# ABATACEPT
# RISK MANAGEMENT PLAN

Data-lock Point for Current EU RMP: 30-Sep-2024

Version Number: 29.1

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.

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| Term | Definition |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ARTIS | Anti-Rheumatic Therapy in Sweden |
| BC | British Columbia |
| BMS | Bristol-Myers Squibb |
| CI | Confidence Interval |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| COPD | Chronic Obstructive Pulmonary Disease |
| CSF | Cerebral Spinal Fluid |
| CSR | Clinical Study Report |
| CTLA4 | Cytotoxic T-lymphocyte-associated antigen 4 |
| DMARD | Disease-modifying Anti-rheumatic Drug |
| DREAM | Dutch Rheumatoid Arthritis Monitoring |
| EBV | Epstein-Barr virus |
| EMA | European Medicines Agency |
| EU | European Union |
| EULAR | European League against Rheumatism |
| Fc | Fragment Crystaline |
| HIV | Human Immunodeficiency Virus |
| HLGT | High Level Group Term |
| HLT | High Level Term |
| ICD | International Coding Dictionary |
| Ig | Immunoglobulin |
| IL-6 | Interleukin 6 |
| IV | Intravenous |
| JIA | Juvenile Idiopathic Arthritis |
| JRA | Juvenile Rheumatoid Arthritis |
| KLH | Keyhole Limpet Hemocyanin |
| LCV | Lymphocryptovirus |
| LT | Long term |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Term | Definition |
|---|---|
| MLV | Murine Leukemia Virus |
| MS | Multiple Sclerosis |
| MSSO | Maintenance and Support Services Organization |
| MTX | Methotrexate |
| NMSC | Non-melanoma Skin Cancer |
| NSAID | Nonsteroidal Anti-inflammatory Drug |
| OL | Open-label |
| OTIS | Organization of Teratology Information Specialists |
| PIL | Patient Information Leaflet |
| PK | Pharmacokinetic |
| PML | Progressive Multifocal Leukoencephalopathy |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PsA | Psoriatic Arthritis |
| PSUR | Periodic Safety Update Report |
| p-y | Person-years |
| RA | Rheumatoid Arthritis |
| RABBIT | Rheumatoid Arthritis Observation of Biologic Therapy |
| RMP | Risk Management Plan |
| RR | Relative Risk |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |
| SCS | Summary of Clinical Safety |
| SLE | Systemic Lupus Erythematosus |
| SMQ | Standardized MedDRA query |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| ST | Short Term |
| TB | Tuberculosis |
| TNF | Tumor necrosis factor |
| UK | United Kingdom |
| USA | United States of America |

# EU RISK MANAGEMENT PLAN (RMP) FOR ABATACEPT

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

Version Number: 29.1

Data-lock Point for this RMP: 30-Sep-2024

Date of Final Sign-off: 10-Dec-2025

Rationale for submitting an updated RMP:

- Removal of Completed Studies from the Additional Pharmacovigilance Activities (APVA) List
  - Clinical studies IM101803, IM101121, IM101301 and IM101816 have been completed and are therefore removed from the APVA list.
- Updated to reflect Post-Authorisation Exposure Data
- Removal of Non-Product-Specific Adverse Drug Reaction (ADR) Follow-Up Forms
  - Follow-up forms related to adverse drug reactions that are not specific to the product have been removed.
- Editorial changes to the product overview to align with the current EU Label
- Removal of 'Immunogenicity in paediatric patients' as missing information from the list of safety concerns
- Incorporated extent of exposure data for subcutaneous abatacept during the 5-year extension period (IM101301)
- Removal of 'Malignancies' from the list of important potential risks
- Updated QPPV contact person

## Summary of Significant Changes in this RMP

| Part/Module | Summary of Major Changes | Version # / Date of Positive Opinion for Module Update |
|---|---|---|
| **Part I Product Overview**<br>Product details | Editorial changes to align with the current EU Label | V29.1 / pending |
| **Part II Safety Specification** | | |
| **SI** Epidemiology of the indication(s) and target population(s) | N/A | V22.1 /05-May-2017 |
| **SII** Non-clinical part of the safety specification | N/A | V15.0 /25-July-2013 |
| **SIII** Clinical trial exposure | Incorporated extent of exposure data for subcutaneous abatacept during the 5-Year extension period (IM101301) | V29.1 / pending |

## Summary of Significant Changes in this RMP

| Part/Module | Summary of Major Changes | Version # / Date of Positive Opinion for Module Update |
|---|---|---|
| **SIV** Populations not studied in clinical trials | N/A | V26.2 / 11-Jul-2019 |
| **SV** Post-authorization experience | Updates to Post-authorisation Exposure Data | V29.1 / pending |
| **SVI** Additional EU requirements for the safety specification | N/A | V19.0 / 01-Apr-2016 |
| **SVII** Identified and potential risks | Updates to reflect the removal of malignancies and immunogenicity in paediatric patients from the list of safety concerns. | V29.1 / pending |
| **SVIII** Summary of the safety concerns | Removal of immunogenicity in paediatric patients and malignancies from the summary of safety concerns. | V29.1/ pending |
| **Part III Pharmacovigilance Plan** | Removal of immunogenicity and malignancy language. Removed Table: 3.1-1 and Removal of language for Non-Product-Specific ADR Follow-Up Forms. Removed completed studies from Table 3.2-1 and Table 3.2-2 | V29.1 / pending |
| **Part IV Plan for post-authorization efficacy studies** | N/A | V21.0 /26-Aug-2017 |
| **Part V Risk Minimisation Measures** | Removal of immunogenicity and malignancy language. Removal of language for Non-Product-Specific ADR Follow-Up Forms | V29.1/ pending |
| **Part VI Summary of the Risk Management Plan** | Removal of immunogenicity and malignancy language. Removed completed studies from ongoing and planned additional pharmacovigilance activities | V29.1/ pending |
| **Part VII Annexes** | | |
| **ANNEX 2** Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme | Removal of immunogenicity and malignancies from the list of safety concern addressed in IM101240. Updated to reflected Completed Studies for Pharmacovigilance activities | V29.1 / pending |
| **ANNEX 3** Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan | Updated to reflected Completed Studies for Pharmacovigilance activities | V29.1/ pending |

## Summary of Significant Changes in this RMP

| Part/Module | Summary of Major Changes | Version # / Date of Positive Opinion for Module Update |
|---|---|---|
| **ANNEX 4**<br>Specific adverse drug reaction follow-up forms | Removal of language for Non-Product-Specific ADR Follow-Up Forms | V29.1 / pending |
| **ANNEX 5**<br>Protocols for proposed and on-going studies in RMP Part IV | N/A | V25.2 / -31-Jan-2019 |
| **ANNEX 6**<br>Details of proposed additional risk minimisation activities | N/A | V27.1 / 18-Nov-2019 |
| **ANNEX 7**<br>Other supporting data | N/A | V23.0 /25-Jul-2017 |
| **ANNEX 8**<br>Summary of changes to the risk management plan over time | Aligned with proposed changes in current RMP. | V29.1 / Pending |

