**EU Risk Management Plan**

**Gobivaz 50 mg solution for injection in pre-filled pen**

**Gobivaz 50 mg solution for injection in pre-filled syringe**

**Gobivaz 100 mg solution for injection in pre-filled pen**

**Gobivaz 100 mg solution for injection in pre-filled syringe**

**(golimumab)**

**Date: 28-Mar-2025**

**RMP version to be assessed as part of this application:**

| | |
|---|---|
| RMP Version number: | V1.0 |
| Data lock point for this RMP: | 17-Apr-2024 |
| Date of final sign off: | 28-Mar-2025 |
| Rationale for submitting an updated RMP: | The RMP has been updated in line with CHMP Day 120 List of questions to include Gobivaz 100 mg solution for injection in pre-filled pen and 100 mg solution for injection in pre-filled syringe. |
| Summary of significant changes in this RMP | Information regarding Gobivaz 100 mg solution for injection in pre-filled pen and 100 mg solution for injection in pre-filled syringe has been included in all the applicable section throughout the document.<br>The additional monitoring status in EU has been amended from “No” to “Yes” |

**Other RMP versions under evaluation:**

| | |
|---|---|
| RMP Version number: | Not Applicable |
| Submitted on: | Not Applicable |
| Procedure number: | Not Applicable |

**Details of the currently approved RMP:**

| | |
|---|---|
| Version number: | Not Applicable |
| Approved with procedure: | Not Applicable |
| Date of approval (opinion date): | Not Applicable |

**Signature:**

| | |
|---|---|
| Name of EU QPPV/Deputy EU QPPV: | Nowel Redder |
| Signature of EU QPPV/Deputy EU QPPV | [redacted] |

**TABLE OF CONTENTS**

**LIST OF TABLES**

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| 6-MP | 6-mercaptopurine |
| AS | Ankylosing spondylitis |
| AZA | Azathioprine |
| BCG | Bacillus Calmette-Guérin |
| CI | Confidence interval |
| CNS | Central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| CRP | C-reactive protein |
| DMARD | Disease-modifying anti-rheumatic drug |
| EEA | European Economic Area |
| EPAR | European Public Assessment Report |
| HBV | Hepatitis B virus |
| HIV | Human immunodeficiency virus |
| HSTCL | Hepatosplenic T-cell lymphoma |
| JIA | Juvenile idiopathic arthritis |
| MAA | Marketing Authorisation Applicant |
| MCC | Merkel cell carcinoma |
| MRI | Magnetic resonance imaging |
| MS | Multiple sclerosis |
| MTX | Methotrexate |
| NMSC | Nonmelanoma skin cancer |
| nr-Axial SpA | Non-radiographic axial spondyloarthritis |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| pJIA | Polyarticular juvenile idiopathic arthritis |
| PL | Package leaflet |
| PsA | Psoriatic arthritis |
| RA | Rheumatoid arthritis |
| RMP | Risk management plan |
| SCC | Squamous cell carcinoma |
| SmPC | Summary of Product Characteristic |
| TB | Tuberculosis |
| TEAE | Treatment Emergent Adverse Event |
| TEAESI | Treatment Emergent Adverse Event of Special Interest |
| TNF | Tumour necrosis factor |
| TNF-α | Tumour necrosis factor alpha |
| UC | Ulcerative colitis |
| UV | Ultraviolet |

**Part I: Product(s) Overview**

| | |
|---|---|
| **Active Substance(s) (INN or common name)** | Golimumab |
| **Pharmacotherapeutic Group(s) (ATC Code)** | Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors<br>L04AB06 |
| **Marketing Authorisation Applicant** | Advanz Pharma Limited |
| **Medicinal products to which this RMP refers** | 4 |
| **Invented name(s) in the EEA** | Gobivaz 50 mg solution for injection in pre-filled pen<br>Gobivaz 50 mg solution for injection in pre-filled syringe<br>Gobivaz 100 mg solution for injection in pre-filled pen<br>Gobivaz 100 mg solution for injection in pre-filled syringe |
| **Marketing Authorisation Procedure** | Centralised Procedure |
| **Brief description of the product** | |
| • **Chemical class** | Disulphide with human monoclonal CNTO 148 k-chain anti-(human tumour necrosis factor a) (human monoclonal CNTO 148 g1-chain) immunoglobulin G1 dimer |
| • **Summary of mode of action** | Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors. Increased TNFα is associated with chronic inflammation. Golimumab binds and inhibits soluble and transmembrane human TNFα. |
| • **Important information about its composition** | **Gobivaz 50 mg solution for injection (pre-filled)**<br>One 0.5 mL pre-filled pen contains 50 mg of golimumab.<br>One 0.5 mL pre-filled syringe contains 50 mg of golimumab.<br><u>Excipient with known effect:</u><br>Each pre-filled pen contains 20.5 mg sorbitol per 50 mg dose.<br>Each pre-filled syringe contains 20.5 mg sorbitol per 50 mg dose.<br>**Gobivaz 100 mg solution for injection (pre-filled)**<br>Each 1 mL pre-filled pen contains 100 mg of golimumab.<br>Each 1 mL pre-filled syringe contains 100 mg of golimumab.<br><u>Excipient with known effect:</u><br>Each pre-filled pen contains 41 mg sorbitol per 100 mg dose.<br>Each pre-filled syringe contains 41 mg sorbitol per 100 mg dose. |

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| | |
| **Hyperlink to the Product Information** | Module 1.3.1 of Dossier |
| **Indication(s) in the EEA** | **Current:**<br>**Rheumatoid arthritis (RA)**<br>Gobivaz in combination with methotrexate (MTX), is indicated for:<br>• the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.<br>• the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.<br>**Juvenile idiopathic arthritis**<br>*Polyarticular juvenile idiopathic arthritis (pJIA)*<br>Gobivaz in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.<br>**Psoriatic arthritis (PsA)**<br>Gobivaz alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.<br>**Axial spondyloarthritis**<br>*Ankylosing spondylitis (AS)*<br>Gobivaz is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.<br>*Non-radiographic axial spondyloarthritis (nr-Axial SpA)*<br>Gobivaz is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).<br>**Ulcerative colitis (UC)**<br>Gobivaz 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. |
| | **Proposed:** Not Applicable |

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| **Dosage in the EEA** | **Current:**<br>**Rheumatoid arthritis**<br>Gobivaz 50 mg given once a month, on the same date each month. Gobivaz should be given concomitantly with MTX.<br>**Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis**<br>Gobivaz 50 mg given once a month, on the same date each month.<br>Patients with body weight greater than 100 kg<br>For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.<br>**Ulcerative colitis**<br>Patients with body weight less than 80 kg<br>Gobivaz given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter.<br>Patients with body weight greater than or equal to 80 kg<br>Gobivaz given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter.<br>**Polyarticular juvenile idiopathic arthritis**<br>Gobivaz 50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg.<br>Note: Dosage form for Gobivaz in pre-filled pen that allows for a 45 mg/0.45 mL for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg is not available. Thus, it is not possible to administer Gobivaz to patients that require a 45 mg dose. If a 45 mg/0.45 mL dose is required, another golimumab product should be used instead.<br>Gobivaz 100 mg is not recommended in children aged less than 18. |
| | **Proposed:** Not Applicable |
| **Pharmaceutical form(s) and strengths** | **Current:**<br>50 mg solution for injection in pre-filled pen (injection)<br>50 mg solution for injection in pre-filled syringe (injection)<br>100 mg solution for injection in pre-filled pen (injection)<br>100 mg solution for injection in pre-filled syringe (injection) |
| | **Proposed:** Not Applicable |

| | |
|---|---|
| **Is/will the product be subject to additional monitoring in the EU?** | ☒ Yes ☐ No |

**Part II: Safety Specification**

**Module SI - Epidemiology of the Indication(s) and Target Population(s)**

Not Applicable. The MAA product information is aligned to reference product Simponi.

**Module SII - Non-Clinical Part of the Safety Specification**
No non-clinical studies have been performed.

**Module SIII - Clinical Trial Exposure**

AVT05 (Gobivaz/golimumab) is being developed as a proposed biosimilar to Simponi®. As part of the development for AVT05, two clinical studies have been conducted:

AVT05-GL-P01: A pharmacokinetics (PK) similarity clinical study to compare the PK, safety, tolerability, and immunogenicity profiles of AVT05, US-licensed Simponi, and EU-approved Simponi in healthy adult participants (AVT05-GL-P01) has been performed. This study has been completed.

AVT05-GL-C01: A confirmatory efficacy and safety trial to compare the efficacy, safety, and immunogenicity between AVT05 and EU-approved Simponi® (EU-Simponi) in combination with methotrexate in adult participants with moderate to severe rheumatoid arthritis (RA). While the study is ongoing, data up to Week 24 database freeze has been included in this RMP.

