGEVITA n (subject-years)	≥ 18 years to < 65 years Exposure to Humira® n (subject-years)	≥ 65 years Exposure to Humira® n (subject-years)
Male				
Global phase 1 studies	227 (0.62)	-	83 (0.23)	-
Japan phase 1 study	40 (0.11)	-	47 (0.13)	-
Rheumatoid arthritis	39 (15.09)	11 (3.85)	38 (16.02)	12 (4.85)
Rheumatoid arthritis open-label extension	69 (86.69)	19 (23.77)	-	-
Psoriasis	277 (131.67)	17 (7.19)	364 (142.49)	33 (14.34)
Total	618 (234.18)	39 (34.81)	532 (158.87)	45 (19.18)
Female				
Global phase 1 studies	210 (0.57)	-	53 (0.15)	-
Japan phase 1 study	51 (0.14)	-	41 (0.11)	-
Rheumatoid arthritis	166 (68.03)	48 (19.03)	159 (65.86)	53 (21.72)
Rheumatoid arthritis open-label extension	294 (362.62)	84 (100.25)	-	-
Psoriasis	128 (64.41)	15 (7.14)	181 (68.86)	20 (5.89)
Total	701 (495.76)	108 (126.42)	434 (134.97)	73 (27.61)

- = not applicable; n = number of subjects exposed to AMGEVITA or Humira®

Note: Subject-years of exposure is calculated as (the last dose date of investigational product - the first dose date of investigational product + 1)/365.25.

Subjects in psoriasis Study 20120263 who initially received Humira® and switched to AMGEVITA after week 16 re-randomization were counted to the Humira® exposure column for the first 16 weeks and were counted to the AMGEVITA exposure column after switching treatment.

Subjects in psoriasis Study 20200497 who were treated in the switching group were counted to the Humira® exposure column during the lead-in period and from week 16 to week 18; and were counted to the AMGEVITA exposure column from week 12 to week 14, and from week 20 to week 28.

[a] Data from completed studies: global phase 1 Study 20110217 (last subject last visit: 26 October 2012); rheumatoid arthritis Study 20120262 (last subject last visit: 19 November 2014); psoriasis Study 20120263 (last subject last visit: 18 March 2015); Japan phase 1 Study 20120176 (last subject last visit: 04 December 2015); rheumatoid arthritis open-label extension Study 20130258 (last subject last visit: 11 April 2016); global phase 1 Study 20200286 (last subject last visit: 03 December 2021); psoriasis Study 20200497 (last subject last visit: 19 December 2022). Of the 466 subjects treated with AMGEVITA in rheumatoid arthritis open-label extension Study 20130258, 229 subjects were previously treated with AMGEVITA and 237 subjects were previously treated with Humira® in rheumatoid arthritis Study 20120262, thus the 229 subjects are not counted again in total subjects.

A study is considered completed if a clinical study report has been finalized and reports unblinded or open-label results.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source Dataset: ADSL, Program: t-cum-exp-age-sex.sas, Output: t-cum-exp-age-sex.rtf, Generated on: 13NOV2023 08:03

Table 5. Total Subject Exposure to AMGEVITA or Humira® in All Completed Clinical Trials by Product Indication and Ethnic Group or Race (Safety Analysis Set)

Indication Ethnic Group Race	Exposure to AMGEVITA n (subject-years)	Exposure to Humira® n (subject-years)
Global phase 1 studies		
Ethnic Group		
Hispanic or Latino	185 (0.51)	4 (0.01)
Not Hispanic or Latino	252 (0.69)	132 (0.36)
Total	437 (1.20)	136 (0.37)
Race		
White	323 (0.88)	118 (0.32)
Black or African American	57 (0.16)	12 (0.03)
Asian	33 (0.09)	0 (0)
Other	2 (0.01)	4 (0.01)
Mixed Race or Other	16 (0.04)	0 (0)
Native Hawaiian or Other Pacific Islander	2 (0.01)	0 (0)
American Indian or Alaska Native	4 (0.01)	2 (0.01)
Total	437 (1.20)	136 (0.37)
Japan phase 1 study		
Ethnic Group		
Not Hispanic or Latino	91 (0.25)	88 (0.24)
Total	91 (0.25)	88 (0.24)
Race		
Asian - first generation Japanese	83 (0.23)	80 (0.22)
Asian - second generation Japanese	8 (0.02)	8 (0.02)
Total	91 (0.25)	88 (0.24)

Footnotes, including abbreviations, are defined on the last page of this table.

Table 5. Total Subject Exposure to AMGEVITA or Humira® in All Completed Clinical Trials by Product Indication and Ethnic Group or Race (Safety Analysis Set)

Indication Ethnic Group Race	Exposure to AMGEVITA n (subject-years)	Exposure to Humira® n (subject-years)
Rheumatoid arthritis		
Ethnic Group		
Hispanic or Latino	33 (13.36)	25 (9.87)
Not Hispanic or Latino	230 (92.22)	236 (98.16)
Not Allowed to Collect	1 (0.42)	1 (0.42)
Total	264 (106.00)	262 (108.45)
Race		
White	251 (100.87)	249 (102.93)
Black or African American	9 (3.44)	12 (5.09)
Asian	3 (1.30)	0 (0)
Other	1 (0.39)	1 (0.43)
Total	264 (106.00)	262 (108.45)
Rheumatoid arthritis open-label extension		
Ethnic Group		
Hispanic or Latino	45 (51.51)	-
Not Hispanic or Latino	419 (519.20)	-
Not Allowed to Collect	2 (2.61)	-
Total	466 (573.33)	-
Race		
White	441 (543.93)	-
Black or African American	20 (23.17)	-
Asian	3 (3.93)	-
Other	2 (2.30)	-
Total	466 (573.33)	-

Footnotes, including abbreviations, are defined on the last page of this table.