**Details of the currently approved RMP:**

Version number: 27.1

Approved with procedure: EMEA/H/C/000701/II/0134

EC Decision Date: 12-Dec-2019

**EU RMP Contact Person: PharmD. Roberta Di Menno Di Bucchianico, EU QPPV**

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

# 1 PART 1: PRODUCT OVERVIEW

## Table 1-1: Product Details

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Abatacept |
| **Pharmacotherapeutic group(s) (ATC Code)** | Selective immunosuppressants; L04AA24 |
| **Marketing Authorization** | Bristol-Myers Squibb Pharma EEIG |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | ORENCIA |
| **Marketing authorization procedure** | Centralized |
| **Brief description of the product** | Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1). Abatacept selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. |
| **Hyperlink to the Product Information** | Refer to eCTD sequence number 0345 |
| **Indication(s) in the EEA** | **Current**<br>ORENCIA 250 mg powder for concentrate for solution for infusion<br>Rheumatoid arthritis<br>ORENCIA, in combination with methotrexate, is indicated for:<br>• The treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.<br>• The treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with MTX<br>A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.<br>Psoriatic arthritis<br>ORENCIA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including<br>MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required. |

**Table 1-1: Product Details**

Polyarticular juvenile idiopathic arthritis

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 6 years of age and older who have had an inadequate response to previous DMARD therapy.

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

ORENCIA solution for injection in pre-filled syringe

Rheumatoid arthritis

ORENCIA, in combination with methotrexate, is indicated for:

- The treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.
- The treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate.

A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.

Psoriatic arthritis

ORENCIA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required

Polyarticular juvenile idiopathic arthritis

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 2 years of age and older who have had an inadequate response to previous DMARD therapy.

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate

ORENCIA 125 mg solution for injection in pre-filled pen

Rhuematoid arthritis

ORENCIA, in combination with methotrexate, is indicated for:

- The treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.

**Table 1-1: Product Details**

- The treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate.

A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.

Psoriatic arthritis

ORENCIA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy including MTX has been inadequate and for whom additional systemic therapy for psoriatic skin lesions is not required.

**Dosage in the EEA**

ORENCIA 250 mg powder for concentrate for solution for infusion

Rheumatoid arthritis and psoriatic arthritis

Adults: Abatacept should be administered as a 30-minute intravenous infusion at the dose specified by body weight (see below). Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter:

**Table 1-2: Dose of ORENCIA[a]**

| Body Weight of Patient | Dose | Number of Vials[b] |
|---|---|---|
| < 60 kg | 500 mg | 2 |
| ≥ 60 kg to ≤ 100 kg | 750 mg | 3 |
| >100 kg | 1,000 mg | 4 |

[a] Approximating 10 mg/kg.

[b] Each vial provides 250 mg of abatacept for administration

Paediatric population:
The recommended dose of Orencia for patients 6 to 17 years of age with JIA is body weight-based.
Paediatric patients weighing less than 75 kg is:
10 mg/kg calculated based on the patient's body weight at each administration.
Paediatric patients weighing 75 kg or more should be administered Orencia following the adult dosing regimen, not to exceed a maximum dose of 1,000 mg.
Orencia should be administered as a 30-minute intravenous infusion.
Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Subcutaneous

Rheumatoid arthritis (adults)
ORENCIA SC may be initiated an intravenous (IV) loading dose.

**Table 1-1: Product Details**

| | |
|---|---|
| | ORENCIA SC should be administered weekly at a dose of 125 mg abatacept by subcutaneous injection regardless of weight (see section 5.1 of the SmPC).<br>If a single IV infusion is given to initiate treatment (IV loading dose before SC administration), the first 125 mg Orencia SC should be administered within a day of the IV infusion, followed by the weekly 125 mg Orencia SC injections (for the posology of the intravenous loading dose, please refer to section 4.2 of the SmPC of ORENCIA 250 mg powder for concentrate for solution for infusion).<br>Patients switching from abatacept IV therapy to SC administration should administer the first SC dose instead of the next scheduled IV dose.<br>**Psoriatic arthritis (adults)**<br>ORENCIA should be administered weekly at a dose of 125 mg by subcutaneous (SC) injection the need for an intravenous (IV) loading dose.<br>Patients switching from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose<br><br>**Polyarticular juvenile idiopathic arthritis**<br>Paediatric population: The recommended weekly dose of ORENCIA solution for injection in pre-filled syringe for patients 2 to 17 years of age with juvenile idiopathic arthritis should be initiated without an intravenous loading dose and administered utilising the weight range-based dosing as specified in Table 1-3: |

**Table 1-3: Weekly Dose of ORENCIA**

| Body Weight of Patient | Dose |
|---|---|
| 10 kg to less than 25 kg | 50 mg |
| 25 kg to less than 50 kg | 87.5 mg |
| 50 kg or more | 125 mg |

Patients switching from abatacept IV therapy to SC administration should administer the first SC dose instead of the next scheduled IV dose.

| | |
|---|---|
| **Pharmaceutical form (s) and strength(s)** | Powder for concentrate for solution for infusion. Each vial contains 250 mg of abatacept.<br>Solution for injection in pre-filled syringe. Each prefilled syringe contains 125 mg, 87.5 mg, or 50 mg of abatacept in one mL, 0.7 mL or 0.4 mL, respectively.<br><br>Solution for injection in pre-filled pen. Each pre-filled pen contains 125 mg of abatacept in one mL. |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

# 2 PART II: SAFETY SPECIFICATION

## 2.1 Epidemiology of the Indication(s) and Target Population(s)

### *2.1.1 Rheumatoid Arthritis*

**Table 2.1.1-1: Epidemiologic Characteristics of Adult RA Population**

| **Rheumatoid Arthritis** | |
|---|---|
| Incidence | The incidence rate of RA has been reported in several studies in various regions of the world.<br>In North American and North European countries, the annual incidence rate of RA varies between 30 and 60 cases per 100,000 inhabitants for females and between 10 and 30 cases per 100,000 inhabitants for males.[1,2,3,4,5,6,7,8,9,10,11,12]<br>Studies from Southern European countries indicate a relatively lower occurrence of the disease (10 to 20 cases per 100,000 inhabitants per year).[13,14,15] |
| Prevalence | Several prevalence studies of RA have been reported during the last decades, suggesting considerable variation among different populations.<br>The majority of prevalence studies conducted in Northern European and North American areas estimate a prevalence of 0.5-1.1%.[1,2,4,16,17,18,19,20,21,22,23]<br>A study conducted in Italy with an administrative cohort data source reported a gross prevalence rate of 0.48%, slightly lower than reported from similar administrative databases in Northern Europe.[3] A similar slightly lower rate was seen in a study with data from electronic databases in a county in Estonia which found an overall crude prevalence rate of 0.46%.[24]<br>Studies from Southern European countries report a prevalence of 0.3-0.7%.[13,25,26,27,28,29]<br>A study conducted in two regions of Serbia using medical documentation reported a prevalence of 0.22 % for each region.[30]<br>Research in Turkey showed the prevalence of RA was 1% in the general population.[31] |
| Demographics of the population - age, sex, race and/or ethnic origin | RA affects females 2- to 4-times more frequently than males;[8,32] however, it is generally more severe in males.[33]<br>The disease can occur at any age. In the USA, the UK, and Norway the peak age of incidence is around 55-64 in women and 65-75 in men.[34] There is evidence that the peak age of incidence has risen in recent years.[35] |
| Risk factors for the disease | The risk factors for developing RA include increased age, female sex, family history for rheumatic disease, smoking, and obesity.[1,7,20,32] |
| Main treatment options | DMARDs and biologic response modifiers. Corticosteroids and NSAIDs may also be used to treat pain and inflammation. |
| Mortality and morbidity (natural history) | The majority of studies examining RA and mortality have shown an increased risk of mortality associated with RA, which appears to result from a combination of the disease itself and the co-morbidities associated with RA.[36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54] Most of these studies report an increase of between 1.5 and 2-fold associated with RA compared |