**Cumulative subject exposure from completed clinical trials:**

**Table 1: Study AVT05-GL-P01: Cumulative subject exposure***

| Treatment | Number of Subjects |
|---|---|
| AVT05 | 115 |
| US-Simponi | 110 |
| EU-Simponi | 111 |
| **Total** | **336** |

*Source : Module 5.3.3.1., CSR AVT05-GL-P01

**Table 2: Study AVT05-GL-C01: Cumulative Subject Exposure Up to Week 16 (Safety Analysis Set) ***

| | AVT05 (N=251) n (%) | EU-Simponi (N=251) n (%) |
|---|---|---|
| Number of participants who received injections | | |
| Baseline | 251 (100.0) | 251 (100.0) |
| Week 4 | 248 (98.8) | 251 (100.0) |
| Week 8 | 239 (95.2) | 240 (95.6) |
| Week 12 | 227 (90.4) | 231 (92.0) |

*Source : Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.3.5.1.1

**Table 3: Study AVT05-GL-C01: Cumulative Subject Exposure from Week 16 to Week 24 (Safety Analysis Set) ***

| | AVT05/AVT05 (N=223) n (%) | EU-Simponi/ AVT05 (N=112) n (%) | EU-Simponi/EU-Simponi (N=113) n (%) |
|---|---|---|---|
| Number of participants who received injections | | | |
| Week 16 | 223 (100.0) | 112 (100.0) | 113 (100.0) |
| Week 20 | 217 (97.3) | 110 (98.2) | 110 (97.3) |
| Week 24 | 220 (98.7) | 109 (97.3) | 111 (98.2) |

*Source: Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.3.5.1.2

**Table 4: SIII.2: Duration of exposure to AVT05 from completed clinical trials*:**

| Study | Duration | Number of subjects |
|---|---|---|
| **AVT05-GL-P01** | <4 weeks | 0 |
| | 4 weeks to ≤ 16 weeks | 115 |
| **AVT05-GL-C01** | 4 weeks to ≤16 weeks | 366 |
| | 16 weeks to ≤24 months | 335 |

*Source : Module 5.3.3.1., CSR AVT05-GL-P01 and Module 5.3.5.1., CSR#1 AVT05-GL-C01

**Table 5: SIII.2: Cumulative subject exposure to AVT05 from completed clinical trials by age***

| Study | Age Group | Number of subjects |
|---|---|---|
| **AVT05-GL-P01** | 18 years to ≤54 years | 115 |
| **AVT05-GL-C01** | < 65 years | 201 |
| | >= 65 years | 50 |
| **Total subjects** | | **366** |

*Source: Module 5.3.3.1., CSR Study AVT05-GL-P01, Table 14.1.3.1; Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.1.3.1

**Table 6: SIII.3: Cumulative subject exposure to AVT05 from completed clinical trials by gender***

| Gender | AVT05-GL-P01 | AVT05-GL-C01 |
|---|---|---|
| Male | 50 | 44 |
| Female | 65 | 207 |
| **Total** | **115** | **251** |

*Source: Module 5.3.3.1., CSR Study AVT05-GL-P01, Table 14.1.3.1; Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.1.3.1

**Table 7: SIII.4: Cumulative subject exposure to AVT05 from completed clinical trials by race***

| Race | AVT05-GL-P01 | AVT05-GL-C01 |
|---|---|---|
| [redacted] | 17 | 0 |
| [redacted] | 43 | 0 |
| [redacted] | 46 | 250 |
| [redacted] | 2 | 0 |
| [redacted] | 1 | 0 |
| Multiple | 1 | 1 |
| Other | 5 | 0 |
| **Total** | **115** | **251** |

*Source: Module 5.3.3.1., CSR Study AVT05-GL-P01, Table 14.1.3.1; Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.1.3.1

**Table 8: SIII.5: Cumulative subject exposure to AVT05 from completed clinical trials by ethnicity***

| Ethnicity | AVT05-GL-P01 | AVT05-GL-C01 |
|---|---|---|
| [redacted] | 11 | 0 |
| [redacted] | 104 | 0 |
| [redacted] | 0 | 2 |
| [redacted] | 0 | 249 |
| **Total** | **115** | **251** |

*Source: Module 5.3.3.1., CSR Study AVT05-GL-P01, Table 14.1.3.1; Module 5.3.5.1., CSR#1 AVT05-GL-C01, Table 14.1.3.1

**Module SIV - Populations not Studied in Clinical Trials**

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Discuss the important exclusion criteria in the pivotal clinical studies across the development programme.

| Criterion | Reason for exclusion | Is it considered to be included as missing information | Rationale |
|---|---|---|---|
| Known or suspected clinically relevant drug hypersensitivity to golimumab, or any of its constituents, which in the opinion of the PI, contraindicates the participant's participation. | Individuals with a known hypersensitivity to human IgG proteins or any of the components of golimumab would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure. | No | Golimumab is contraindicated in patients with a history of hypersensitivity to golimumab or to any of the excipients. |
| Have any past or concurrent medical conditions that could potentially increase the participant's risks or that would interfere with the study evaluation, procedures, or study completion. Examples of these include medical history with evidence of clinically relevant pathology (e.g., malignancies or demyelinating disorders). | Anti-TNFα agents have been associated with demyelinating diseases (central and peripheral) and these events are considered a class effect for these agents.<br>Published medical literature suggests that certain types of malignancies may be adversely affected by TNFα blockade. The potential role of TNF-blocking therapy in the development of certain types of malignancies is not known. | No | Demyelinating disorders and Malignancy are an important identified risk.<br>The risk to the patient population is adequately addressed in the SmPC. |
| Presence of chronic heart failure of New York Heart Association (NYHA) class III or IV. | In a clinical trial with another TNF-antagonist, worsening congestive heart failure (CHF) and increased mortality due to CHF have been observed. | No | Moderate or severe heart failure (New York Heart Association [NYHA] class III/IV) is a contraindication in the SmPC. The risk to this patient population is adequately addressed in the SmPC. |
| Any current active infections, including localized infections, | Treatment with anti-TNFα agents may increase the risk | No | Serious infections are an important identified risk. |

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| or any recent history (within 1 week prior to study drug administration) of active infections, cough or fever, or a history of recurrent or chronic (including opportunistic) infections | of the development of infections or worsen an existing infection. | | Information about infections is described in the SmPC. The risk to this patient population is adequately addressed in the SmPC and the Patient Reminder Card. |
| Subject has a history of tuberculosis (TB) diagnosis or evidence of active or latent infection with Mycobacterium tuberculosis | Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection. | No | Serious infections are an important identified risk. Information about infections, including TB is described in the SmPC. The risk to this patient population is adequately addressed in the SmPC and the Patient Reminder Card. |
| Vaccination with a live vaccine (with the exception of flu vaccine) within the 4 weeks prior to Screening or have the intention to receive a live vaccination up to 5 weeks after the last dose of study drug. | Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection. | No | Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* is an important potential risk. The risk of live vaccinations is adequately addressed in the SmPC and the Patient Reminder Card. |
| Previous exposure to other TNF-α inhibitors including golimumab. | The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions. | No | Serious infections are an important identified risk. Information about infections is described in the SmPC. |
| Major chronic inflammatory disease or connective tissue disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis (PsA), seronegative spondyloarthropathy, Lyme disease), or any active autoimmune disease (e.g., | Interference with the evaluation of efficacy and safety data. | No | Prescribing physicians will be expected to follow the labelling information for other concomitant medications as appropriate. |

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|---|---|---|---|
| systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or any overlap syndrome) or diagnosis of juvenile idiopathic arthritis, and/or RA before the age of 16, or joint disease other than RA. | | | |
| Previous treatment with any synthetic disease-modifying anti-rheumatic drug (sDMARD) other than MTX (including injectable gold, sulfasalazine, antimalarials, D-penicillamine, cyclosporine, leflunomide, azathioprine, calcineurin inhibitors) within 3 months prior to Screening. | | | |
| Presence of chronic obstructive pulmonary disease. | In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. | No | Malignancy is an important identified risk. Information about this risk is described in the SmPC. |

**SIV.2 Limitations to detect adverse reactions in clinical trial development programmes:**

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with long latency or those caused by prolonged or cumulative exposure.

**SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes:**

| Type of Special Population | Exposure |
|---|---|
| • Pregnant women<br>• Breastfeeding women | Not included in the clinical trials. |

| | |
|---|---|
| **Patients with relevant comorbidities:**<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• Patients with a disease severity different from<br>• inclusion criteria in clinical trials | Patients with these comorbidities were not included in the clinical trial.<br><br>However, by default, subjects participating in golimumab clinical trials are immunocompromised as a result of their underlying disease, their concomitant medications, and by virtue of receiving treatment with a TNFα inhibitor. |
| Population with relevant different ethnic origin | Data not available. |
| Subpopulations carrying relevant genetic polymorphisms | Not included in the clinical development program. |
| Other:<br>Pediatric population (less than 18 years of age) | The safety and efficacy of golimumab in patients aged less than 18 for indications other than pJIA have not been established. Not included in clinical trials. |

**Module SV - Post-Authorisation Experience**

Not Applicable

**Module SVI - Additional EU Requirements for the Safety Specification**

***Potential for misuse for illegal purposes***

Based on the pharmacological properties of golimumab, there is no rationale to suggest that golimumab is a medicinal product with abuse potential; therefore, drug abuse with golimumab is unlikely.