Table 5. Total Subject Exposure to AMGEVITA or Humira® in All Completed Clinical Trials by Product Indication and Ethnic Group or Race (Safety Analysis Set)

Indication Ethnic Group Race	Exposure to AMGEVITA n (subject-years)	Exposure to Humira n (subject-years)
Psoriasis		
Ethnic Group		
Hispanic or Latino	32 (8.53)	75 (26.03)
Not Hispanic or Latino	401 (200.02)	519 (204.09)
Not Allowed to Collect	3 (1.65)	3 (1.24)
Unknown	1 (0.21)	1 (0.22)
Total	437 (210.41)	598 (231.58)
Race		
White	397 (195.03)	529 (207.89)
Black or African American	5 (1.41)	14 (3.98)
Asian	22 (8.79)	31 (11.68)
Other	6 (2.35)	13 (4.31)
Unknown	3 (1.65)	3 (1.24)
Mixed Race or Other	1 (0.18)	2 (0.54)
Native Hawaiian or Other Pacific Islander	1 (0.61)	1 (0.25)
American Indian or Alaska Native	2 (0.39)	5 (1.68)
Total	437 (210.41)	598 (231.58)

- = not applicable; n = number of subjects exposed to AMGEVITA or Humira®

Note: Subject-years of exposure is calculated as (the last dose date of investigational product - the first dose date of investigational product + 1)/365.25.

Subjects in psoriasis Study 20120263 who initially received Humira® and switched to AMGEVITA after week 16 re-randomization were counted to the Humira® exposure column for the first 16 weeks and were counted to the AMGEVITA exposure column after switching treatment.

Subjects in psoriasis Study 20200497 who were treated in the switching group were counted to the Humira® exposure column during the lead-in period and from week 16 to week 18; and were counted to the AMGEVITA exposure column from week 12 to week 14, and from week 20 to week 28.

Data from completed studies: global phase 1 Study 20110217 (last subject last visit: 26 October 2012); rheumatoid arthritis Study 20120262 (last subject last visit: 19 November 2014); psoriasis Study 20120263 (last subject last visit: 18 March 2015); Japan phase 1 Study 20120176 (last subject last visit: 04 December 2015); rheumatoid arthritis open-label extension Study 20130258 (last subject last visit: 11 April 2016); global phase 1 Study 20200286 (last subject last visit: 03 December 2021); psoriasis Study 20200497 (last subject last visit: 19 December 2022). Of the 466 subjects treated with AMGEVITA in rheumatoid arthritis open-label extension study 20130258, 229 subjects were previously treated with AMGEVITA and 237 subjects were previously treated with Humira® in rheumatoid arthritis study 20120262, thus the 229 subjects are not counted again in total subjects.

A study is considered completed if a clinical study report has been finalized and reports unblinded or open-label results.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source Dataset: ADSL, Program: t-cum-exp-race.sas, Output: t-cum-exp-race.rtf, Generated on: 13NOV2023 12:43

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

AMGEVITA has been developed as a biosimilar for Humira®. Important exclusion criteria listed for AMGEVITA reflect exclusion criteria presented in the EU RMP for Humira®. Table 6 reflects the important exclusion criteria for AMGEVITA.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients	AMGEVITA is immunologically similar to the reference medicinal product.	No	It is not recommended for use in patients with known hypersensitivity to active substance or excipients. Contraindicated for the reference medicinal product, Humira® and AMGEVITA.
Active tuberculosis (TB) or other severe infections such as sepsis and opportunistic infections	AMGEVITA has immunosuppressive effects similar to the reference medicinal product.	No	Due to immunosuppressant effect patients are at increased risk of serious infections including active TB, sepsis, and opportunistic infections. Contraindicated for the reference medicinal product, Humira® and AMGEVITA.
Moderate to severe heart failure (NYHA class III or IV)	AMGEVITA is structurally, functionally, and clinically similar to the reference medicinal product.	No	Treatment for patients with class III or IV heart failure is not recommended. This is based on studies in patients with CHF and other TNF inhibitors including Humira® which showed an increased risk for worsening of CHF. Contraindicated for the reference medicinal product, Humira® and AMGEVITA.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Patients with immune-compromised conditions	These patient subpopulations are known to have a high risk for adverse events in the context of the reference medicinal product. AMGEVITA is highly similar to the reference medicinal product.	No	A safety signal for Humira® in this patient population has not been observed from standard safety surveillance and is applicable to AMGEVITA.
Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease	AMGEVITA is approved for use in Crohn's disease based on extrapolation from the data in RA and Psoriasis.	Yes	Not applicable
Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis	The other indications were approved by extrapolation.	Yes	Not applicable
Long-term safety data in the treatment of children with uveitis	Not applicable	Yes	Not applicable
Subject treated with other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives (whichever is longer) prior to the baseline visit and included: anakinra, etanercept within 1 month prior to first dose of investigational product; infliximab, abatacept, tocilizumab, golimumab, certolizumab within 3 months prior to first dose of investigational product; rituximab within 9 months prior to investigational product along with evidence of B cell recovery	Considered standard criterion due to missing information on unknown effects in patients regarding potential interactions with investigational biologic or drug. A potential bias on the efficacy and safety results of the study can be avoided by this criterion.	No	A safety signal for Humira® and concomitant use of an investigational drug has not been observed from postmarketing observational studies and postmarketing spontaneous reports and is applicable to AMGEVITA.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Recurrent or chronic infections	A potential bias on the efficacy and safety results of the study can be avoided by this criterion.	No	In line with the reference medicinal product, Humira®, chronic infections are currently addressed in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.
Any active infection for which systemic anti-infectives were used within 28 days prior to first dose of investigational product. A serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first dose of investigational product	A potential bias on the efficacy and safety results of the study can be avoided by this criterion.	No	In line with the reference medicinal product, Humira®, language concerning infections is currently in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC. Patients with adequately treated infections may begin or restart the use of AMGEVITA.
History of neurologic symptoms suggestive of central nervous system demyelinating diseases	Demyelinating disease could be activated by TNF-antagonists including Humira® and AMGEVITA.	No	In line with the reference medicinal product, Humira®, language concerning demyelination is currently addressed in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.
Known history of human immunodeficiency virus (HIV) and history of invasive infection (eg, listeriosis and histoplasmosis)	Use in patients with infections that commonly become latent or HIV, which results in an immunocompromised state, is not recommended.	No	In line with the reference medicinal product, Humira®, language concerning infections is currently in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subjects with an active systemic viral infection or any active viral infection that in the opinion of the investigator, could cause this study to be detrimental to the subject	To avoid the impact of known immunosuppression effect in patients with systemic viral infection or active viral infection.	No	In line with the reference medicinal product, Humira®, language concerning infections is currently addressed in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.
Hepatitis B surface antigen, hepatitis B virus (HBV) core antibody/ hepatitis B surface antibody, or hepatitis C virus antibody positivity at screening	Patients who received TNF-antagonists have had reactivation of hepatitis B.	No	In line with the reference medicinal product, Humira®, language concerning reactivation of hepatitis B is currently addressed in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.
Recent cerebrovascular accident (CVA) and any other condition that in the opinion of the investigator, could cause this study to be detrimental to the subject	This criterion allows the investigator to consider the impact of other factors that may affect the overall results of the study.	No	In line with the reference medicinal product, Humira®, language concerning CVAs is currently addressed in Section 4.8 “Undesirable effects” of the AMGEVITA SmPC.
Malignancy within 5 years except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma	Patients with risk of some cancers although treated are at an increased risk of recurrence. These patients have not been studied with Humira® and AMGEVITA and no information is available.	No	In line with the reference medicinal product, Humira®, language concerning malignancy is currently addressed in Section 4.4 "Special warnings and precautions for use" of the AMGEVITA SmPC.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Active substance abuse (within 24 weeks of screening) was an exclusion criterion for AMGEVITA clinical studies. History of drug and alcohol abuse for the past 12 months was used as an exclusion criteria for Humira® clinical studies	To avoid potential bias on the overall results of the study including efficacy and safety.	No	There are no postmarketing reports that indicate a safety signal with use of Humira® and AMGEVITA in this patient population.
For adult trials: Clinically significant abnormal screening laboratory results as evaluated by the investigator: hemoglobin < 9 g/dL; platelet count < 100 000/mm^3; white blood cell count < 3000 cells/mm^3; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 2.0 x the upper limit of normal (ULN); creatinine clearance < 50 mL/min (Cockroft-Gault formula); any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.	To avoid the impact of lab abnormalities on the safety data of the study.	No	In line with the reference medicinal product, Humira®, language concerning elevated liver enzymes and hematologic abnormalities is currently addressed in Section 4.8 "Undesirable effects" of the AMGEVITA SmPC.