| | |
|---|---|
| | to the general population. A few studies have found no excess mortality associated with RA; these were all studies of subjects with early RA.[55, 56, 57]<br>Several studies have shown that the increased mortality in RA subjects is related to disease severity.[38,39,40,42,44,51,52,53, 58, 59] Two groups studied the effect of anti-TNF use on mortality in RA subjects and neither found an increased risk associated with anti-TNF use. [60, 61]<br>The effect of the use of non-biologic anti-rheumatic drugs on mortality in RA subjects has also been investigated; glucocorticoid treatment has been shown to increase the risk of mortality[62] and MTX has been shown to decrease the risk.[63]<br>Morbidities in RA consist of cardiovascular disease, malignancies, and infections which could be exacerbated as a result from medications for RA treatment. |
| Important co-morbidities | An international, cross sectional study on the prevalence of comorbidities in RA conducted in 2013 reported the most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5% and chronic obstructive pulmonary disease, 3.5% though variability among countries was wide.[64] |

### *2.1.2 Polyarticular Juvenile Idiopathic Arthritis*

**Table 2.1.2-1: Epidemiologic Characteristics of Polyarticular JIA Population**

| **Polyarticular JIA** | |
|---|---|
| Incidence | JIA is the most common rheumatic disease among children. [65 , 66] Epidemiology studies in North America and Western Europe have reported an incidence rate of JIA between 1.3 and 22.6 per 100,000 patient-years (p-y).[67, 68, 69, 70, 71, 72] In population-based studies specifically from the USA[73] and Northern European countries,[74,75] the incidence ranges from 7 to 21 per 100,000 p-y. Because of different diagnostic criteria and study designs, it is difficult to compare studies. |
| Prevalence | The prevalence of JIA in children is difficult to estimate because of differences in nomenclature (e.g., "JRA, JCA, and most recently JIA), diagnostic criteria between studies, and different study designs. In addition, variability in disease course among subtypes of JIA may make it difficult to compare prevalence estimates for JIA across different study settings.<br>Prevalence figures between 121 and 220 per 100,000 have been reported in population-based studies, and an overall figure of 132 per 100,000 (95% CI 119-145) was determined in a meta-analysis including practitioner- and clinic-based studies.[76]<br>Prevalence reported in a comprehensive review ranged from 0.07 to 4.01 per 1000 children across a broad diversity of geographic regions, a greater than 50-fold difference between extremes.[77, 78]<br>The prevalence of JRA in the USA in different published studies ranged from 1.6 to 86.1 per 100,000.[78] |

**Table 2.1.2-1: Epidemiologic Characteristics of Polyarticular JIA Population**

| **Polyarticular JIA** | |
|---|---|
| | The prevalence of JCA in a population-based study in Australia was far higher, 400 per 100,000, than was reported in other studies.[79]<br>Oligoarthritis represents the most common onset type of JIA in both Europe and North America, accounting for 50% to 75% of all cases, with a meta-analysis producing an overall 58% estimate (95% CI 56-60) within population-based studies.[76] In a study from Northern Europe, 66% of cases were oligoarticular onset type when EULAR criteria were applied and only 46% when ILAR criteria were applied.[74] In Europe and North America, polyarticular onset is seen in 27% of patients (95% CI 25-28) while systemic onset accounts for 11% (95% CI 10-12).[76] |
| Demographics of the population - age, sex, race/ethnic origin | An epidemiology study investigating ethnicity as a risk factor for developing JIA was conducted in Toronto, Canada.[67] Overall children of European ancestry had an increased RR (1.26) whereas children of non-European ancestry had a decreased RR of developing JIA (RR 0.43) when compared with predicted values. Median age at diagnosis of JIA was significantly younger among patients of European origin, 6.5 years (95% CI 6.1-6.8 years) as compared with non-European origin whose mean age at diagnosis was 7.8 years (95% CI 7.1-8.4). |
| Risk factors for the disease | Risk factors for the development of JIA include a family history of a disease. In a study conducted in Brazil, cigarette smoke exposure (intrauterine and after birth), exposure to ozone in the second year of life, and maternal occupational exposure were also identified as potential risk factors for JIA.[80] |
| Main treatment options | DMARDs such as MTX given non-concurrently with NSAIDs. |
| Mortality and morbidity (natural history) | The mortality risk in patients with JIA has been estimated to be 3- to 5-fold higher than in the general population.[65, 81] Much of the increase in the standardized mortality ratio is attributable to secondary amyloidosis and macrophage activation syndrome, both of which occur most frequently in patients with system onset JIA.<br>A cohort study by Minden et al. evaluating 215 patients with all subtypes of JIA showed no deaths after a median follow-up time of 16.5 years.[82]<br>Morbidities constitute a health risk among pediatric patients diagnosed with polyarticular JIA. However, there exists a paucity of published data specific to JIA alone. |
| Important co-morbidities | Type 1 diabetes is a comorbidity associated with JIA. A case control study conducted at the Seattle's Children's Rheumatology clinic in Seattle, Washington including Children 6–11 years, 68 with JIA and 67 controls, it was found that elevated OAHI is suggestive of obstructive sleep apnea and a comorbidity in JIA that may predispose children with JIA to daytime sleepiness and impaired neurobehavioral performance.[83] |