**Module SVII - Identified and Potential Risks**

**SVII.1 Identification of safety concerns in the initial RMP submission**

| | |
|---|---|
| **Important identified risk(s)** | • Serious infections<br>• Demyelinating disorders<br>• Malignancy |
| **Important potential risk(s)** | • Serious depression including suicidality<br>• Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* |
| **Missing information** | • Long-term safety in paediatric patients |

**SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP:**

Reason for not including as identified or potential risk in the list of safety concerns in the RMP:

| | |
|---|---|
| Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) | • Insomnia<br>• Dizziness<br>• Headache<br>• Paraesthesia<br>• Pyrexia<br>• Asthenia<br>• Conjunctivitis |
| Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated | • Thrombocytopenia<br>• Pancytopenia<br>• Aplastic anemia<br>• Agranulocytosis<br>• Serious systemic hypersensitivity reactions (including anaphylactic reaction)<br>• Ischemic coronary artery disorders<br>• Interstitial lung disease<br>• Cholelithiasis<br>• Bone fractures<br>• Arrhythmia<br>• Congestive heart failure<br>• Asthma and related symptoms (such as wheezing and bronchial hyperactivity)<br>• Bladder disorders, renal disorders<br>• Lupus-like syndrome<br>• Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)<br>• Worsening of symptoms of dermatomyositis<br>• Vasculitis (systemic)<br>• Sarcoidosis<br>• Hepatosplenic T-cell lymphoma<br>• Kaposi's sarcoma |

| | |
|---|---|
| | • Thrombosis (such as deep venous and aortic)<br>• Raynaud's phenomenon |
| Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers | • Allergic reactions (bronchospasm, hypersensitivity, urticaria)<br>• Hypertension<br>• Gastrointestinal inflammatory disorders<br>• Alanine aminotransferase increased.<br>• Aspartate aminotransferase increased.<br>• Anemia<br>• Injection site reaction<br>• Leukopenia (including neutropenia),<br>• Balance disorders<br>• Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)<br>• Pyelonephritis<br>• Interstitial lung disease |
| Known risks that do not impact the risk-benefit profile | • Chest discomfort<br>• Pruritus<br>• Rash<br>• Alopecia<br>• Dermatitis<br>• Visual disorders |
| Other reasons for considering the risks not important | • None |

**SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP:**

| **Important identified risk(s)** | |
|---|---|
| **Serious infections** | Because they suppress the immune system, drugs that inhibit TNFα have been associated with an increased risk of serious infections (some fatal), including opportunistic infections, tuberculosis (TB), and invasive fungal infections. Drugs that inhibit TNFα have also been associated with HBV reactivation in patients who are chronic carriers of the virus.<br><br>Serious infections, including opportunistic infections and TB, have been reported in patients treated with golimumab in clinical trials and in the post-marketing setting. Hepatitis B virus reactivation has been reported in the post-marketing setting in patients treated with golimumab.<br><br>These findings are consistent with nonclinical data and published medical literature. Serious infections are considered an important identified risk because of the consistency of evidence across multiple sources, including data from products in the same class.[1] |
| **Demyelinating disorders** | Since TNF-α is implicated in demyelinating processes, TNF-α blockers were considered as a potential therapeutic choice in multiple sclerosis. However, the negative outcomes of these agents in multiple sclerosis trials and the reports of demyelinating events following their use for other |

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| | disorders raised the suspicion that use of these drugs could be a risk factor of demyelination.[2]<br><br>Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy.[3] |
| **Malignancy** | Reports of malignancies in golimumab-treated subjects, including lymphoma, skin cancer, and leukemia, have been received in clinical trials and in the post-marketing setting for MAA reference product SIMPONI[1].<br><br>For non-lymphoma malignancies (excluding nonmelanoma skin cancer [NMSC]), the incidence was similar between the golimumab and the control groups in the controlled portions of the golimumab pivotal trials for MAA reference product SIMPONI and through approximately 4 years of follow-up. The incidence was also similar to the incidence in the general population. For lymphoma, more cases have been observed among patients receiving anti-TNFα treatment compared with control patients in the controlled portions of clinical trials of all TNFα-blocking agents, including golimumab. However, there is an increased background risk for lymphoma in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.[1]<br><br>During the golimumab (SIMPONI) Phase 2b and 3 SC clinical trials in RA, PsA, and AS, the incidence of lymphoma in golimumab-treated subjects was higher than expected compared to the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Looking specifically at children, adolescents, and young adults (up to 22 years of age), post-marketing cases of malignancies, some fatal, have been reported in patients who received TNFα inhibitors (initiation of therapy ≤18 years of age) to treat juvenile idiopathic arthritis (JIA), Crohn's disease, or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as MTX, azathioprine, or 6-mercaptopurine. It is not clear whether children with certain autoimmune conditions have an increased risk for malignancy given limited data. For Hepatosplenic T-cell lymphoma (HSTCL), there have been rare reports in the post-marketing setting in patients treated with other TNFα inhibitors. The development of |

| | |
|---|---|
| | malignancy is considered an important identified risk because the effects attributed to TNFα in published medical literature, suggesting that certain types of malignancies may be adversely affected by TNFα blockade may apply to golimumab.[1] |
| **Important potential risk(s)** | |
| **Serious depression including suicidality** | Golimumab has been investigated in multiple settings. In clinical trials, serious depression including suicidality has been reported in patients treated with golimumab. Depression has also been reported in the post-marketing setting and is described in published medical literature.<br><br>Although serious depression has been reported in patients treated with golimumab, a causal association between the development or worsening of serious depression (including suicidality) and golimumab has not been established.<br><br>Complicating the assessment is evidence that patients with RA, AS, and PsA have increased rates of depression compared to the general population.[4]<br><br>Additionally, while some researchers have found no evidence of an association between depression and ulcerative colitis, others have suggested that depression and anxiety are common in patients with inflammatory bowel disease.[5] |
| **Breakthrough infection after administration of live vaccines in infants exposed to Golimumab *in utero*** | Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection.[3]<br><br>In infants exposed *in utero* to infliximab (another TNFα- blocking agent), fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.[6]<br><br>Therefore, administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy.[3] |
| **Missing Information** | |
| **Long-term safety in paediatric patients** | The safety and efficacy of Golimumab in patients aged less than 18 for indications other than pJIA have not been established.<br><br>The safety of Golimumab has been studied in a Phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.[3] |

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| | Although no risks of clinical significance were identified in golimumab-treated subjects, the effect of long-term treatment with golimumab in this patient population has not been studied. |

### SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not Applicable

### SVII.3 Details of important identified risks, important potential risks, and missing information

*SVII.3.1. Presentation of important identified risks and important potential risks*

| **Important Identified Risk – Serious Infections** | |
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| **Potential mechanism(s)** | Tumour necrosis factor alpha is a mediator of cellular immune responses and inflammation, which are important in host defense against certain pathogens, especially intracellular pathogens. Anti-TNFα agent therapy reduces the ability to mount an inflammatory response against such pathogens. Golimumab may therefore inhibit protective immune responses to intracellular bacteria (including mycobacteria) and opportunistic pathogens and may also allow HBV reactivation.[1] |
| **Evidence source(s) and strength of evidence** | Because they suppress the immune system, drugs that inhibit TNFα have been associated with an increased risk of serious infections (some fatal), including opportunistic infections, TB, and invasive fungal infections. Drugs that inhibit TNFα have also been associated with hepatitis B virus (HBV) reactivation in patients who are chronic carriers of the virus.<br>Serious infections, including opportunistic infections and TB, have been reported in patients treated with golimumab in clinical trials and in the post-marketing setting. Hepatitis B virus reactivation has been reported in the post-marketing setting in patients treated with golimumab.[3]<br>These findings are consistent with nonclinical data and published medical literature. |
| **Characterisation of the risk** | Serious infections are considered a class effect of anti-TNFα agents and are listed side effect of golimumab.<br>Pooled data from three double-blind, randomized trials of IV golimumab (MAA reference product SIMPONI) in patients with RA, PsA, and AS, each with a placebo-controlled period and an extension of active treatment reported the following: In total, 49 (3.9%) of all golimumab-treated patients (N=1248) had a serious infection; the incidence/100 PY (95% CI) was 3.4 (2.5, 4.4) across the three trials (4.0 [2.9, 5.4] in the RA trial; 2.6 [1.3, 4.7] in the PsA trial, and 1.5 [0.3, 4.3] in the AS trial. Serious infections included pneumonia (n = 11), urinary tract infection (n = 5), sepsis (n = 4), appendicitis (n = 2), empyema (n = 2), and erysipelas (n = 2); other serious infections were singular events and included infected dermal cyst, acute pyelonephritis, periodontitis, and acute hepatitis of mixed etiology. Among the golimumab-treated patients, six cases of active TB occurred (RA trial, n = 3; PsA trial, n = 2; AS trial, n = 1), all in patients who screened negative for TB at baseline and lived in countries endemic for TB (Argentina, Lithuania, Malaysia, Mexico, and Ukraine). No opportunistic infections occurred in the PsA or AS trials. Four opportunistic |

| Important Identified Risk – Serious Infections | |
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| | infections occurred among golimumab-treated patients in the RA trial: cryptococcal pneumonia (n = 1) and localized vertebral candidiasis (n = 1) (both classified as serious and led to discontinuation of golimumab), and two golimumab-treated patients were diagnosed with non-serious esophageal candidiasis infection.[7]<br><br>Post-marketing data are consistent with what is currently known about the risk of serious infections in patients treated with SIMPONI (MAA reference product). A 5-year trend analysis of the reporting rate (RR) of spontaneously reported cases of serious infections (including opportunistic infection and TB) in patients exposed to IV and SC SIMPONI in the post-marketing setting showed an overall decrease. For HBV reactivation, similar 5-year post-marketing trend in patients exposed to SC SIMPONI showed a stable profile.[1]<br><br>In study AVT05-GL-C01, safety analysis performed up to week 24 revealed that a total of 31 and 15 subjects in the AVT05 treatment group reported TEAESIs related to "Infections and Infestations", respectively.<br><br>One subject in AVT05 group reported serious severe TEAE of pleural effusion (up to week 16) leading to treatment discontinuation and early termination from the study. No serious TEAE related to "Infections and Infestations" was identified from week 16 to week 24.<br><br>No AESIs of serious infections were reported in study AVT05-GL-P01. |
| **Risk factors and risk groups** | <u>Serious Infections</u><br><br>Risk factors for the development of serious infections include the use of steroids, other immunosuppressive drugs (including MTX), or other biologics at the same time as golimumab.<br><br><u>Opportunistic Infections</u><br><br>People whose immune status is compromised are susceptible to opportunistic infections. Risk factors for opportunistic infections may therefore include human immunodeficiency virus (HIV) disease, increased age, having an organ transplant, immunosuppressive drug therapy (corticosteroids, MTX, azathioprine, and biologic agents), chronic pulmonary disease, and chronic renal failure.<br><br><u>Invasive Fungal Infections</u><br><br>People who have resided in or travelled to regions where invasive fungal infections are common are at increased risk.<br><br><u>Tuberculosis</u><br><br>The most common risk factors for the development of TB include conditions that weaken the immune system such as advanced age, HIV infection, alcohol abuse, malignancy, use of corticosteroids or other immunosuppressive drugs such as MTX, connective tissue disease, renal failure, diabetes, and pregnancy.<br><br>Other risk factors for the development of TB include contact with a person with active TB infection and having been born in, lived in, or travelled to countries where the incidence of TB is high. Exposure to TB may occur through various health care |