Table 6. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
For Psoriasis study Subject diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (eg, eczema).	To avoid impact on the overall results of the study including efficacy and safety.	No	There are no postmarketing reports that indicate a safety signal with use of Humira® and AMGEVITA in this patient population.

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SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, this is a biosimilar medicinal product and there is extensive experience of clinical and postmarketing use of the reference medicinal product Humira®.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 7. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women have not been studied in AMGEVITA and reference medicinal product Humira® clinical programs. A total of 257 pregnant women treated with Humira® for RA or Crohn's disease were enrolled in a prospective cohort registry (Humira® SmPC, October 2022). Results of this registry are summarized in Table 2.
Breastfeeding women	Breastfeeding women have not been studied in AMGEVITA and reference medicinal product Humira® clinical programs.
Patients with relevant comorbidities	
Patients with hepatic impairment	Patients with hepatic impairment have not been studied in AMGEVITA and reference medicinal product Humira® clinical programs.
Patients with renal impairment	Patients with renal impairment have not been studied in AMGEVITA and reference medicinal product Humira® clinical programs.
Patients with cardiovascular impairment	Data not available.
Immunocompromised patients	Immunocompromised patients have not been studied in AMGEVITA and reference medicinal product Humira® clinical programs.
Patients with a disease severity different from inclusion criteria in clinical trials	More severe forms and less severe forms of disease indications are not approved for Humira® and applicable to AMGEVITA.
Population with relevant different ethnic origin	AMGEVITA and Humira® have been studied in subject populations that included men and women of a variety of racial backgrounds and ethnicity in clinical studies.
Subpopulations carrying relevant genetic polymorphisms	No relevant polymorphisms are known that impact anti-TNF agents including Humira® and AMGEVITA.

Table 7. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Other	
Pediatric patients	Pediatric patients were not studied in the AMGEVITA clinical program as per the Guidelines for Biosimilars (Regulation [EC] No 1901/2006 [Paediatric Regulation] amended by Regulation [EC] No 1902/2008).
Elderly patients	The elderly age group (over 65 years) was studied in the AMGEVITA RA and Psoriasis clinical study program. Patients with comorbid conditions including cardiac disorders, diabetes, and the use of multiple concomitant medications were not studied in the AMGEVITA clinical studies in line with the reference medicinal product, Humira®.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person-count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

Table 8. Estimated Number of Patient-years of Exposure to AMGEVITA, by Region, in the Postmarketing Setting

Region	Cumulative[a]
Australia and New Zealand	8642
Europe	357 578
Global	415 022

Europe = European Union, European Economic Area, Switzerland, and the United Kingdom;

[a] Cumulative through 31 December 2022.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed. The reference medicinal product, Humira®, is not associated with any abuse potential.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 9. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Reclassification of Safety Concerns		
Missing Information		
Patients With Immune-compromised Conditions	The missing information of 'patients with immune-compromised conditions' was removed from the RMP	This safety concern was removed with submission of this EU RMP to align with the reference medicinal product Humira®
Long-term safety data in the treatment of adults and children with uveitis	The missing information of 'long-term safety data in the treatment of adults and children with uveitis' was reclassified as 'long-term safety data in the treatment of children with uveitis'	This safety concern was reclassified with submission of this EU RMP to align with the reference medicinal product Humira®

EU = European Union; RMP = Risk Management Plan

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified risks, important potential risks, and missing information presented in Sections SVII.3.1 and SVII.3.2 for AMGEVITA are presented as per Humira®.

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 10. Important Identified Risk: Serious Infections

Potential mechanisms	Tumor necrosis factor antagonists, may affect host defense against infection possibly by mediating inflammation and modulating cellular immune response. Thus, serious infections are the most frequently reported serious adverse events of interest across indications for the anti-TNF drug class.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, October 2022 and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Study 20120262 (RA): The subject incidence of adverse events of infections and infestations was 23.1% (61 of 264 subjects) in the AMGEVITA treatment group; and 26.0% (68 of 262 subjects) in the Humira® group. Study 20130258 (RA OLE): Results from the RA OLE Study 20130258 were similar to Study 20120262. No new safety concerns were identified. Study 20120263 (Psoriasis): In the pivotal adult psoriasis study of AMGEVITA, through week 16, overall subject incidence of adverse events of infection and infestations was 33.9% (59 of 174 subjects) in AMGEVITA group and 33.5% (58 of 173 subjects) in the Humira® group. In the re-randomized group post week 16 subject incidence of adverse events of infection was 44.1% (67 of 152 subjects) in AMGEVITA/AMGEVITA group; and 36.7% (29 of 79 subjects) in Humira®/Humira® group; and 48.1% (37 of 77 subjects) in the Humira®/AMGEVITA group. Study 20200497 (Psoriasis): Serious infections were reported in no subjects in the switching group (switching from Humira® to AMGEVITA twice) and 2 (1.0%) subjects (diverticulitis intestinal perforated and tuberculosis) in the continued use group. **Humira® studies** In the pivotal controlled studies of Humira® in adults and children, the rate of infection was 1.51 per PY in the Humira®-treated patients and 1.46 per PY in the placebo and active control-treated patients. Most patients continued on Humira® after the infection resolved. The incidence of serious infections was 0.04 per PY in Humira®-treated patients and 0.03 per PY in placebo and active-control treated patients (Humira® SmPC, October 2022).