### 2.1.3 Psoriatic Arthritis

**Table 2.1.3-1: Epidemiologic Characteristics of PsA**

| **Psoriatic Arthritis** | |
|---|---|
| Incidence | The incidence rate of PsA has been reported in several studies in various regions of the world. A wide variation of annual incidence within the PsA population has been reported, ranging from 0.1–23.1 cases per 100,000 inhabitants.[84]<br>In the US, the incidence rate was 7.2 per 100,000.[84] In European countries, the reported incidence ranged between 8 in Sweden to 23.1 in Finland per 100,000 inhabitants. Additional literature reported similar incidence rates across the Americas and Europe.[85, 86, 87, 88]<br>The country with the lowest incidence rate is Japan at 0.1 per 100,000 and the country with the highest incidence rate is Norway at 41.3 per 100,000.[84,88] Collectively, compared to Americas and Europe, Asia has lower incidence of PsA. |
| Prevalence | A review article reported that the prevalence rates in PsA ranged from 0.001% to 0.67% in the various regions of the world population.[84] The prevalence of PsA in Europe and America varies from 0.02%-0.42%, and the lowest prevalence of 0.001% was reported in Japan.<br>The highest prevalence of PsA was reported in a study conducted in Norway with 0.67% of the population with PsA.[88]<br>Two claims-based studies reported the prevalence of PsA in the UK and the US. UK: Among 4.8 million patients in the health improvement network in the UK (THIN) between the ages of 18 and 90 years, 9045 patients had at least one medical code for PsA, giving an overall prevalence of 0.19% (95% CI 0.19%, 0.19%).[89] In the US, ICD-9 codes with 5187 patients of a managed care population reported an overall prevalence of PsA, with or without psoriasis, of 68 (95% CI, 54-84) per 100,000.[90] |
| Demographics of the target population | The age range where PsA usually occurs is 40 to 50 years old with the disease possibly also occurring in young children and elderly patients. Psoriasis vulgaris is the most common type of psoriasis associated with PsA. A small proportion (4%-5%) of PsA cases are related to guttate and pustular psoriasis. One to two percent of cases involve single nail without skin involvement. The male-to-female ratio is from 0.7:1 to 2.1:1.[84] Approximately 10%-37% of patients have skin and joint disease simultaneously, and 6%-18% of patients have arthritis preceding psoriasis.<br>PsA is a chronic progressive inflammatory disease that affects over 500,000 Americans and can cause permanent joint damage and severe disability.[89] |
| Risk factors for the disease | Risk factors for PsA include psoriasis and family history of PsA and/or psoriasis. Smoking has recently been shown to be a risk factor for the development of PsA.[91]<br>The major clinical features of PsA are spondylitis (18%-46%), inflammatory neck pain (23%-39%), thoracic inflammatory pain (13%-21%), and axial symptoms (25%-50%).[92] Sacroiliitis is a common symptom among PsA patients. Males have a 3-fold greater risk of developing sacroiliitis than females. Dactylitis was present in 32%-48% of patients with PsA in various studies; 25%-53% patients |

**Table 2.1.3-1: Epidemiologic Characteristics of PsA**

| **Psoriatic Arthritis** | |
|---|---|
| | present enthesitis, and 4% to 18% of patients were found to have acute anterior uveitis.[84]<br>Among patients with PsA, metabolic syndrome and insulin resistance are highly prevalent, and are independently associated with the severity of underlying PsA.[93]<br>In addition, it was reported that patients with psoriatic arthritis had an elevated odds ratio for 21 examined autoimmune diseases with the most frequent association being rheumatoid arthritis.[90] |
| Main treatment options | NSAIDs with or without local glucocorticoid injection are commonly prescribed as an initial therapy for active psoriatic arthritis.[84,94]<br>DMARDs are commonly prescribed for the treatment of PsA, from mild to moderate or severe forms of the disease, with or without NSAIDs.<br>MTX is the most commonly used DMARDs[94] but the only randomized placebo controlled trial failed to show efficacy of MTX for PsA.[95] Other DMARDs that may be used in PsA include leflunomide, sulfasalazine, or cyclosporine A.[84]<br>Corticosteroids: Local intra-articular glucocorticoid injections have been used in combination with NSAIDs to manage the mild disease. Intra-articular corticosteroids may represent a therapeutic option in cases of mono- or oligoarticular joint involvement in PsA. The systemic use of corticosteroids is not recommended due to a lack of evidence regarding its efficacy and due to the risk of severe adverse events and relapse of skin psoriasis upon discontinuation.[84]<br>Biological agents: Biologics can be initiated in those patients who have predominantly axial disease or enthesitis, or are unable to achieve treatment target within 3-6 months with DMARD treatment.[94] Usually a TNF-inhibitor is used as the first-line biologic.[96,97,98,99] If patients do not respond well or are unable to tolerate TNF-inhibitor due to drug toxicity, another biologics with different mode of action should be considered, eg, IL-12/23[100] or IL-17-inhibitor.[101] |
| Mortality and morbidity (natural history) | There were variable reports of increased mortality in PsA that may be explained by factors such as pattern of referral, the severity of arthritis and/or skin psoriasis, and treatment exposure. It has been reported that patients with RA and psoriasis have increased mortality compared with the general population. There appears to be a greater incidence of cardiovascular death in psoriatic disease.[102] Metabolic syndrome and insulin resistance was also reported.[93] However, patients with PsA do not have a significantly increased risk of mortality.[89]<br>Morbidities among PsA patients include metabolic syndrome and insulin resistance.[93] |
| Important comorbidities | Comorbidities that have been associated with PsA include cardiovascular disease, diabetes/insulin resistance, and Crohn's disease.[103] |

## 2.2 Nonclinical Part of the Safety Specification

The nonclinical toxicology of abatacept has been well characterized in a comprehensive, drug safety evaluation program evaluating IV and SC administrations with the IV formulation and local tolerance studies with both the IV and SC formulations. Overall, the nonclinical toxicology and drug-safety evaluation program supports both the 30/~10 mg/kg IV dose regimen (the weight-tiered dosing regimen approximating 10 mg/kg IV) and doses of 125 mg SC weekly for abatacept.

Abatacept was well tolerated in mice and monkeys following treatment for up to 6 months or 1 year, respectively. Abatacept was pharmacologically active in these species, and exposure was consistent throughout the study period. All findings were reversible and generally related to the pharmacology of the drug (eg, decreased serum immunoglobulin [IgG and/or IgA] levels and lymphoid-tissue germinal-center activity) with no clinical manifestations of infections or dose-limiting or significant target-organ toxicities. The results of these evaluations support the long-term safety of abatacept in humans.

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections (including opportunistic infections) leading to death (juvenile rats) as well as inflammation of the thyroid and pancreas (both juvenile and adult rats). Studies in adult mice and monkeys have not demonstrated similar findings. The increased susceptibility to opportunistic infections observed in juvenile rats (treatment beginning on post-natal day 4) is likely associated with the exposure to abatacept prior to development of memory responses. The relevance of these results to humans greater than 2 years of age, where memory responses have more time to develop, is unknown (Table 2.2-1).

Safety specifications for nonclinical findings are summarized in Table 2.2-1. A summary of preclinical safety is provided in **Appendix 2**.