| Important Identified Risk – Serious Infections | |
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| | settings (e.g., hospitals and nursing homes) or high-density institutions (e.g., prisons).<br><br>Hepatitis B Virus (HBV) Reactivation<br><br>Risk factors for the acquisition of HBV include being born to a mother from a highly endemic area, emigration from a highly endemic area, history of IV drug use, and a history of multiple sexual partners. Patients at risk for HBV reactivation are those who are chronic carriers of this virus (i.e., surface antigen-positive), especially those who become immunosuppressed. Approximately 14% to 50% of immunosuppressed patients who are chronic carriers of HBV will experience acute reactivations during the natural history of their disease. Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (e.g., chemotherapy, corticosteroids, MTX, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies. |
| **Preventability** | Golimumab is contraindicated in patients with active tuberculosis (TB) or other severe infections such as sepsis and opportunistic infections.<br><br>Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and golimumab should not be administered until the infection resolves.<br><br>For patients who have resided in or travelled to regions where invasive fungal infections are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of therapy.<br><br>Patients who are being considered for Golimumab therapy should be evaluated for TB infection. Golimumab should not be given to patients with active TB. Golimumab should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering golimumab, including those patients with a history of latent TB in whom an adequate course of treatment cannot be confirmed. Patients receiving golimumab should be monitored closely for signs and symptoms of active TB during and after treatment.<br><br>All patients should be screened for HBV infection prior to initiation of golimumab. In patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of HBV infection is recommended. Chronic carriers of HBV should be appropriately evaluated and monitored prior to initiation of, during treatment with, and for several months following discontinuation of golimumab. |

| Important Identified Risk – Serious Infections | |
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| | In addition, the MAA proposes an additional risk minimisation measure of "Patient Reminder Card" to educate patients on important safety information that they need to be aware of before and during treatment with golimumab and to enhance patient knowledge regarding the risk of infection associated with golimumab treatment. (Refer Part V.2 for complete details).[3] |
| **Impact on the risk-benefit balance of the product** | The observed incidence of serious infections has not had a significant impact on the risk-benefit balance of the product. Risk minimization measures are in place and considered adequate and proportionate to the risk; the SmPC and PL provide information to the prescriber and patient on how to manage this important identified risk. In addition, the safety concern is addressed in the Patient Reminder Card to enhance patient knowledge regarding the risk of infection associated with golimumab treatment. |
| **Public health impact** | The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorized product label. |

| Important Identified Risk – Demyelinating Disorders | |
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| **Potential mechanism(s)** | Several theories have been proposed in an attempt to clarify the potential biological role of TNF-α blockers in triggering or aggravating demyelination:<br>1. TNF-α blockers cannot penetrate the intact BBB to suppress demyelination but they can enhance demyelination through increased ingress of peripheral autoreactive T-cells into the CNS (lack of entry theory). This theory provides a possible explanation for the failure of anti-TNF-α blockers in reducing demyelination and for their effect on aggravating MS.<br>2. TNF-α blockers may aggravate CNS demyelination by decreasing TNFR2 receptors, which are necessary for the proliferation of immature oligodendrocytes and myelin repair.<br>3. TNF-α blockers could alter cytokine responses by downregulating interleukin-10 and upregulating interleukin-12 and interferon-γ, creating a profile similar to that of MS patients.<br>4. TNF-α blockers may deactivate TNF-α systemically, but not within the CNS (due to BBB impermeability), leading to a high concentration of TNF-α in the CNS ("sponge effect").<br>5. There may be systematic dysregulation of TNF-α in patients with RRMS, as was shown in a recent study of Mausner-Fainberg et al., in which increased serum neutralization capacity of TNF-α in RRMS patients was observed. These findings offer a possible explanation for the demyelinating events after TNF-α blockade.<br>6. Finally, TNF-α blockers may unmask an underlying latent infection, which can lead to autoimmune demyelination.[8] |
| **Evidence source(s) and strength of evidence** | Since TNF-α is implicated in demyelinating processes, TNF-α blockers were considered as a potential therapeutic choice in multiple sclerosis. However, the |

| Important Identified Risk – Demyelinating Disorders | |
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| | negative outcomes of these agents in multiple sclerosis trials and the reports of demyelinating events following their use for other disorders raised the suspicion that use of these drugs could be a risk factor of demyelination.[8]<br><br>Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy.[3] |
| **Characterisation of the risk** | Golimumab demyelinating disorders are considered a class effect for anti-TNFα agents and are listed side effect of golimumab treatment.[1]<br>In the "All Randomized Blinded Trials Population" of "All Trials" with MAA reference product SIMPONI, the frequency of demyelinating disorders was <0.1% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator. One demyelinating event (non-infectious encephalomyelitis) occurred in a patient receiving golimumab in the SIMPONI Phase III PsA trial.[7]<br>Post-marketing data are consistent with what is currently known about the risk of demyelinating disorders in patients treated with SIMPONI. A 5-year trend analysis of the RR of spontaneously reported cases of demyelinating disorders in patients exposed to subcutaneous SIMPONI showed a decreasing Reporting Ratio.[1]<br>No AESIs of demyelinating disorders were reported in study AVT05-GL-P01 and AVT05-GL-C01. |
| **Risk factors and risk groups** | Multiple sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk of developing MS than the general population.[9] Whites, particularly of northern European descent, are also more likely to develop MS.[10]<br>Several studies have suggested an association between smoking and MS. [10]<br>Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS.[10] |
| **Preventability** | Although CNS demyelination after treatment with TNF-α blockers is not necessarily associated with the duration of the therapy and drug discontinuation does not always lead to improvement, treatment should be discontinued at the appearance of unexplained neurologic symptoms.[8]<br>As per the SmPC, in patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNFα agents should be carefully considered before initiation of therapy with golimumab. Discontinuation of golimumab should be considered if these disorders develop. |

| Important Identified Risk – Demyelinating Disorders | |
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| **Impact on the risk-benefit balance of the product** | The SmPC and PL provide information to the prescriber and patient on how to manage this important identified risk; and are considered adequate and proportionate to the risk. |
| **Public health impact** | The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorized product label. |

| Important Identified Risk – Malignancy | |
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| **Potential mechanism(s)** | Immunomodulation by TNFα may be important in tumour surveillance, although the literature is not consistent on this point. While TNFα was shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines, some malignant cell lines are TNFα-resistant or even proliferate in the presence of low levels of TNFα and TNFα may behave as a tumour promoter particularly in the setting of unresolved, chronic inflammation (Balkwill 2006). Therefore, the effects attributed to TNFα in published medical literature suggesting that certain types of malignancies may be adversely affected by TNFα blockade may apply to golimumab.<br>Of note, Hepatosplenic T-cell lymphoma (HSTCL) is a rare and rapidly progressive subtype of peripheral T-cell lymphoma and has been reported following TNFα-blocker therapy. Most patients who developed HSTCL were adolescent or young adult males. Almost all these patients had also received azathioprine or 6-mercaptopurine. Hypothetical mechanisms include inhibition of TNF signaling resulting in impaired immune surveillance particularly affecting the detection and elimination of cells with chromosomal abnormalities resulting from azathioprine or 6-mercaptopurine therapy-alterations in azathioprine or 6-mercaptopurine metabolism in patients receiving anti-TNF therapy.[1] |
| **Evidence source(s) and strength of evidence** | Reports of malignancies in golimumab-treated subjects, including lymphoma, skin cancer, and leukemia, have been received in clinical trials and in the post-marketing setting.<br><br>For non-lymphoma malignancies (excluding nonmelanoma skin cancer [NMSC]), the incidence was similar between the golimumab and the control groups in the controlled portions of the golimumab pivotal trials for MAA reference product SIMPONI and through approximately 4 years of follow-up. The incidence was also similar to the incidence in the general population.[1]<br><br>For lymphoma, more cases have been observed among patients receiving anti-TNFα treatment compared with control patients in the controlled portions of clinical trials of all TNFα-blocking agents, including golimumab. However, there is an increased background risk for lymphoma in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.[1]<br><br>During the golimumab (SIMPONI) Phase 2b and 3 SC clinical trials in RA, PsA, and AS, the incidence of lymphoma in golimumab-treated subjects was higher than expected |

| Important Identified Risk – Malignancy | |
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| | compared to the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg.[1]<br><br>Looking specifically at children, adolescents, and young adults (up to 22 years of age), post-marketing cases of malignancies, some fatal, have been reported in patients who received TNFα inhibitors (initiation of therapy ≤18 years of age) to treat JIA, Crohn's disease, or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as MTX, azathioprine, or 6-mercaptopurine. It is not clear whether children with certain autoimmune conditions have an increased risk for malignancy given limited data.[1]<br><br>For HSTCL, there have been rare reports in the post-marketing setting in patients treated with other TNFα inhibitors.[1] |
| **Characterisation of the risk** | Pooled data from three double-blind, randomized trials of IV golimumab in patients with RA, PsA, and AS reported the following: Malignancies occurred in 2 (0.4%) patients receiving placebo (non-small cell lung cancer and esophageal neoplasm in the PsA trial. In addition, one case of non-treatment-emergent lung adenocarcinoma occurred in a patient randomized to placebo in the RA trial. Among IV golimumab-treated patients, eight malignancies occurred in seven (0.6%) patients: basal cell carcinoma, breast cancer, cervical carcinoma in situ, and chronic lymphocytic leukaemia, and one patient with both Bowen's disease and basal cell carcinoma (all in the RA trial) and gastric cancer and colon cancer (one patient each) in the PsA trial. The incidence of malignancies/100 PY (95% CI) across the three studies was 0.4, 0.2, 0.9. There were no cases of lymphoma.<br><br>In the All Randomized, Blinded Trials Population of All Trials for reference product SIMPONI, the frequencies of certain types of malignancies were as follows:<br>• Malignancies (excluding lymphoma, skin cancer, and leukemia): 0.2% for golimumab-treated subjects compared with 0.3% for those who received placebo or comparator.<br>• Lymphoma (excluding HSTCL): <0.1% for golimumab-treated subjects compared with 0% for those who received placebo or comparator.<br>• Skin cancer: Nonmelanoma skin cancer: <0.2% for golimumab-treated subjects compared with 0.3% for those who received placebo or comparator. Melanoma skin cancer: None for both golimumab-treated subjects and those who received placebo or comparator.<br>• Leukemia: None for both golimumab-treated subjects and those who received placebo or comparator. |