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Identified Risk: Serious Infections

Characterization of the risk (continued)	
Severity	The majority of infection events in the AMGEVITA group were mild or moderate in severity, which was comparable with the Humira® comparator group. No fatal infection events were reported in AMGEVITA clinical studies.
Reversibility	Serious infections may resolve with appropriate management. However, fatal outcomes associated with infections have been reported for Humira® (Humira® SmPC, October 2022).
Long-term outcomes	Long-term outcome data are not available for this risk for AMGEVITA, but are expected to be comparable to Humira®.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of the infection. Hospitalization or fatal outcomes have been reported for Humira® (Humira® SmPC, October 2022).
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, 2002).
Preventability	Clinicians must consider patient comorbidities, concomitant treatment and infection history when actively monitoring their patients for infection while treating with anti-TNF agents.
Impact on the risk-benefit balance of the product	The risk of serious infections has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the Patient Reminder Card.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

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OLE = open-label extension; PY = patient year; RA = rheumatoid arthritis; SmPC = summary of product characteristics; TNF = tumor necrosis factor

Table 11. Important Identified Risk: Tuberculosis

Potential mechanisms	Tumor necrosis factor antagonists may affect host defense against infection possibly by mediating inflammation and modulating cellular immune response.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, October 2022 and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Study 20120262 (RA) and Study 20130258 (RA OLE): There were no cases of tuberculosis reported. Study 20120263 (Psoriasis): There were no cases of tuberculosis in the AMGEVITA group and 1 case of latent tuberculosis reported in the Humira® group. Study 20200497 (Psoriasis): One of the events of serious infections in the continued use group (0.5%) was reported to be tuberculosis. **Humira® studies:** Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection) have been reported uncommonly in clinical trials and in the postmarketing setting (Humira® SmPC, October 2022).
Severity	The event of latent tuberculosis in the Humira® group was severe.
Reversibility	Tuberculosis may resolve with appropriate management. However, in controlled and open-label adult and pediatric studies with Humira®, serious infections (including fatal infections) have been reported, which include reports of TB (including miliary and extra-pulmonary locations) (Humira® SmPC, October 2022).
Long-term outcomes	Long-term outcome data are not available for this risk for AMGEVITA, but are expected to be comparable to Humira®. Recurrence of TB has been reported during treatment with Humira® (Humira® SmPC, October 2022).
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of the infection. Fatal outcomes have been reported for Humira® (Humira® SmPC, October 2022).
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, 2002).
Preventability	Clinicians must consider patient comorbidities, concomitant treatment and infection history when actively monitoring their patients for infection while treating with anti-TNF agents. All patients must be screened for latent TB before initiating anti-TNF agents.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 11. Important Identified Risk: Tuberculosis

Impact on the risk-benefit balance of the product	The risk of tuberculosis has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the Patient Reminder Card.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®. However, there is a potential for increased rates of TB transmission in regions with larger populations with TB risk factors or risk groups.

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OLE = open-label extension; RA = rheumatoid arthritis; SmPC = summary of product characteristics; TB = tuberculosis; TNF = tumor necrosis factor

Table 12. Important Identified Risk: Malignancies

Potential mechanisms	Alterations in T-cell mediated immunity may be a possible mechanism of action in the development of malignancies. However, exact mechanisms are unknown.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medical product Humira®. Evidence sources: Literature reports (Burmester et al, 2014; Burmester et al, 2013); Humira® United States prescribing information [USPI], March 2020; Humira® SmPC, October 2022; and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Study 20120262 (RA): In the pivotal adult RA study of AMGEVITA, 1 subject (0.4%) in the AMGEVITA treatment group experienced 2 events of non-melanoma skin cancer (NMSC): basal cell carcinoma (left shoulder) and squamous cell carcinoma (left thigh). In the Humira® treatment group, 1 subject (0.4%) experienced 1 event of squamous cell carcinoma of the skin (cheek and scalp). No cases of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukemia, melanoma, or Merkel cell carcinoma were reported. Other malignancies were reported in no subjects (0%) in the AMGEVITA group and 3 subjects (1.1%) in the Humira® group. Study 20130258 (RA OLE): There was 1 case of diffuse large B-cell lymphoma reported in the AMGEVITA/AMGEVITA group. Results for NMSC were similar to those for Study 20120262. No cases of HSTCL, leukemia, melanoma, or Merkel cell carcinoma were reported. Other malignancies were reported in 2 subjects (0.9%) in the AMGEVITA/AMGEVITA group and 2 subjects (0.8%) in the Humira®/AMGEVITA. Study 20120263 (Psoriasis): In the pivotal adult psoriasis study of AMGEVITA, post week 16, in the AMGEVITA/AMGEVITA group 1 subject (0.7%) had 1 event of squamous cell carcinoma. The subject incidence of melanoma was 0.6% (1 of 174 subjects) in the AMGEVITA treatment group in the pivotal study of psoriasis through week 16. None were reported in the re-randomized post week 16 period. No cases of lymphoma, HSTCL, leukemia, or Merkel cell carcinoma were reported. Other malignancies were reported in no subjects (0%) in the AMGEVITA group and 1 subject (0.6%) in the Humira® group. Study 20200497 (Psoriasis): Malignancies were reported in 1 (0.5%) subject (basal cell carcinoma) in the switching group and no subjects in the continued use group.