## Table 2.2-1: Nonclinical Part of Safety Specification

| Key Safety findings (from nonclinical studies) | Relevance to human usage |
|---|---|
| **Infection** | |
| Increased incidence of infections has not been observed in nonclinical toxicity studies or in host resistance models conducted with abatacept in adult animals.<br>Literature suggests that the protective in vivo immune responses to most pathogens are largely preserved in animals with blockade of the CD80/86:CD28 pathway, although susceptibility to some pathogens (HSV and Listeria) have been observed.<br>Parental administration of abatacept to rats from postnatal day 4 to 94 at doses of 0, 20, 65, and 200 mg/kg once every 3 days caused infections leading to moribundity or deaths in a low number of animals. | Increased incidence of infections has been observed in abatacept-treated subjects. |
| **Malignancies** | |
| Increased incidence of virally-mediated tumors following long-term abatacept treatment has been observed in mice.<br>A similar signal has not been detected in monkeys over a 1-year abatacept-treatment period, despite the presence of viruses known to induce these changes in immunosuppressed monkeys. | Risk of malignancies may be increased in abatacept-treated subjects. |
| **Autoimmunity** | |
| Inflammation of the pancreatic islet cells and thyroid were observed in rats following up to 3 months of exposure and this inflammation increased during the 2-month recovery period.<br>Similar findings have not been observed in mice or monkeys following exposure for up to 20 and 12 months, respectively. | Risk of autoimmunity may be increased in abatacept-treated subjects. |
| **Developmental Toxicity** | |
| Abatacept treatment of rats during early gestation throughout the lactation period showed alterations of immune function which consisted of a 9-fold increase in the T-cell dependent antibody response in female pups and inflammation of the thyroid in one female pup out of 10 males and 10 females evaluated at exposures 11-fold a human 10 mg/kg dose based on AUC.<br>Increased incidence of infections was observed in rats treated with abatacept beginning on postnatal day 4. Other findings on the immune system were consistent with those observed in adult rats. | Abatacept may increase the risk for development of autoimmune diseases in humans exposed in utero to abatacept.<br>Risk for infection may be increased in young children treated with abatacept. |

**Table 2.2-1: Nonclinical Part of Safety Specification**

| Key Safety findings (from nonclinical studies) | Relevance to human usage |
|---|---|
| **Immunogenicity** | |
| Abatacept is immunogenic in animals when drug levels fall below biologically active levels.<br>Immunogenicity of human proteins in animals is not predictive of its clinical immunogenicity. | Immunogenicity of abatacept may increase risk for immune-mediated toxicities, or decrease exposure or efficacy. If antibodies are induced that cross react with endogenous CTLA4, they could theoretically lead to autoimmunity. |

## 2.3 Clinical Trial Exposure

Abatacept has been studied in a comprehensive clinical development program in multiple Phase 1, 2, and 3 studies. An overview of the abatacept clinical program summarized in this RMP is provided in Table 2.3-1.

**Table 2.3-1: Abatacept Clinical Studies Supporting Exposure and Safety Analyses in the RMP**

| Study Number (Indication) | Study Title | Number Treated Subjects |
|---|---|---|
| **Abatacept - Intravenous Administration (Adults)** | | |
| IM101100 (RA) | A Phase 2b, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and clinical efficacy of 2 different doses of BMS-188667 administered IV to subjects with active RA while receiving MTX. | Abatacept 10 mg/kg + MTX: 115<br>Abatacept 2 mg/kg + MTX: 105<br>Placebo + MTX: 119 |
| IM101101 (RA) | A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and clinical efficacy of IV infusions of BMS-188667 (2 mg/kg) given monthly in combination with SC injections of etanercept (25 mg) given twice weekly to subjects with active RA. | Abatacept + Etanercept: 85<br>Placebo + Etanercept: 36 |
| IM101102 (RA) | A Phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 in combination therapy with MTX vs MTX alone in subjects with active RA and inadequate response to MTX. | Abatacept + MTX: 433<br>Placebo + MTX: 219 |
| IM101029 (RA) | A Phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept vs placebo in subjects with active RA on background DMARDS who have failed TNF-antagonist therapy. | Abatacept: 258<br>Placebo: 133 |
| IM101031 (RA) | A Phase 3, multi-center, randomized, double-blind, placebo-controlled clinical use study to evaluate the safety and tolerability of abatacept administered IV to subjects with active RA with or without medical co-morbidities receiving DMARDS and/or biologics | Abatacept: 959<br>Placebo: 482 |

**Table 2.3-1: Abatacept Clinical Studies Supporting Exposure and Safety Analyses in the RMP**

| Study Number (Indication) | Study Title | Number Treated Subjects |
|---|---|---|
| | approved for RA. | |
| IM101043 (RA) | A Phase 3, multi-center, randomized, double-blind, placebo-controlled comparative study of abatacept or infliximab in combination with MTX in controlling disease activity in subjects with rheumatoid arthritis having an inadequate clinical response to MTX. | Abatacept + MTX: 156<br>Infliximab + MTX: 165<br>Placebo + MTX: 110 |
| IM101064 (RA) | A Phase 3, multi-center, open-label study to evaluate the efficacy, tolerability, and safety of abatacept (BMS-188667) in subjects with active RA on background non-biologic DMARDs who have an inadequate response to anti-TNF therapy and have limited therapeutic options. | Abatacept: 1046 |
| IM101015 (RA) | A Phase 3, exploratory study of changes in synovial immune responses following abatacept therapy in subjects with active rheumatoid arthritis on background DMARDs who have failed anti-TNF therapy. | 16 |
| IM101023 (RA) | A Phase 3b multi-center, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate naive early erosive RA subjects treated with abatacept plus methotrexate compared with methotrexate. | Abatacept + MTX: 256<br>Placebo + MTX: 253 |
| IM101174[a] (RA) | A Phase 3b multi-center, randomized, double-blind double-dummy study to compare the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis | Abatacept SC: 736<br>Abatacept IV: 721 |
| **Abatacept - Subcutaneous Administration (Adults)** | | |
| IM101173 (RA) | A Phase 3b, 4-month open-label study conducted in adults with active RA with a primary objective to evaluate the immunogenicity and safety of SC abatacept in the absence of an IV loading dose, when given as monotherapy vs. with concomitant MTX, and to assess whether the use of concomitant MTX influenced the development of immunogenicity | Abatacept SC monotherapy: 49<br>Abatacept SC + MTX: 51 |
| IM101167 (RA) | A Phase 3b, 9-month study designed to evaluate the impact on immunogenicity and safety, of interruption and reintroduction of SC abatacept, with or without an IV loading dose, in subjects with active RA treated concomitantly with MTX who had an initial response to SC abatacept | Abatacept SC: 167 |
| IM101185 (RA) | A Phase 3b, open-label study that was designed to evaluate the safety of conversion from chronic IV abatacept use to SC abatacept | Abatacept: 123 |
| IM101063 (RA) | A Phase 2, clinical pharmacology, multiple-dose study in adult subjects with active RA | Abatacept: 51<br>Placebo: 17 |