| Important Identified Risk – Malignancy | |
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| | In the post-marketing setting, 5-year trend analyses of spontaneously reported cases for MAA reference product SIMPONI were consistent with what is currently known about the risk of malignancies in patients treated with golimumab.[1]<br><br>In study AVT05-GL-C01 (up to week 16), one subject in AVT05 group reported serious severe TEAE of "Benign Neoplasm of Thyroid Gland". One subject died of metastatic neoplasm in the EU-Simponi group, which was considered conservatively, related to the treatment.<br><br>No AESIs of malignancies were reported in study AVT05-GL-P01. |
| **Risk factors and risk groups** | Immunosuppressive therapy itself can facilitate the development of malignant neoplasms, accelerate tumour growth, and favour the onset of metastases. The types of tumours most associated with its use are lymphoproliferative tumours and non-melanoma skin cancer.<br>Information regarding additional risk factors for the malignancy subtypes included in the broad category of malignancy is given below.<br><br><u>Lymphoma:</u><br>Risk factors for the development of lymphoma include older age, male gender, family history, immunosuppression (due to medications [such as immunosuppression for organ transplants, chemotherapy for cancer or treatment for autoimmune diseases], infection with HIV, or from immune deficiencies due to an inherited syndrome), autoimmune diseases with chronic inflammation (RA, systemic lupus erythematosus, Sjögren's syndrome, celiac disease), infections that directly transform lymphocytes (human T-cell lymphotropic virus, Epstein-Barr virus, human herpes virus 8), infections that cause chronic immune stimulation (Helicobacter pylori, Chlamydophila psittaci, Campylobacter jejuni, chronic hepatitis C infection), radiation exposure, and exposure to certain chemicals among others.<br><br>Hepatosplenic T-cell lymphoma: young men, the immunocompromised, and patients undergoing solid organ transplantation appear to be at a higher risk for HSTCL.<br><br><u>Skin Cancer</u><br>Melanoma: Risk factors for the development of melanomas can be categorized as environmental or host factors. Exposure to ultraviolet (UV) light, especially in patients with a fair complexion, history of sunburns, and poor ability to tan, is the most strongly correlated environmental risk factor with the development of melanoma. Patients with xeroderma pigmentosum who do not have the ability to repair UV light-induced DNA damage are particularly susceptible. Family or personal history of melanoma and/or certain gene mutations are strong host risk factors. Additional host risk factors include the presence of 5 or more dysplastic nevi, a large number of nevi, and giant congenital nevus. Patients with conditions that are associated with immune suppression (ie, HIV, organ transplantation) are at higher risk of developing melanomas.<br><br>Nonmelanoma skin cancer: The risk factors for squamous cell carcinoma (SCC) include chronic UV light exposure (UVA and UVB), increasing age, arsenic exposure, |

| Important Identified Risk – Malignancy | |
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| | genetic predisposition, therapeutic radiation exposure, and immunosuppression. The risk factors for basal cell carcinoma include all those for SCC in addition to basal cell nervous syndrome. With respect to patients with RA, epidemiological trials have generally shown that skin cancers are increased in this group, and immunosuppression may potentiate this risk by shortening the time taken to develop a malignancy. With respect to psoriasis patients, a higher risk of NMSC is seen in those with prior coal tar, UVB therapy, psoralen plus UVA light, retinoids, and cyclosporine therapy.<br><br>Merkel cell carcinoma (MCC): Although the cause of MCC remains unclear, risk factors associated with its development include exposure to UV radiation, immunosuppression, and possibly viral causes. Most MCCs are located on sun exposed areas, particularly the head and neck, extremities, and trunk. Merkel cell carcinoma occurs most frequently in elderly white patients and affects males more commonly than females. Immunosuppression increases the risk of MCC in patients with HIV and in solid organ transplant patients. Patients with other tumors, such as SCC and chronic lymphocytic leukemia, also have an increased risk of MCC.<br><br><u>Leukemia</u><br>Risk factors for the development of leukemia include genetic abnormalities, family history, radiation exposure, chemotherapy, autoimmune diseases with chronic inflammation and exposure to certain chemicals among others. |
| **Preventability** | The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Therefore, caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.<br>All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma, or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. In patients with newly diagnosed colon dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.<br>Caution should be exercised when using any TNF-antagonist in chronic obstructive pulmonary disease (COPD) patients, as well as in patients with an increased risk of malignancy due to heavy smoking.<br>Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer. |
| **Impact on the risk-benefit balance of the product** | The observed incidence of malignancy through the available data (including lymphoma, HSTCL, skin cancer and leukemia) does not have a significant impact on the risk-benefit balance of the product.<br>The risk of malignancy will be further characterized by the routine PV activities. |

| Important Identified Risk – Malignancy | |
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| | Risk minimization measures described in the SmPC, and PL are considered adequate and proportionate to the risk at present. |
| **Public health impact** | The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorized product label. |

| Important Potential Risk – Serious Depression Including Suicidality | |
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| **Potential mechanism(s)** | The exact biological mechanism of depression is not known. Cytokines may be involved with serotonin metabolism. More specifically, pro-inflammatory cytokines such as TNFα are associated with major depression; reducing the effect of these cytokines may reverse depressive symptoms.[1] |
| **Evidence source(s) and strength of evidence** | The MAA reference product SIMPONI has been investigated in multiple settings. In clinical trials, serious depression including suicidality has been reported in patients treated with SIMPONI. Depression has also been reported in the post-marketing setting and is described in published medical literature.[1]<br>Although serious depression has been reported in patients treated with SIMPONI, a causal association between the development or worsening of serious depression (including suicidality) and SIMPONI has not been established. Complicating the assessment is evidence that patients with RA, AS, and PsA have increased rates of depression compared to the general population. Additionally, while some researchers have found no evidence of an association between depression and UC, others have suggested that depression and anxiety are common in patients with IBD.[1] |
| **Characterisation of the risk** | In the All Randomized, Blinded Trials Population of All Trials of the MAA reference product SIMPONI, the frequency of serious depression (including suicidality) was <0.1% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.[1]<br>In study AVT05-GL-C01 and AVT05-GL-P01, no TEAESIs related to "Depression" were reported. |
| **Risk factors and risk groups** | Risk factors for depression include older age and associated neurologic conditions, recent childbirth, stressful life events, a personal or family history of depression, and selected medical comorbid conditions. Suicide rates are twice as high in families of suicide victims. |
| **Preventability** | There is no known means of preventing depression. Patients with a history of untreated or inadequately treated depression should be treated for such. |
| **Impact on the risk-benefit balance of the product** | The observed incidence of serious depression, including suicidality, with MAA reference product SIMONI has not had a significant impact on the risk-benefit of the product. This safety concern will be evaluated through routine pharmacovigilance activities and routine risk minimisation measures (SmPC and PL) are considered adequate and proportionate to the risk. |

| Important Potential Risk – Serious Depression Including Suicidality | |
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| **Public health impact** | The public health impact of the development of serious depression (including suicidality) during treatment with golimumab is not known at present. |

| Important Potential Risk – Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* | |
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| **Potential mechanism(s)** | Due to its inhibition of TNF and potential to cross the placenta, golimumab administered during pregnancy could affect normal immune responses in the new-born.<br>Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Because TNFα inhibitors reduce the immune response, administration of a TNFα inhibitor during pregnancy may predispose infants to breakthrough infections when receiving live (attenuated) vaccines within 6 months after birth.[3] |
| **Evidence source(s) and strength of evidence** | In infants exposed *in utero* to another TNFα-blocking agent infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.[6] |
| **Characterisation of the risk** | There have been no reported cases of breakthrough infections following administration of live (attenuated) vaccines in infants born to women who received the MAA reference product SIMPONI in clinical trials or in the post-marketing setting. Breakthrough infection after administration of live vaccines in infants exposed to TNFα inhibitors in utero is considered a class effect, and therefore included as an important potential risk for golimumab. |
| **Risk factors and risk groups** | Infants exposed to golimumab *in utero* and who receive live (attenuated) vaccines within 6 months after birth may be at risk for developing breakthrough infection. |
| **Preventability** | Administration of live (attenuated) vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy.<br>In addition, the MAA proposes an additional risk minimisation measure of "Patient Reminder Card" to educate patients on important safety information that they need to be aware of before and during treatment with golimumab and to enhance patient knowledge regarding the risk of infection after administration of live vaccines in infants exposed to golimumab *in utero* (Refer Part V.2 for complete details). |
| **Impact on the risk-benefit balance of the product** | No cases of breakthrough infection following administration of live vaccines in infants exposed to golimumab in-utero has been reported with SIMPONI. This safety concern will be evaluated through routine pharmacovigilance activities. Routine Risk minimization measures such as SmPC, PL, and additional risk minimisation measure of Patient Reminder Card are considered adequate and proportionate to the risk at present. |

| Important Potential Risk – Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* | |
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| **Public health impact** | The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the authorized product label. |