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 12. Important Identified Risk: Malignancies

Characterization of the risk	
Frequency (continued)	**Humira® studies:** In the postmarketing long-term observational study of Humira® in RA population standardized incidence ratio for lymphomas was 1.99 (95% CI: 1.11 to 15 observed/7.55 expected). Data for events of lymphoma derived from 71 Humira® global clinical trials including randomized controlled trials, open-label trials and long-term extension studies showed standardized incidence ratio of lymphoma in RA subjects was 2.74 (95% CI: 1.83, 3.93); 1.93 (95% CI: 0.03, 10.7) in ankylosing spondylitis subjects; 5.88 (95% CI: 0.66, 21.2) in psoriatic arthritis subjects; 0.63 (95% CI: 0.01, 3.49) in psoriasis subjects; and 2.58 (95% CI: 0.29, 9.31) in Crohn's disease subjects (Burmester et al, 2014). During controlled portions of pivotal Humira® trials in adults of at least 12 weeks in duration, malignancies other than lymphoma and NMSC were observed at a rate of 6.8 per 1000 PYs (95% CI: 4.4, 10.5) among Humira®-treated patients and 6.3 per 1000 PYs (95% CI: 3.4, 11.8) among control patients; the rate of lymphomas was 0.7 per 1000 PYs (95% CI: 0.2, 2.7) among Humira®-treated patients and 0.6 per 1000 PYs (95% CI: 0.1, 4.5) among control patients; and the rate of NMSC was 8.8 per 1000 PYs (95% CI: 6.0, 13.0) among Humira®-treated patients and 3.2 per 1000 PYs (95% CI: 1.3, 7.6) among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates of 2.7 per 1000 PYs (95% CI: 1.4, 5.4) among Humira®-treated patients and 0.6 per 1000 PYs (95% CI: 0.1, 4.5) among control patients (Humira® SmPC, October 2022). Fatal cases of lymphoma have been reported among children, adolescents, and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Humira® in the postmarketing setting (Humira® SmPC, October 2022). In randomized controlled trials, open-label clinical trials and long-term extension studies of Humira® in psoriasis, the standardized incidence ratio for melanoma was 4.37 (95% CI: 1.89, 8.61). In patients with RA, the standardized incidence ratio for melanoma was of 1.5 (95% CI: 0.84, 2.47) and did not show a higher incidence relative to the general population (Burmester et al, 2013). In the postmarketing setting, rare cases of HSTCL have been reported in patients treated with Humira® (Humira® SmPC, October 2022). Cases of leukemia (rare) and Merkel cell carcinoma (frequency not known) have been reported in clinical trials and postmarketing setting (Humira® USPI, March 2020; Humira® SmPC, October 2022).
Severity	The event of diffuse large B-cell lymphoma reported in association with AMGEVITA was considered severe. Fatal outcomes have been observed in Humira® clinical trials. No cases of HSTCL, leukemia, or Merkel cell carcinoma were reported in AMGEVITA clinical studies. All events of basal cell carcinoma and squamous cell carcinoma were mild in severity. The serious event of lentigo malignant in the Psoriasis study at week 16 was severe. The majority of the reported cases of other malignancies ranged from mild to severe.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 12. Important Identified Risk: Malignancies

Characterization of the risk (continued)	
Reversibility	Malignancies including lymphoma, leukemia, and melanoma may resolve with appropriate treatment; however, these events may be fatal. Hepatosplenic T-cell lymphoma is rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal. Events of NMSC generally resolve with appropriate treatment. Patients would require treatment if Merkel cell carcinoma occurs; this disease may have a fatal outcome.
Long-term outcomes	Long-term outcome data are not available for this risk for AMGEVITA, but are expected to be comparable to Humira®. Fatal events of lymphoma, leukemia, and HSTCL have been reported in patients treated with Humira® (Humira® SmPC, October 2022).
Impact on quality of life	The impact on the individual depends on the general health of the patient and the clinical stage of the malignancy. Hepatosplenic T-cell lymphoma is usually fatal.
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 HIV/acquired immune deficiency syndrome [AIDS]) and among individuals with certain auto-immune diseases (ie, RA, systemic lupus erythematosis, psoriasis, Sjogren's syndrome, and celiac disease, etc) (Zhang et al, 2011). Risk factors for Hodgkin's lymphoma include genetic predisposition, Epstein-Barr virus infection, HIV infection and immune diseases (Mani and Jaffe, 2009). Some events of HSTCL reported with Humira® have occurred in young adult patients on concomitant treatment with AZA or 6-MP used for inflammatory bowel disease (Humira® SmPC, October 2022). Established risk factors for HSTCL 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, RA, systemic lupus erythematosis, psoriasis, Sjogren's syndrome, celiac disease, etc) (Zhang et al, 2011). 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, 1999).

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 12. Important Identified Risk: Malignancies

Risk factors and risk groups (continued)	The risk of NMSC and melanoma may be higher in patients who are predisposed to this event. Significant risk factors for NMSC 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, 2007; Miller and Weinstock, 1994). 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, 2006). 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, 2015; Becker, 2010; Agelli and Clegg, 2003). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Preventability	All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of psoralen plus ultraviolet A (PUVA) treatment should be examined for the presence of NMSC before and during treatment with AMGEVITA. Avoidance of ultraviolet radiation exposure and patient education through product labeling may reduce the risk of melanoma and Merkel cell carcinoma. For other types of malignancies, no preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of malignancies has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through use of the Patient Reminder Card.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

AIDS = acquired immune deficiency syndrome; AZA = azathioprine; HIV = human immunodeficiency virus; HSTCL = hepatosplenic T-cell lymphoma; NMSC = non-melanoma skin cancer; OLE = open-label extension; PUVA = psoralen plus ultraviolet A; PY = patient year; RA = rheumatoid arthritis; SmPC = summary of product characteristics; USPI = United States prescribing information

Table 13. Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

Potential mechanisms	Possibly by alteration of T-cell mediated immunity.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medical product Humira®. Evidence sources: Literature report (Burmester et al, 2013) and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Studies 20120262 (RA), 20130258 (RA OLE), 20120263 (Psoriasis), and 20200497 (Psoriasis): No cases of demyelinating disorders were reported. **Humira® studies:** The incidence rate of serious demyelinating disorders is low and uncommon and in clinical trials reported to be < 0.1 per 100 PYs of exposure in RA, ankylosing spondylitis and 0.1 per 100 PYs in Crohn's disease (Burmester et al, 2013).
Severity	No cases of demyelinating disorders were reported in AMGEVITA clinical studies. New onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome have been reported in association with TNF-antagonists including Humira® (Humira® SmPC, October 2022). These diseases may involve serious disability and death.
Reversibility	Demyelinating disorders are not reversible but associated disability may improve with treatment.
Long-term outcomes	Long-term outcome data are not available for this risk; some cases may result in disability or death.
Impact on quality of life	The impact on the individual depends on the general health of the patient and severity of demyelinating disease.