## Table 2.3-1: Abatacept Clinical Studies Supporting Exposure and Safety Analyses in the RMP

| Study Number (Indication) | Study Title | Number Treated Subjects |
|---|---|---|
| IM101013 (RA) | A Study to assess the PK, safety, and immunogenicity of single doses of BMS-188667 administered subcutaneously to healthy subjects | Abatacept: 40<br>Placebo: 8 |
| IM101226 (RA) | A Phase 3b randomized active controlled trial to evaluate the efficacy and safety of abatacept SC in combination with MTX in inducing clinical remission compared to MTX monotherapy in adults with very early RA. | Abatacept + MTX: 119<br>Abatacept monotherapy: 116<br>MTX monotherapy: 116 |
| **Abatacept - Juvenile Idiopathic Arthritis (Pediatric)** | | |
| IM101033 (JIA) | A Phase 3 multi-center, multi-national, randomized, withdrawal study to evaluate the safety and efficacy of abatacept in children and adolescents with active polyarticular juvenile rheumatoid arthritis | Abatacept: 190 |
| IM101301 | A Phase 3 Multi-center, Open-label Study to Evaluate Pharmacokinetics, Efficacy and Safety of Abatacept Administered Subcutaneously in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to Biologic or Non-biologic Disease Modifying Anti-rheumatic Drugs (DMARDs). | Abatacept: 219 |
| **Abatacept - Psoriatic Arthritis (Adults)** | | |
| IM101332 (PsA) | A Phase 3 randomized placebo controlled study to evaluate the efficacy and safety of abatacept subcutaneous injection in adults with active psoriatic arthritis | Abatacept: 213<br>Placebo: 211 |
| IM101158 (PsA) | A Phase 2b, multi-dose, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept versus placebo in the treatment of psoriatic arthritis | Abatacept:128<br>Placebo: 42 |

[a] IV and SC

# DATA INCLUDED IN THIS RISK MANAGEMENT PLAN

## Rheumatoid Arthritis (SC and IV Formulations)

The integrated cumulative safety experience for IV and SC abatacept use in adults with RA extends from short-term through long-term periods of 16 RA clinical trials (Table 2.3-2). The data contributing to this integrated safety database are from randomized, controlled (either placebo or active comparator), BMS studies of RA that included at least one abatacept + MTX treatment group in which study drug was administered more than one time.[105]

**Table 2.3-2: Studies Included in the Integrated Safety Database**

| Core IV Studies (included in initial sBLA) | Supporting IV Studies | Core SC Studies |
|---|---|---|
| IM101029 | IM101015 | IM101063 |
| IM101031 | IM101023 | IM101167 |
| IM101101 | IM101043 | IM101173 |
| IM101100 | IM101064 | IM101174 |
| IM101102 | | IM101185 |
| | | IM101226 |
| | | IM101235 |

Note: Early phase, PK studies and country specific studies were not included.

## Juvenile Idiopathic Arthritis

### Study IM101033- IV Abatacept

Assessment of safety of IV abatacept in children is based on a Phase 3, multi-national study (IM101033) in children and adolescents (6 to 17 years of age) with polyarticular JIA and who had failed at least 1 DMARD.[104]

This study[104] included 3 phases

- Period A - lead in phase where subjects were treated with open-label abatacept for 4 months
- Period B - double-blind phase where subjects classified as responders at the end of Period A were randomized to a double-blind phase (Period B) with either abatacept or placebo for 6 months.
- Period C - open label phase where subjects received open-label therapy with abatacept in a follow-up treatment phase.

**Study IM101301 - SC Abatacept**

Study IM101301 is a Phase 3 open-label study to assess PK, safety, and efficacy of SC abatacept in polyarticular JIA. The study consisted of a 4-month ST period, a 20-month LTE period and 5-year extension follow up of the study summarized in this RMP.

**Psoriatic Arthritis (SC and IV Formulations)**

Assessment of safety of abatacept in PsA is based on a Phase 3 randomized, placebo controlled study (IM101332) and a Phase 2b, multi-dose, randomized, placebo-controlled study (IM101158).

**Table 2.3-3: PsA Data Presented in this RMP**

| Study | Safety Data included in The RMP |
|---|---|
| IM101332 | ST period – 24 week randomized, double blind placebo controlled; |
| | Cumulative abatacept period up to 1 year (ST + 6 month OL period); |
| | Cumulative abatacept period up to 2 years (ST + 6 month OL period + available data from the LTE ongoing at the time of DBL). |
| IM101158[a] | 6 month ST period, the (18-month or longer) OL |
| | LT period or the cumulative ST+LT period |

[a] Subjects who were treated with placebo in the ST period and did not enter the LT period (never received abatacept) were excluded.

### *2.3.1 Rheumatoid Arthritis*

Pooled analyses for abatacept in RA is provided in Table 2.3.1-1 and Table 2.3.1-2. Clinical trial exposure analyses for RA trials in the integrated safety database by age, race and gender are provided in Appendix 3.

**Abatacept Pooled RA Studies - Double-Blind, Controlled Period: SC: IM101226, IM101063, IV: IM101023, IM101043, IM101031, IM101029, IM101102, IM101101, IM101100**

**Table 2.3.1-1: Exposure to Abatacept During the Double-Blind, Controlled Period - All Treated Subjects**

| Months of Exposure | Number (%) of Subjects: Abatacept (N=2653) | | Number (%) of Subjects: Placebo (N=1485) | |
|---|---|---|---|---|
| <3 | 134 | (5.1) | 116 | (7.8) |
| 3-<6 | 342 | (12.9) | 207 | (13.9) |
| 6-<12 | 300 | (11.3) | 181 | (12.2) |
| 12-<18 | 1868 | (70.4) | 978 | (65.9) |
| 18-<24 | 6 | (0.2) | 2 | (0.1) |
| 24-<36 | 3 | (0.1) | 1 | (0.1) |
| Mean Months of Exposure (SD) | 10.8 | (3.31) | 10.3 | (3.52) |
| Median (Range) | 12 | (2-30) | 12 | (0-27) |
| Total Exposure in Patient-Years | 2356.6 | | 1253.68 | |

For subjects who continued in the long-term study after more than 56 days or 60 days (IV Phase 2) after the last dose in the short-term period or who did not enter the long-term
(Exposure in months = date of last short-term dose - date of first dose + 56 or 60 (IV Phase 2))/30.
For subjects who entered the long-term period within 56 days or 60 days (IV Phase 2) of the
last dose in the short-term period Exposure in months = (date of first long-term dose - date of first dose)/30.
Interruptions in therapy were not deducted from calculation of months of exposure.
Studies Included: SC: IM101226, IM101063, IV: IM101023, IM101043, IM101031, IM101029, IM101102, IM101101, IM101100

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Source: Table S.4.2 in the Abatacept 2016 Integrated Clinical Safety Database.[105]

**Abatacept Pooled RA Studies - Cumulative Period: SC: IM101226, IM101235, IM101173, IM101167, IM101174, IM101063, IM101185, IV: IM101174, IM101023, IM101043, IM101031, IM101029, IM101102, IM101101, IM101100, IM101015, IM101064**