*SVII.3.2. Presentation of the missing information*

| Missing Information – Long-term safety in paediatric patients | |
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| **Evidence source(s)** | The safety and efficacy of golimumab in patients aged less than 18 years for indications other than pJIA have not been established.<br>The safety of golimumab (SIMPONI) has been studied in a Phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.[1]<br><br>Although no risks of clinical significance were identified in golimumab-treated subjects, the effect of long-term treatment with golimumab in this patient population has not been studied. |
| **Population in need of further characterisation** | Paediatric patients ≥ 2 years of age who have been treated with golimumab long term. Long-term safety information on golimumab use in this patient population will be monitored through routine pharmacovigilance activities. |

**Module SVIII - Summary of the Safety Concerns**

**Table 9: Summary of safety concerns***

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| **Important identified risk(s)** | • Serious infections<br>• Demyelinating disorders<br>• Malignancy |
| **Important potential risk(s)** | • Serious depression including suicidality<br>• Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* |
| **Missing information** | • Long-term safety in paediatric patients |

* ***Source***: *e.g., The list of safety concerns is aligned with the reference product SIMPONI's list of safety concerns*

**Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)**

**III.1 Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection**

**III.1.1 Specific adverse reaction follow-up questionnaires**

| List of Safety Concern | Specific adverse reaction follow-up questionnaires |
|---|---|
| **Serious infections** | Specific adverse reaction follow-up questionnaires to collect information on serious infections and opportunistic infections, TB and progressive multifocal leukoencephalopathy/reversible posterior leukoencephalopathy syndrome. |
| **Malignancy** | Specific adverse reaction follow-up questionnaires to collect information on malignancy events (including lymphoma, second and secondary malignancies). Particular attention is paid to subjects ≤30 years of age. |

**III.1.2 Other forms of routine pharmacovigilance activities**

Not Applicable

**III.2 Additional Pharmacovigilance Activities**

No additional pharmacovigilance activities are planned or required for product.

**III.3 Summary Table of additional Pharmacovigilance activities**

Not Applicable

**Part IV: Plans for Post-Authorisation Efficacy Studies**

No post-authorisation efficacy study is planned or required for product.

**Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)**

**V.1 Routine Risk Minimisation Measures**

**Table 10: Description of Routine Risk Minimisation Measures by Safety Concern**

| ***Important Identified Risk(s)*** | |
|---|---|
| **Serious infections** | **Routine risk communication:**<br>Summary of Product Characteristic (SmPC) sections 4.3, 4.4, 4.5, 4.8<br>Package Leaflet (PL) sections 2 and 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Guidance on evaluating patients for infections prior to treatment initiation, monitoring patients for infections during and after treatment, and managing patients who develop infections have been included in SmPC section 4.4.<br>Recommendations regarding the administration of live vaccines to patients receiving golimumab have been included in SmPC section 4.5.<br>Advice to patients to notify their doctor if they have an infection before using golimumab or if they experience symptoms of an infection during the treatment have been included in the PL.<br>In addition, specific adverse reaction follow-up questionnaire (routine PV activity) for serious infections (including opportunistic infections, TB and progressive multifocal leukoencephalopathy/reversible posterior leukoencephalopathy syndrome) is in place which shall aid the MAA in obtaining additional details regarding this risk.<br>**Other routine risk minimization measures beyond the Product**<br>Legal status: Restricted medical prescription |
| **Demyelinating disorders** | **Routine risk communication:**<br>SmPC sections 4.4, 4.8<br>PL sections 2 and 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Guidance to discontinue use of golimumab if demyelinating disorders develop have been included in SmPC section 4.4.<br>Advice to patients to notify their doctor if they have been diagnosed with nervous system disease before using golimumab or if they experience any symptoms of nervous system disease have been included in the PL.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Restricted medical prescription |
| Malignancy | **Routine risk communication:** |

| | |
|---|---|
| | SmPC sections 4.4, 4.8<br>PL sections 2 and 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Recommendation to screen patients with ulcerative colitis who are at increased risk of or have a history of colon dysplasia or colon carcinoma for dysplasia before treatment initiation and throughout their disease course have been included in SmPC section 4.4.<br>Recommendation to perform periodic skin examination, particularly for patients with risk factors for skin cancer have been included in SmPC section 4.4.<br>Advice to patients to notify their doctor if have been diagnosed with lymphoma or any other cancer before using golimumab, if they experience symptoms of lymphoma, skin cancer, or leukemia and discuss whether treatment with a TNF blocker is appropriate, have been included in the PL.<br>In addition, specific adverse reaction follow-up questionnaire (routine PV activity) for malignancy is in place which shall aid the MAA in obtaining additional details regarding this risk.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Restricted medical prescription |
| ***Important Potential Risk(s)*** | |
| **Serious depression including suicidality** | **Routine risk communication:**<br>SmPC section 4.8<br>PL section 4<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Restricted medical prescription |
| **Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*** | **Routine risk communication:**<br>SmPC sections 4.4 and 4.6<br>PL section 2<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>Recommendations to avoid administration of live vaccines to infants exposed to golimumab *in utero* for 6 months following the mother's last golimumab injection during pregnancy have been included in SmPC section 4.6. |

| | |
|---|---|
| | Advice to patients exposed to golimumab during pregnancy to notify the paediatrician and other HCPs about their use of golimumab before the child receives any vaccine.<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Restricted medical prescription |
| ***Missing Information*** | |
| **Long-term safety in paediatric patients** | **Routine risk communication:**<br>None<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>None<br>**Other routine risk minimization measures beyond the Product Information:**<br>Legal status: Restricted medical prescription |

**V.2 Additional Risk Minimisation Measures**

| | |
|---|---|
| **Important Identified Risk: Serious infections**<br>**Important Potential Risk: Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*** | |
| **Additional Risk Minimization Measure:** Patient Reminder Card | |
| **Objective(s)** | To educate patients on important safety information that they need to be aware of before and during treatment with golimumab.<br>The Patient Reminder Card addresses the following important risks:<br>-Serious infections (including opportunistic infections, tuberculosis, hepatitis B virus reactivation)<br>-Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* |
| **Rationale** | -To enhance patient knowledge regarding the risk of infection associated with golimumab treatment.<br>-To remind patients who received golimumab during pregnancy to inform their infant's physician before the infant receives any live vaccine. |
| **Target audience and planned distribution path** | Target Audience: All the patients who administer golimumab.<br>Distribution path: The Patient Reminder Card shall be provided as part of the product packaging. |
| **Plans to evaluate the effectiveness of the interventions and criteria for success** | Through routine PV activity. |

### V.3 Summary of Risk Minimisation Measures

**Table 11: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| ***Important Identified Risk(s)*** | | |
| **Serious infections** | **Routine risk minimisation measures:**<br>SmPC sections 4.3, 4.4, 4.5, 4.8<br>PL sections 2 and 4<br>**Additional risk minimisation measures:**<br>Patient Reminder Card | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Specific adverse reaction follow-up questionnaire for serious Infections, opportunistic infections, TB and Progressive Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)<br>**Additional pharmacovigilance activities:**<br>None |
| **Demyelinating disorders** | **Routine risk minimization measures:**<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |
| **Malignancy** | **Routine risk minimization measures:**<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Specific adverse reaction follow-up questionnaire for malignancies (including lymphoma, second and secondary malignancies)<br>**Additional pharmacovigilance activities:**<br>None |
| ***Important Potential Risk(s)*** | | |
| **Serious depression including suicidality** | **Routine risk minimization measures:**<br>SmPC sections 4.8<br>PL sections 4<br>**Additional risk minimization measures:** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | None | **Additional pharmacovigilance activities:**<br>None |
| **Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*** | **Routine risk minimization measures:**<br>SmPC sections 4.4, 4.6<br>PL sections 2<br>**Additional risk minimization measures:**<br>Patient Reminder Card | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |
| ***Missing Information*** | | |
| **Long-term safety in pediatric patients** | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |

**Part VI: Summary of the Risk Management Plan**

**Summary of risk management plan for Gobivaz 50 mg/100 mg solution for injection in pre-filled pen and 50 mg/100 mg solution for injection in pre-filled syringe (herein referred as Gobivaz)**

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

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

This summary of the RMP for Gobivaz should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Gobivaz is authorised for the following indications:

- In combination with methotrexate (MTX) for the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate and the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.
- In combination with MTX for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.
- Alone or in combination with MTX, for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
- For the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.
- For the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).
- 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.

It contains golimumab as the active substance and it is given by subcutaneous route.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER assessment if PBRER is required by Health Authority, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

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

**II.A. List of important risks and missing information**

Important risks of Gobivaz are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered/taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Gobivaz. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of Important Risks and Missing Information** | |
|---|---|
| **Important identified risk(s)** | • Serious infections<br>• Demyelinating disorders<br>• Malignancy |
| **Important potential risk(s)** | • Serious depression including suicidality<br>• Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* |
| **Missing information** | • Long-term safety in paediatric patients |