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Footnotes, including abbreviations are defined on the last page of this table.

Table 13. Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

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 infection, and smoking behavior are strongly implicated and able to influence genetic predisposition to multiple sclerosis (Disanto et al, 2012). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Preventability	Exercise caution in considering the use of AMGEVITA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of AMGEVITA and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.
Impact on the risk-benefit balance of the product	The risk of demyelinating disorders has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the Patient Reminder Card.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

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OLE = open-label extension; PY = patient year; RA = rheumatoid arthritis; SmPC = summary of product characteristics; TNF = tumor necrosis factor

Table 14. Important Identified Risk: BCG Disease Following Live BCG Vaccination in Infants With In Utero Exposure to AMGEVITA

Potential mechanisms	Alterations in T-cell mediated immunity may be a possible mechanism of action.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medical product Humira®. Evidence sources: Humira® SmPC, October 2022 and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Studies 20120262 (RA), 20130258 (RA OLE), 20120263 (Psoriasis), and 20200497 (Psoriasis): No cases of BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA were reported. **Humira® studies:** No data available.
Severity	No cases of BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA were reported in AMGEVITA clinical studies.
Reversibility	No data available.
Long-term outcomes	No data available.
Impact on quality of life	No data available.
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.
Preventability	AMGEVITA should only be used during pregnancy if clearly needed. AMGEVITA may cross the placenta into the serum of infants and these infants may be at increased risk for infection. 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.
Impact on the risk-benefit balance of the product	The risk of BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the Patient Reminder Card.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

BCG = Bacillus Calmette-Guérin; OLE = open-label extension; RA = rheumatoid arthritis; SmPC = summary of product characteristics

Table 15. Important Potential Risk: Progressive Multifocal Leukoencephalopathy

Potential mechanisms	The mechanism is unknown.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medical product Humira®. Evidence sources: Published literature (Burmester et al, 2013) and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Studies 20120262 (RA), 20130258 (RA OLE), 20120263 (Psoriasis), and 20200497 (Psoriasis): No cases of progressive multifocal leukoencephalopathy (PML) were reported. **Humira® studies:** No cases of PML were reported in Humira® clinical trials (Burmester et al, 2013).
Severity	No cases of PML were reported in AMGEVITA clinical studies.
Reversibility	Serious neurological disability associated with PML may not be fully reversible and would require treatment. Severe events may result in death.
Long-term outcomes	Long-term outcome data are not available for this risk.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of PML.
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 RA and other rheumatic conditions, particularly in those using cytotoxic and biologic therapies including rituximab, natalizumab, efalizumab, and less commonly TNF inhibitors (Bharat et al, 2012). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Preventability	Adequate treatment of the immune disorders and infections.
Impact on the risk-benefit balance of the product	The risk of progressive multifocal leukoencephalopathy has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

HIV = human immunodeficiency virus; OLE = open-label extension; PML = progressive multifocal leukoencephalopathy; RA = rheumatoid arthritis; TNF = tumor necrosis factor

Table 16. Important Potential Risk: Reversible Posterior Leukoencephalopathy Syndrome

Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medical product Humira®. Evidence sources: Case reports and AMGEVITA clinical studies of RA and Psoriasis.
Characterization of the risk	
Frequency	**AMGEVITA studies:** Studies 20120262 (RA), 20130258 (RA OLE), 20120263 (Psoriasis), and 20200497 (Psoriasis): No cases of reversible posterior leukoencephalopathy syndrome (RPLS) were reported. **Humira® studies:** There were no reports of RPLS in clinical studies. Isolated cases of RPLS have been reported in the postmarketing setting.
Severity	No cases of RPLS were reported in AMGEVITA clinical studies.
Reversibility	Early recognition of this condition is of paramount importance because prompt control of blood pressure or withdrawal of immunosuppressive agents will cause reversal of the syndrome. Serious disability and death may occur with this risk.
Long-term outcomes	Long-term outcome data are not available for this risk.
Impact on quality of life	The impact on the individual patient depends on the patient's health status as well as the severity of the RPLS.
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, 2001). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	The risk of reversible posterior leukoencephalopathy syndrome has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

OLE = open-label extension; RA = rheumatoid arthritis; RPLS = reversible posterior leukoencephalopathy syndrome

Table 17. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis Patients

Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medical product Humira®. Evidence source: Humira® SmPC, October 2022.
Characterization of the risk	
Frequency	This risk is not applicable for AMGEVITA studies of RA, RA OLE, and Psoriasis. **Humira® studies:** With current data, it is not known if Humira® treatment influences the risk for developing dysplasia or colon cancer (Humira® SmPC, October 2022).
Severity	Data not available.
Reversibility	Patients would require treatment if adenocarcinoma of colon occurs in ulcerative colitis patients. This event may result in death.
Long-term outcomes	Long-term outcome data are not available for this risk.
Impact on quality of life	The impact on the individual depends on the general health of the patient and the severity of adenocarcinoma of colon.
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, 2008). No additional risk factors or risk groups specific for patients treated with AMGEVITA are known.
Preventability	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 history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.
Impact on the risk-benefit balance of the product	The risk of adenocarcinoma of colon in ulcerative colitis patients has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Humira®.

OLE = open-label extension; RA = rheumatoid arthritis; SmPC = summary of product characteristics

SVII.3.2 Presentation of the Missing Information

Table 18. Missing Information: Long-term Safety Information in the Treatment of Children, Aged From 6 Years to Less Than 18 Years With Crohn's Disease

Evidence source	Missing information for AMGEVITA is presented as per Humira®. A total of 192 pediatric patients aged from 6 to 17 years with an exposure of 498.1 PY were included in a multicenter, randomized, double-blind clinical trial of Humira® in pediatric patients with moderate to severe Crohn's disease (Humira® SmPC, October 2022).
Population in need of further characterization	Pediatric patients were not studied in AMGEVITA clinical program as per the Guidelines for Biosimilars (Regulation [EC] No 1901/2006 [Paediatric Regulation] amended by Regulation [EC] No 1902/2008).