**Table 2.3.1-2: Exposure to Abatacept During the Cumulative Period- All Treated Subjects**

| Months of Exposure | Number (%) of Subjects | | |
|---|---|---|---|
| | SC Abatacept (N=2485) | IV Abatacept (N=5360) | Total (N=7044) |
| <3 | 34 (1.4) | 159 (3.0) | 187 (2.7) |
| 3-<6 | 87 (3.5) | 979 (18.3) | 380 (5.4) |
| 6-<12 | 179 (7.2) | 853 (15.9) | 1009 (14.3) |
| 12-<18 | 219 (8.8) | 584 (10.9) | 798 (11.3) |
| 18-<24 | 161 (6.5) | 188 (3.5) | 349 (5.0) |
| 24-<36 | 360 (14.5) | 659 (12.3) | 1028 (14.6) |
| 36-<48 | 194 (7.8) | 300 (5.6) | 432 (6.1) |
| 48-<60 | 763 (30.7) | 471 (8.8) | 1020 (14.5) |
| 60-<72 | 480 (19.3) | 833 (15.5) | 1382 (19.6) |
| 72-<84 | 8 (0.3) | 224 (4.2) | 239 (3.4) |
| 84-<96 | | 43 (0.8) | 50 (0.7) |
| >=96 | | 67 (1.3) | 170 (2.4) |
| Mean Months of Exposure (SD) | 40.1 (20.71) | 29.9 (25.55) | 36.9 (26.21) |
| Median (Range) | 48 (2-74) | 22 (2-104) | 28 (2-130) |
| Total Exposure in Patient-Years | 8182.9 | 13151.93 | 21334.84 |

Months of Exposure = [(date of the last dose - date of the first dose + 1 - adjustment +56 or 60 (IV Phase 2))]/30.
Adjustment is the time span in excess of 56 days or 60 (IV Phase 2): between the last dose in short-term and the first dose in the long-term period and for subjects in the placebo group in IM101167 between the last dose in Period I and the first dose in Period III.
Studies Included: SC: IM101226, IM101235, IM101173, IM101167, IM101174, IM101063, IM101185, IV: IM101174, IM101023, IM101043, IM101031, IM101029, IM101102, IM101101, IM101100, IM101015, IM101064

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Source Table S.4.3 in the Abatacept 2016 Integrated Clinical Safety Database[105]

### 2.3.2 Juvenile Idiopathic Arthritis

Clinical trial exposure for the OL period (Period C) of the JIA study IM101033 is presented in Table 2.3.2-1.

Clinical trial exposure analyses by age, race and gender for Period A and Period B and overall is provided in Appendix 3.

Clinical trial exposure for the cumulative period of study IM101301 is presented in Table 2.3.2-2.

**Table 2.3.2-1: Extent of Exposure (Months) to Abatacept During Open-Label Period C (IM101033): All Period C Treated Subjects**

| | Number (%) of Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Months | Per A-Non-resp (N=36) | | Per B-Abatacept (N=58) | | Per B-Placebo (N=59) | | Total (N=153) | |
| < 6 | 5 | (13.9) | 2 | (3.4) | 4 | (6.8) | 11 | (7.2) |
| 6 - < 12 | 4 | (11.1) | 0 | | 2 | (3.4) | 6 | (3.9) |
| 12 - < 18 | 5 | (13.9) | 4 | (6.9) | 5 | (8.5) | 14 | (9.2) |
| 18 - < 24 | 0 | | 2 | (3.4) | 2 | (3.4) | 4 | (2.6) |
| 24 - < 30 | 3 | (8.3) | 3 | (5.2) | 3 | (5.1) | 9 | (5.9) |
| 30 - < 36 | 1 | (2.8) | 3 | (5.2) | 3 | (5.1) | 7 | (4.6) |
| 36 - < 42 | 1 | (2.8) | 3 | (5.2) | 0 | | 4 | (2.6) |
| 42 - < 48 | 2 | (5.6) | 0 | | 4 | (6.8) | 6 | (3.9) |
| 48 - < 54 | 1 | (2.8) | 2 | (3.4) | 0 | | 3 | (2.0) |
| 54 - < 60 | 0 | | 7 | (12.1) | 4 | (6.8) | 11 | (7.2) |
| 60 - < 66 | 5 | (13.9) | 17 | (29.3) | 11 | (18.6) | 33 | (21.6) |
| 66 - < 72 | 7 | (19.4) | 2 | (3.4) | 5 | (8.5) | 14 | (9.2) |
| >= 72 | 2 | (5.6) | 13 | (22.4) | 16 | (27.1) | 31 | (20.3) |
| Mean (SD) | 37.4 | (27.0) | 53.2 | (21.0) | 50.0 | (24.8) | 48.2 | (24.6) |
| Median (Range) | 34.2 | (1.9,80.5) | 60.8 | (3.8,77.5) | 60.7 | (3.7,77.5) | 60.5 | (1.9,80.5) |

All subjects received a fixed dose of abatacept in Period C.
For subjects who discontinued or completed:
Months of exposure = (date of last dose in Period C - date of first dose in Period C + 1 + 56 days)/30.

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**Table 2.3.2-2: Summary of Extent of Exposure to Subcutaneous Abatacept During the Cumulative Period: All Treated Subjects (IM101301)**

| | Number (%) of Subjects N = 219 | |
|---|---|---|
| | **2-5 age cohort (N=46)** | **6-17 age cohort (N=173)** |
| **Months of Exposure** | | |
| **Mean (SD)** | 22.3 (6.21) | 21.8 (6.87) |
| **Median (Range)** | 24.3 (4.0 - 26.2 | 24.3 (1.9 - 28.0) |
| **Number of Injections** | | |
| **Mean (SD)** | 90.6 (28.02) | 87.0 (30.25) |
| **Median (Range)** | 102.0 (9 - 104) | 102.0 (1 - 105) |

Source: IM101301 CSR Addendum 2-Year[106]; IM101301 CSR Addendum 24-Month[107]

**Table 2.3.2-3: Summary of Extent of Exposure to Subcutaneous Abatacept During the 5-Year Extension Period: All Treated Subjects (IM101301)**

| | **2-5 age cohort (N=31)** | **6-17 age cohort (N=78)** |
|---|---|---|
| **Months of Exposure** | | |
| **Mean (SD)** | 32.2 (18.74) | 38.3 (18.54) |
| **Median (Range)** | 24.9 (4.5 - 62.6) | 37.6 (4.2 - 78.9) |
| **Number of Injections** | | |
| **Mean (SD)** | 126.4 (78.8) | 149.9 (77.59) |
| **Median (Range)** | 86.0 (12 - 260) | 102.0 (1 - 259) |

Source: IM101301 CSR Closeout[108]

### *2.3.3 Psoriatic Arthritis*

Extent of exposure to abatacept for the cumulative abatacept period up to Year 1 for IM101332 is presented in Table 2.3.3-1. Exposure for the ST period and the ongoing cumulative abatacept period up to Year 2 is provided in the IM101332 Year 1 Addendum.[109]

Extent of exposure to abatacept during the cumulative ST+LT period in IM101558 is presented in Table 2.3.2-2.