**II.B. Summary of important risk**

| **Important Identified Risk – Serious infections** | |
|---|---|
| **Evidence for linking the risk to the medicine** | Because they suppress the immune system, drugs that inhibit TNFα have been associated with an increased risk of serious infections (some fatal), including |

| Important Identified Risk – Serious infections | |
|---|---|
| | opportunistic infections, TB, and invasive fungal infections. Drugs that inhibit TNFα have also been associated with hepatitis B virus (HBV) reactivation in patients who are chronic carriers of the virus.<br>Serious infections, including opportunistic infections and TB, have been reported in patients treated with golimumab in clinical trials and in the post-marketing setting. Hepatitis B virus reactivation has been reported in the post-marketing setting in patients treated with golimumab.[3]<br>These findings are consistent with nonclinical data and published medical literature. |
| **Risk factors and risk groups** | <u>Serious Infections</u><br>Risk factors for the development of serious infections include the use of steroids, other immunosuppressive drugs (including MTX), or other biologics at the same time as golimumab.<br><u>Opportunistic Infections</u><br>People whose immune status is compromised are susceptible to opportunistic infections. Risk factors for opportunistic infections may therefore include human immunodeficiency virus (HIV) disease, increased age, having an organ transplant, immunosuppressive drug therapy (corticosteroids, MTX, azathioprine, and biologic agents), chronic pulmonary disease, and chronic renal failure.<br><u>Invasive Fungal Infections</u><br>People who have resided in or travelled to regions where invasive fungal infections are common are at increased risk.<br><u>Tuberculosis</u><br>The most common risk factors for the development of TB include conditions that weaken the immune system such as advanced age, HIV infection, alcohol abuse, malignancy, use of corticosteroids or other immunosuppressive drugs such as MTX, connective tissue disease, renal failure, diabetes, and pregnancy.<br>Other risk factors for the development of TB include contact with a person with active TB infection and having been born in, lived in, or travelled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (e.g., hospitals and nursing homes) or high-density institutions (e.g., prisons).<br><u>Hepatitis B Virus (HBV) Reactivation</u><br>Risk factors for the acquisition of HBV include being born to a mother from a highly endemic area, emigration from a highly endemic area, history of IV drug use, and a history of multiple sexual partners. Patients at risk for HBV reactivation are those who are chronic carriers of this virus (i.e., surface antigen-positive), especially those who become immunosuppressed. Approximately 14% to 50% of immunosuppressed patients who are chronic |

| Important Identified Risk – Serious infections | |
|---|---|
| | carriers of HBV will experience acute reactivations during the natural history of their disease. Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (e.g., chemotherapy, corticosteroids, MTX, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>SmPC sections 4.3, 4.4, 4.5, 4.8<br>Package Leaflet (PL) sections 2 and 4<br>**Additional risk minimisation measures:**<br>Patient Reminder Card |

| Important Identified Risk – Demyelinating Disorders | |
|---|---|
| **Evidence for linking the risk to the medicine** | Since TNF-α is implicated in demyelinating processes, TNF-α blockers were considered as a potential therapeutic choice in multiple sclerosis. However, the negative outcomes of these agents in multiple sclerosis trials and the reports of demyelinating events following their use for other disorders raised the suspicion that use of these drugs could be a risk factor of demyelination.[8]<br><br>Use of TNF-blocking agents, including golimumab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy.[3] |
| **Risk factors and risk groups** | Multiple sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk of developing MS than the general population.[9] Whites, particularly of northern European descent, are also more likely to develop MS.[10]<br>Several studies have suggested an association between smoking and MS. [10]<br>Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS.[10] |
| **Risk minimisation measures** | **Routine risk minimization measures:**<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>**Additional risk minimization measures:** |

| Important Identified Risk – Demyelinating Disorders | |
|---|---|
| | None |

| Important Identified Risk – Malignancy | |
|---|---|
| **Evidence for linking the risk to the medicine** | Reports of malignancies in golimumab-treated subjects, including lymphoma, skin cancer, and leukemia, have been received in clinical trials and in the post-marketing setting.<br><br>For non-lymphoma malignancies (excluding nonmelanoma skin cancer [NMSC]), the incidence was similar between the golimumab and the control groups in the controlled portions of the golimumab pivotal trials for MAA reference product SIMPONI and through approximately 4 years of follow-up. The incidence was also similar to the incidence in the general population.[1]<br><br>For lymphoma, more cases have been observed among patients receiving anti-TNFα treatment compared with control patients in the controlled portions of clinical trials of all TNFα-blocking agents, including golimumab. However, there is an increased background risk for lymphoma in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.[1]<br><br>During the golimumab (SIMPONI) Phase 2b and 3 SC clinical trials in RA, PsA, and AS, the incidence of lymphoma in golimumab-treated subjects was higher than expected compared to the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg.[1]<br><br>Looking specifically at children, adolescents, and young adults (up to 22 years of age), post-marketing cases of malignancies, some fatal, have been reported in patients who received TNFα inhibitors (initiation of therapy ≤18 years of age) to treat JIA, Crohn's disease, or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as MTX, azathioprine, or 6-mercaptopurine. It is not clear whether children with certain autoimmune conditions have an increased risk for malignancy given limited data.[1]<br><br>For HSTCL, there have been rare reports in the post-marketing setting in patients treated with other TNFα inhibitors.[1] |

| Important Identified Risk – Malignancy | |
|---|---|
| **Risk factors and risk groups** | Immunosuppressive therapy itself can facilitate the development of malignant neoplasms, accelerate tumour growth, and favour the onset of metastases. The types of tumours most associated with its use are lymphoproliferative tumours and non-melanoma skin cancer.<br>Information regarding additional risk factors for the malignancy subtypes included in the broad category of malignancy is given below.<br><br><u>Lymphoma:</u><br>Risk factors for the development of lymphoma include older age, male gender, family history, immunosuppression (due to medications [such as immunosuppression for organ transplants, chemotherapy for cancer or treatment for autoimmune diseases], infection with HIV, or from immune deficiencies due to an inherited syndrome), autoimmune diseases with chronic inflammation (RA, systemic lupus erythematosus, Sjögren's syndrome, celiac disease), infections that directly transform lymphocytes (human T-cell lymphotropic virus, Epstein-Barr virus, human herpes virus 8), infections that cause chronic immune stimulation (Helicobacter pylori, Chlamydophila psittaci, Campylobacter jejuni, chronic hepatitis C infection), radiation exposure, and exposure to certain chemicals among others.<br><br>Hepatosplenic T-cell lymphoma: young men, the immunocompromised, and patients undergoing solid organ transplantation appear to be at a higher risk for HSTCL.<br><br><u>Skin Cancer</u><br>Melanoma: Risk factors for the development of melanomas can be categorized as environmental or host factors. Exposure to ultraviolet (UV) light, especially in patients with a fair complexion, history of sunburns, and poor ability to tan, is the most strongly correlated environmental risk factor with the development of melanoma. Patients with xeroderma pigmentosum who do not have the ability to repair UV light-induced DNA damage are particularly susceptible. Family or personal history of melanoma and/or certain gene mutations are strong host risk factors. Additional host risk factors include the presence of 5 or more dysplastic nevi, a large number of nevi, and giant congenital nevus. Patients with conditions that are associated with immune suppression (i.e., HIV, organ transplantation) are at higher risk of developing melanomas.<br><br>Nonmelanoma skin cancer: The risk factors for squamous cell carcinoma (SCC) include chronic UV light exposure (UVA and UVB), increasing age, arsenic exposure, genetic predisposition, therapeutic radiation exposure, and immunosuppression. The risk factors for basal cell carcinoma include all those for SCC in addition to basal cell nervous syndrome. With respect to patients with RA, epidemiological trials have generally shown that skin cancers are |

| Important Identified Risk – Malignancy | |
|---|---|
| | increased in this group, and immunosuppression may potentiate this risk by shortening the time taken to develop a malignancy. With respect to psoriasis patients, a higher risk of NMSC is seen in those with prior coal tar, UVB therapy, psoralen plus UVA light, retinoids, and cyclosporine therapy.<br><br>Merkel cell carcinoma (MCC): Although the cause of MCC remains unclear, risk factors associated with its development include exposure to UV radiation, immunosuppression, and possibly viral causes. Most MCCs are located on sun exposed areas, particularly the head and neck, extremities, and trunk. Merkel cell carcinoma occurs most frequently in elderly white patients and affects males more commonly than females. Immunosuppression increases the risk of MCC in patients with HIV and in solid organ transplant patients. Patients with other tumors, such as SCC and chronic lymphocytic leukemia, also have an increased risk of MCC.<br><br><u>Leukemia</u><br>Risk factors for the development of leukemia include genetic abnormalities, family history, radiation exposure, chemotherapy, autoimmune diseases with chronic inflammation and exposure to certain chemicals among others. |
| **Risk minimisation measures** | **<u>Routine risk minimization measures:</u>**<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>**<u>Additional risk minimization measures:</u>**<br>None |

| Important Potential Risk – Serious Depression Including Suicidality | |
|---|---|
| **Evidence for linking the risk to the medicine** | The MAA reference product SIMPONI has been investigated in multiple settings. In clinical trials, serious depression including suicidality has been reported in patients treated with SIMPONI. Depression has also been reported in the post-marketing setting and is described in published medical literature.[1]<br>Although serious depression has been reported in patients treated with SIMPONI, a causal association between the development or worsening of serious depression (including suicidality) and SIMPONI has not been established. Complicating the assessment is evidence that patients with RA, AS, and PsA have increased rates of depression compared to the general population. Additionally, while some researchers have found no evidence of an association between depression and UC, others have suggested that depression and anxiety are common in patients with IBD.[1] |

| Important Potential Risk – Serious Depression Including Suicidality | |
|---|---|
| **Risk factors and risk groups** | Risk factors for depression include older age and associated neurologic conditions, recent childbirth, stressful life events, a personal or family history of depression, and selected medical comorbid conditions. Suicide rates are twice as high in families of suicide victims. |
| **Risk minimisation measures** | **Routine risk minimization measures:**<br>SmPC sections 4.8<br>PL sections 4<br>**Additional risk minimization measures:**<br>None |

| Important Potential Risk – Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* | |
|---|---|
| **Evidence for linking the risk to the medicine** | In infants exposed *in utero* to another TNFα-blocking agent infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.[6] |
| **Risk factors and risk groups** | Infants exposed to golimumab *in utero* and who receive live (attenuated) vaccines within 6 months after birth may be at risk for developing breakthrough infection. |
| **Risk minimisation measures** | **Routine risk minimization measures:**<br>SmPC sections 4.4, 4.6<br>PL sections 2<br>**Additional risk minimization measures:**<br>Patient Reminder Card |

| Missing Information – Long-term safety in paediatric patients | |
|---|---|
| **Risk minimisation measures** | **Routine risk minimization measures:**<br>None<br>**Additional risk minimization measures:**<br>None |

**II.C. Post-authorisation development plan**

***II.C.1 Studies which are conditions of the marketing authorisation***

There are no studies which are conditions of the marketing authorisation or specific obligation of Gobivaz..