PY = patient year; SmPC = summary of product characteristics

Table 19. Missing Information: Episodic Treatment in Psoriasis, Ulcerative Colitis, and Juvenile Idiopathic Arthritis

Evidence source	Missing information for AMGEVITA is presented as per Humira®.
Population in need of further characterization	The safety and efficacy of Humira® in these patient groups have not been established and as biosimilar medicinal product is applicable for AMGEVITA.

Table 20. Missing Information: Long-term Safety Data in the Treatment of Children With Uveitis

Evidence source	Missing information for AMGEVITA is presented as per Humira®. A total of 443 adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, were included in 2 randomized, double-masked, placebo-controlled studies of Humira®. An uncontrolled long-term extension of these studies included 424 subjects, of which 269 eligible, evaluable patients reached 78 weeks of open-label Humira® treatment. A total of 90 pediatric patients from 2 to < 18 years of age with active juvenile idiopathic arthritis-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment were included in a randomized, double-masked, controlled study (Humira® SmPC, October 2022).
Population in need of further characterization	The long-term safety of Humira® in this patient population has not been established and as biosimilar medicinal product is applicable for AMGEVITA.

SmPC = summary of product characteristics

Table 21. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Evidence source	Missing information for AMGEVITA is presented as per Humira®.
Population in need of further characterization	The long-term safety of Humira® in this patient group has not been established and as biosimilar medicinal product is applicable for AMGEVITA.

SmPC = summary of product characteristics

Part II: Module SVIII - Summary of the Safety Concerns

Table 22. Summary of Safety Concerns

Important identified risks	Serious infections
	Tuberculosis
	Malignancies
	Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)
	BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA
Important potential risks	Progressive multifocal leukoencephalopathy
	Reversible posterior leukoencephalopathy syndrome
	Adenocarcinoma of colon in ulcerative colitis patients
Missing information	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 children with uveitis
	Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

BCG = Bacillus Calmette-Guérin

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 23.

Table 23. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible.	All safety concerns	To monitor if there are any batch-specific issues in the postmarketing environment.	Not applicable

III.2 Additional Pharmacovigilance Activities

Table 24. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
(AMGEVITA) 20160264 A prospective observational study to evaluate long-term safety of AMGEVITA in patients with rheumatoid arthritis Category 3 Ongoing	Primary objectives: • To estimate the incidence rates of serious infections (ie, infectious events which required IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) Secondary objective: • Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA • Estimate the incidence rates of the safety concerns from both the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) anti-TNF and Non-biologic Disease-modifying Antirheumatic Drug (nbDMARD) comparison cohorts Safety concerns addressed include: • Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Long-term, non-interventional, observational, postauthorization safety study of RA patients initiating AMGEVITA utilizing data from the British Society for Rheumatology Biologics Register	Adult males and females (≥ 18 years) with RA identified on the registry initiating AMGEVITA	Protocol submission: 2019 2Q 1st annual report submitted: 2020 4Q Interim reports no longer an EMA requirement after the first report was submitted Final report: 2028 2Q

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned AMGEVITA category 1 or 2 studies.

Table 25. (Table Part IV.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
(AMGEVITA) 20160264 A prospective observational study to evaluate long-term safety of AMGEVITA in patients with rheumatoid arthritis Ongoing	Primary objectives: • To estimate the incidence rates of serious infections (ie, infectious events which required IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) Secondary objective: • Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA • Estimate the incidence rates of the safety concerns from both the BSRBR-RA anti-TNF and nbDMARD comparison cohorts	• Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Protocol submission Interim reports Final report	2019 2Q (submitted) 1st annual report submitted: 2020 4Q Interim reports no longer an EMA requirement after the first report was submitted 2028 2Q

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

The safety information in the AMGEVITA SmPC is aligned to the reference medicinal product Humira®.

V.1 Routine Risk Minimization Measures

Table 26. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Serious infections	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Dose interruption if a serious infection occurs is described in SmPC Section 4.2. • Close monitoring for infections before, during, and after treatment with AMGEVITA and discontinuation of AMGEVITA should a new serious infection or sepsis occur are described in SmPC Section 4.4. • Symptoms of infection, interruption of treatment with AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept due to increased risk of serious infection is described in PL Section 2. • Symptoms of infection are described in PL Section 4.
Tuberculosis	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Dose interruption if a serious infection occurs is described in SmPC Section 4.2. • Close monitoring for TB before, during, and after treatment with AMGEVITA; treatment of latent TB before initiation of AMGEVITA; and discontinuation of AMGEVITA should a new serious infection or sepsis occur, are described in SmPC Section 4.4. • Symptoms of TB, interruption of treatment with AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept due to increased risk of serious infection is described in PL Section 2.

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 26. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Malignancies	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Examination for the presence of NMSC prior to and during treatment with AMGEVITA is described in SmPC Section 4.4. • Appearance of new skin lesions or change in the appearance of existing lesions during or after AMGEVITA therapy is described in PL Section 2.
Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Neurologic evaluation in patients with non-infectious intermediate uveitis prior to the initiation of AMGEVITA therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders is described in SmPC Section 4.4. • Symptoms of demyelinating disease are described in PL Sections 2 and 4.
BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA	Routine risk communication: • SmPC Sections 4.4 and 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • 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 in SmPC Sections 4.4 and 4.6.
Important Potential Risks	
Progressive multifocal leukoencephalopathy	None
Reversible posterior leukoencephalopathy syndrome	None

Footnotes, including abbreviations, are defined on the last page of this table.

Table 26. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Adenocarcinoma of colon in ulcerative colitis patients	Routine risk communication: • SmPC Section 4.4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Regular screening for the presence of colonic dysplasia prior to and during treatment with AMGEVITA is described in SmPC Section 4.4.
Missing Information	
Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease	Routine risk communication: • SmPC Section 4.2
Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis	None
Long-term safety data in the treatment of children with uveitis	Routine risk communication: • SmPC Section 4.2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for yearly evaluation of benefit-risk is included in SmPC Section 4.2.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	None

BCG = Bacillus Calmette-Guérin; NMSC = non-melanoma skin cancer; PL = package leaflet; SmPC = summary of product characteristics; TB = tuberculosis

V.2 Additional Risk Minimization Measures

Table 27. Additional Risk Minimization Measure: Patient Reminder Card (Adult and Paediatric)

Objectives	The Patient Reminder Card (adult and paediatric) contains measures to inform patients and caregivers on the following key risks of AMGEVITA: • serious infections • tuberculosis • malignancies • demyelinating disorders • BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Humira®. The Patient Reminder Card informs both patients and caregivers about the key risks associated with the use of AMGEVITA and the specific symptoms associated with those risks and to inform their doctor if such symptoms arise. Patients are to carry the card with them in order to show a healthcare professional (HCP) that they are using AMGEVITA, if needed.
Target audience and planned distribution path	Patient Reminder Cards will be provided to prescribers for distribution to patients and caregivers for whom AMGEVITA is prescribed or will be available via a non-promotional website.
Plans to evaluate the effectiveness of the interventions and criteria for success	Due to similarity with the reference product's additional risk minimization measures and the demonstrated effectiveness of those measures, no further evaluation of the effectiveness of this measure is formally proposed. As such, the effectiveness of the Patient Reminder Card will be assessed using routine pharmacovigilance including monthly signal detection and reporting in scheduled PBRER/PSUR or earlier, if required. The Patient Reminder Card will be considered successful if a safety assessment based on the postmarketing data indicates no change in the benefit-risk profile.

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 27. Additional Risk Minimization Measure: Patient Reminder Card (Adult and Paediatric)

Evaluation of the effectiveness of risk minimization activities	Not yet assessed. **Humira®** The effectiveness of the additional risk minimization measures for Humira® has previously been evaluated by AbbVie in a series of annual healthcare provider surveys conducted in 2009, 2010, and 2011 among dermatologists, rheumatologists, and gastroenterologists in 24 EU countries. In addition, a more detailed analysis of the survey data from 2010 was published in 2012 (Smith et al, 2012). Conclusions from this study were that most physicians reported being aware of the attendant risk for reactivation of latent TB infection with anti-TNF treatments and that a high percentage were screening patients for TB prior to initiating Humira® therapy.

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BCG = Bacillus Calmette-Guérin; EU = European Union; HCP = healthcare professional; PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report; TB = tuberculosis; TNF = tumor necrosis factor

V.3 Summary of Risk Minimization Measures

Table 28. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious infections	Routine risk minimization measures: • 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 AMGEVITA, and advice not to take AMGEVITA with medicines containing anakinra or abatacept is discussed • PL Section 4 where symptoms of infection are discussed Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
Tuberculosis	Routine risk minimization measures: • SmPC Section 4.2 where dose interruption is discussed • SmPC Section 4.3 • SmPC Section 4.4 where close monitoring for TB, treatment of latent TB before initiation of AMGEVITA, and discontinuation of AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where symptoms of TB, interruption of AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept is discussed • PL Section 4 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study

Footnotes, including abbreviations, are defined on the last page of this table.

Table 28. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 where examination for the presence of NMSC 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 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Routine risk minimization measures: • 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 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA	Routine risk minimization measures: • 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 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Footnotes, including abbreviations, are defined on the last page of this table.

Table 28. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Progressive multifocal leukoencephalopathy	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Reversible posterior leukoencephalopathy syndrome	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Adenocarcinoma of colon in ulcerative colitis patients	Routine risk minimization measures: • 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: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 28. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease	Routine risk minimization measures: • SmPC Section 4.2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Long-term safety data in the treatment of children with uveitis	Routine risk minimization measures: • SmPC Section 4.2 where recommendation for yearly evaluation of benefit-risk is included Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 28. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

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BCG = Bacillus Calmette-Guérin; NMSC = non-melanoma skin cancer; PL = package leaflet; SmPC = summary of product characteristics; TB = tuberculosis

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for AMGEVITA is presented below.

Summary of Risk Management Plan for AMGEVITA® (adalimumab biosimilar)

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, paediatric 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 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 important risks, below.

In addition to these measures, information about adverse reactions 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 risks	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 risks	Progressive multifocal leukoencephalopathy Reversible posterior leukoencephalopathy syndrome Adenocarcinoma of colon in ulcerative colitis patients
Missing information	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 children with uveitis Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

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, October 2022 and AMGEVITA 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 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 Additional risk minimization measures: • Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • (AMGEVITA) 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, October 2022 and AMGEVITA 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 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 Additional risk minimization measures: • Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • (AMGEVITA) 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® USPI, March 2020; Humira® SmPC, October 2022; and AMGEVITA 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-MP used for inflammatory bowel disease (Humira® SmPC, October 2022). 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).

Important Identified Risk: Malignancies (continued)	
Risk factors and risk groups (continued)	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/skincancer-merkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-risk-factors, 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 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 Additional risk minimization measures: • Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • (AMGEVITA) 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 AMGEVITA 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 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 Additional risk minimization measures: • Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • (AMGEVITA) 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, October 2022 and AMGEVITA 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 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 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 AMGEVITA 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 AMGEVITA 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, October 2022.
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 4.4 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: 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: • SmPC Section 4.2 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 Children With Uveitis	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 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

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
(AMGEVITA) 20160264 A prospective observational study to evaluate long-term safety of AMGEVITA in patients with rheumatoid arthritis	Primary objectives: • To estimate the incidence rates of serious infections (ie, infectious events which required IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) Secondary objective: • Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to AMGEVITA • Estimate the incidence rates of the safety concerns from both the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) anti-tumor necrosis factor and Non-biologic Disease-modifying Antirheumatic Drug (nbDMARD) comparison cohorts Safety concerns addressed include: • Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)

PART VII: ANNEXES

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Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if applicable)

Approved key messages of the additional risk minimization measures

1. **Patient Reminder Card**: The purpose of the Patient Reminder Card is to inform adult patients about the key risks associated with the use of AMGEVITA and the specific symptoms associated with those risks and to inform their doctor if such symptoms arise. Patients are to carry the card with them in order to show a healthcare professional that they are using AMGEVITA, if needed.
2. **Paediatric Patient Reminder Card:** The purpose of this card is similar to that for the Patient Reminder Card except that it is intended for children using AMGEVITA and as such, the card will be distributed to the patient's parent/guardian. The parent/guardian is to carry the card with them in order to show a healthcare professional if needed.