***II.C.2 Other studies in post-authorisation development plan***

There are no studies required for Gobivaz..

**Part VII: Annexes**

**Annex 4: Specific adverse drug reaction follow-up forms**

1. Specific Targeted Follow-up Questionnaire for Serious Infections and Opportunistic Infections
2. Specific Targeted Follow-up Questionnaire for Tuberculosis (TB)
3. Specific Targeted Follow-up Questionnaire for Progressive Multifocal
4. Specific Targeted Follow-up Questionnaire for Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
5. Specific Targeted Follow-up Questionnaire for Malignancies (including Lymphoma, Second and Secondary Malignancies)

**Targeted Follow-up Questionnaire for Serious Infections and Opportunistic Infections**

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. **Medical History and Concurrent Conditions**

☐ Prior history of exposure to TB
Details:
☐ Prior history of exposure to Hepatitis B/C
Details:
Details of vaccination history:
☐ The patient was considered immunocompromised *(underlying diagnoses, immunosuppressive therapy etc.)*
Details:

Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. **Adverse Event Details**

☐ The infection was present prior to starting the product

☐ There were unusual features of the patient's presentation or clinical course
Details:

Type of infection (e.g., pneumonia, endocarditis, etc.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

**Targeted Follow-up Questionnaire for Tuberculosis**

Manufacturer Control Number: Drug generic (TRADE) Name:
Date of Report [dd-MMM-yyyy]

1. **Relevant medical/occupational history** *(Check all that apply and provide details below.)*

☐ Weight loss ≥ 10% of ideal body weight ☐ Head/Neck carcinoma ☐ Silicosis
☐ Diabetes ☐ Leukemia/Lymphoma ☐ Positive HIV test
☐ Gastrectomy or jejunoileal bypass ☐ Household contact/Exposure to TB
☐ Organ/Tissue transplant ☐ Prior/prolonged steroid use
☐ Prior BCG vaccination ☐ IV drug abuse
☐ Recent travel to endemic area ☐ Prior/prolonged immunosuppressant use`
☐ Resident/employee at high risk setting (e.g., correctional institute, homeless shelter, nursing home, refugee camp, etc.)
Details:

2. **Diagnostics**

☐ Purified Protein Derivative (PPD) testing was performed. Indicate test used:
☐ Intradermal skin test
☐ Multipuncture skin test
Number of units administered:
PPD Result: mm of induration (0, if no induration)
Date of PPD: [dd-MMM-yyyy]
2nd PPD results (if applicable): mm of induration
Date of second PPD: [dd-MMM-yyyy]
☐ False negative test (e.g., time of injection to time of evaluation too long/short, evaluator of induration, etc.)? Explain reasons:
☐ The subject had active TB
☐ Prophylactic therapy was given
Time elapsed from onset of TB symptoms to institution of treatment:

Type of tuberculosis:
☐ Pulmonary
☐ Extrapulmonary; Location:
☐ Disseminated; Location:
☐ Multi-drug Resistant TB

**Other laboratory results**

| Laboratory Test | | Test Result | Date: [dd-MMM-yyyy] |
|---|---|---|---|
| AFB Smear | Sputum | | |
| | Other (specify) | | |
| Culture | Sputum | | |
| | Other (specify) | | |
| PCR MTb | | | |
| Quantiferon TB Gold | | | |

**Targeted Follow-up Questionnaire for Progressive Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

Manufacturer Control Number: Drug generic (TRADE) Name:
Date of Report: [dd-MMM-yyyy]

1. **Medical History and Concurrent Conditions**

List relevant concurrent/pre-existing conditions *(e.g., Hodgkin's CLL, CML, AML, ongoing GVHD, long term immunosuppression, pre-existing neurological features/disorders, and any relevant previous imaging or laboratory test results.) List the details with dates of diagnosis*:

History of pre-existing conditions (*Check all that apply*):

- ☐ Systemic hypertension
- ☐ Renal disease (e.g., renal failure)
- ☐ Preceding history of infection (e.g., HIV and/or sepsis)
- ☐ Immune mediated disease (e.g., Systemic lupus erythematosus, Polyarteritis nodosa etc.)

Other relevant medical history (e.g., transplantation, neurological disorders, pre-eclampsia, chemotherapy etc.):

2. **Diagnostics**

Laboratory/radiographic evaluation results as appropriate and accompanying normal ranges, if available. *(Note date performed and other test results as appropriate.)*

- ☐ MRI: Date: [dd-MMM-yyyy], Results:
- ☐ JC Virus DNA test was performed: Date: [dd-MMM-yyyy], Results:
- ☐ CSF Fluid: Date: [dd-MMM-yyyy], Results:
- ☐ Brain tissue biopsy: Date: [dd-MMM-yyyy], Results:
- ☐ Non-CSF sources for JCV DNA testing: Date: [dd-MMM-yyyy], Results:
- ☐ Imaging studies (e.g., CT scan, etc.): Date: [dd-MMM-yyyy], Results:
- ☐ Histopathology of brain biopsy finding: Date: [dd-MMM-yyyy]
  - ☐ Demyelination
  - ☐ Enlarged oligodendroglial nuclei
  - ☐ Bizarre astrocytes
  - ☐ Other findings:

- ☐ Evidence of JC virus in brain tissue by:
  - ☐ Electron microscopy
  - ☐ Immunohistochemistry
  - ☐ In situ Hybridization
  - ☐ PCR
- ☐ Other relevant test results:
- ☐ Neurological evaluation was performed. (*Include the neurology report*):
- ☐ Other findings, including dates *(e.g., clinical features observed - central nervous system and other symptoms and their progression, including dates [these could include neurological deficits such as motor symptoms (e.g., hemiparesis), cognitive dysfunction or changes in behavior or personality, language or speech disturbances (e.g., aphasia/dysarthria), visual disturbances (e.g., hemianopsia), ataxia/loss of motor coordination, seizures, etc.])*:

3. **Prior or Concurrent Immunosuppressant Medications** *(e.g., chemotherapy agents, radiation, transplant regimens, immunotherapy with monoclonal antibodies such as anti-CD-20 monoclonal antibodies and include over-the-counter and herbal medications).*

| Medication | Indication | Total Daily Dose | Start Date [dd-MMM-yyyy] | Stop Date [dd-MMM-yyyy] |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

**Targeted Follow-up Questionnaire for Malignancies (including Lymphoma, Second and Secondary Malignancies)**

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. **Relevant Medical/Family History** *(Provide prior diagnoses and details for checked items below)*

☐ Previous malignancy (Provide specific diagnosis):
☐ Occupational/Exposure history:
☐ Excessive sun exposure (Describe):
☐ History of PUVA (Psoralen + Ultraviolet-A rays)
☐ History of radiation
Dose of radiation:
Area treated:
Age (or date of therapy) of the patient when they were treated with radiation:
Indication for radiation:
Any radiation induced changes?
☐ Pre-malignant lesions, e.g., Barret's oesophagus, Bowen's disease. Details:
Viral infections: ☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV
☐ Other relevant risk factors for malignancy (Excluding medications):
☐ Family history of malignancy (Provide specific diagnoses for each):
☐ In first degree relatives:
☐ In more distant relatives:
☐ Previous history of tumor necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):
Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)

Include drug indication, dose levels, and treatment duration (e.g., methotrexate, clophosphamide, vincristine, doxorubicine, cyclosporine, biologics)

| Medication | Indication | Dose/Route of Administration | Start Date/Stop Date (dd-MMM-yyyy) |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

☐ Cytogenetic abnormalities detected at any point in time? (Include those relevant for any malignancy including myeloma – this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc., or cytogenetic abnormalities relevant to myeloma)

## 2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, metastases, lymph node involvement and staging system used:

Additional diagnostic information, including finding that support specified staging; specialty consultations (Attach reports, if available): Final diagnosis:

☐ **Lymphoma**

☐ Non-Hodgkin's lymphoma

Histologic subtype: Immunophenotype: Cytogenetics:

☐ Hodgkin's lymphoma

Histologic subtype:

Was the lymphoma tissue tested for Epstein-Barr virus (EBV) (e.g., by in situ hybridization and/or immunohistology analysis)? ☐ No ☐ Yes (Attach report)

If Yes, Test Result: ☐ EBV positive ☐ EBV negative

☐ **Second malignancy** (A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) (List):

☐ **Secondary malignancy** (A cancer caused by treatment for a previous malignancy e.g., Treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) (*List*):

(Ref.http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf)

**Malignancy screening/Preventive measures** (Include those that are relevant to the specific malignancy that is being reported, e.g., recent mammography, breast exam, Pap smear, sigmoidoscopy or colonoscopy, faecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine etc.)

| Screening Test/Preventive Measure | Date (dd-MMM-yyyy) | Results (Including units and reference ranges where applicable) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

## 3. Treatment

What was the response to the first treatment for malignancy?

☐ Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease

**Annex 6: Details of proposed additional risk minimisation activities (if applicable)**

**Patient Reminder Card**

The educational program consists of a Patient Reminder Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals (HCPs) treating the patient, about ongoing treatment with the product.

The Patient Reminder Card shall contain the following key messages:

- A reminder to patients to show the Patient Reminder Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using golimumab.
- Provision to record the type, date and result of TB screenings.
- A statement that the brand name and batch number should be recorded.
- That treatment with golimumab may increase the risks of serious infections, opportunistic infections, TB, HBV reactivation, and breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero* and when to seek attention from an HCP.
- Contact details of the prescriber.

The language of the Patient Reminder Card is included in the Gobivaz product information Annex IIIA.