**Table 2.3.3-1: Extent of Exposure (Months) to Subcutaneous Abatacept During the Cumulative Abatacept Period Up to Year 1: Cumulative Abatacept Population (IM101332)**

| Months of Exposure | Number (%) of Subjects<br>Abatacept SC N=213 | Placebo N=185 | Total N=398 |
|---|---|---|---|
| <= 3 | 3 ( 1.4) | 0 | 3 ( 0.8) |
| > 3 - 6 | 8 ( 3.8) | 12 ( 6.5) | 20 ( 5.0) |
| > 6 - 9 | 18 ( 8.5) | 173 (93.5)[a] | 191 (48.0) |
| > 9 - 12 | 75 (35.2) | 0 | 75 (18.8) |
| > 12 | 109 (51.2) | 0 | 109 (27.4) |
| Mean Months of Exposure (SD) | 10.8 (2.3) | 6.5 (0.7) | 8.8 (2.8) |
| Median (Range) | 12.1 (2-14) | 6.5 (3-8) | 7.3 (2-14) |

[a] Many subjects entered the dose for the Month 6 visit on the OL case report form. As a result, the first dose of OL was recorded as being taken after the Month 6 visit. Interruptions in therapy were not deducted from calculation of days of exposure.

For subjects who discontinue in the cumulative abatacept period or subjects who enter the long-term period after 56 days post the last dose of the open-label period, Months of Exposure = ((date of last abatacept dose in the cumulative period- date of first abatacept dose in the cumulative period) + 1 + 56)/30.

For subjects who enter the long-term extension within 56 days of the last dose of the open-label period, Months of Exposure = (date of first abatacept dose in the long-term period - date of first abatacept dose in cumulative period)/30.

Source: IM101332 Year 1 Addendum[109]

**Table 2.3.3-2: Extent of Exposure (Months) to Abatacept during the Short-term Plus Long-term Periods, Study IM101158 - All Abatacept-treated Subjects-**

| Months of Exposure | ----Number (%) of Subjects--<br>All Abatacept (N=161) |
|---|---|
| 1-6 | 24 (14.9) |
| 7-12 | 25 (15.5) |
| 13-18 | 23 (14.3) |
| 19-24 | 7 (4.3) |
| 25-30 | 58 (36.0) |
| 31-36 | 24 (14.9) |
| Mean Months of Exposure (SD) | 20.4(10.74) |
| Median(Range) | 25.0( 0.5,34.8) |

Months of Exposure=[(date of the last dose - date of the first dose +1 - adjustment +56)]/30. Adjustment is the time span in excess of 56 days: between the last dose in short-term and the first dose in the long-term period.

Source: Appendix 3; IM101158 ST + LT CSR[110]

## 2.4 Populations Not Studied in Clinical Trials

### *2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme*

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| Pregnancy | Abatacept may cross the placenta; its effect on fetus is unknown | No | Adverse pregnancy outcome was included as important potential risk in the initial EU RMP. It was removed from the list of important potential risks in EU RMP V26.2 and the reason for removal was provided in Table 2.7.2-1 of the RMP V26.2. |
| Malignancy | Subjects with a history of cancer within 5 years may be a greater risk for malignancy. | No | Malignancies was included as important potential risk in the initial EU RMP. It was removed from the list of important potential risks in EU RMP v29.1 and the reason for removal was provided in Table 2.7.2-1 of the RMP v29.1. |
| Infections | Based on the mechanism of abatacept action, subjects with infections may experience worsening of underlying infection | No | Included as important identified risk (see Section 2.7.3.1). |
| Subjects with known hypersensitivity to abatacept or any of its components | May be potentially life threatening. Alternative therapy should be considered for those patients who are hypersensitive to abatacept. | No | Hypersensitivity to abatacept or any of its components is a contraindication. |
| Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. | Vaccination of a person on immunosuppressant therapy with a live vaccine raises a concern that the patient may develop an infection from the vaccine. | No | Infection associated to immunization with live vaccine is included as important potential risk (see Section 2.7.3.1) |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| Subjects taking other biological DMARDs | Co-administration of abatacept with biologic immunosuppressive or immunomodulatory agents could potentiate the effects of abatacept on the immune system. | No | Combination therapy including biologic therapy was listed as missing information in the initial EU RMP. It was removed from the list of missing information in EU RMP V26.0 and the reason for removal was provided in Table 2.7.2-1 of the RMP V26.0. |

### *2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes*

The clinical development programme for abatacept is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Post-marketing safety monitoring and epidemiology studies will support the identification of these reactions.

### *2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes*

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of special population | Exposure |
|---|---|
| **Pregnant women:** Nonclinical and clinical data do not suggest that abatacept interferes with embryonic development. However, abatacept is not recommended during pregnancy unless the clinical benefit outweighs the potential risk. | Controlled clinical studies in pregnant women have not been conducted. |
| **Breastfeeding women:** It is not known if abatacept is secreted in human milk. | No formal clinical studies conducted. |
| **Patients with relevant comorbidities:** | |
| Patients with hepatic impairment | No formal clinical studies conducted. |
| Patients with renal impairment | No formal clinical studies conducted. |
| Patients with cardiovascular impairment | No formal clinical studies conducted. |
| Immunocompromised patients | No formal clinical studies conducted. |
| Patients with a disease severity different from inclusion criteria in clinical trials | No formal clinical studies conducted. |

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of special population | Exposure |
|---|---|
| **Population with relevant different ethnic origin** | Abatacept has been developed globally with exposure in a wide range of racially and ethnically diverse populations. |
| **Subpopulations carrying relevant genetic polymorphisms** | No formal clinical studies conducted. |
| Other<br>o Elderly patients with RA ≥ 65 years | Refer to Appendix 3 Table S.4.4 for exposure in person years |

## 2.5 Post-Authorization Experience

ORENCIA (abatacept, BMS-188667) has been approved in several countries and is marketed for the treatment of RA, active polyarticular JIA, and PsA.

### *2.5.1 Post-authorization Exposure*

#### *2.5.1.1 Method Used to Calculate Exposure*

There is no readily available information on the actual number of patients treated with marketed abatacept. However, an estimate of the number of treated patients is derived from sales figures as described below.

Vendors provide sales figures to BMS for abatacept on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk of the Company's worldwide sales of abatacept, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data only capture an estimated 80% - 85% of the true total worldwide sales data. Additionally, the sales data from vendors may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country.

#### *2.5.1.2 Exposure*

Abatacept has a well-characterized safety profile that is consistent across approved indications (see Section 2.7.3.1). The cumulative number of patients treated from 23-Dec-2005 through 30-Sep-2024 is estimated to be 1,415,352 (sum of IV and SC). This number also equals the estimated patient-years of exposure to abatacept during this period. This is an estimate and should be interpreted with caution, taking into account all of the above mentioned limitations.

## 2.6 Additional EU Requirements for the Safety Specification

### *2.6.1 Potential for Misuse for Illegal Purposes*

Abatacept is not a controlled substance. It is administered by prescription as an IV infusion or subcutaneously under medically controlled conditions. Therefore, the potential for misuse as a recreational drug is unlikely.

## 2.7 Identified and Potential Risks

### *2.7.1 Identification of Safety Concerns in the Initial RMP Submission*

Safety concerns identified in the initial IV abatacept RMP from 2007[111] are summarized in Table 2.7.1-1..

**Table 2.7.1-1: Safety Concerns in the Initial RMP**

| | |
|---|---|
| ***Important identified risks*** | Infections |
| | Infusion-related reactions |
| ***Important potential risks*** | Malignancy |
| | Autoimmune symptoms and disorders |
| | Immunogenicity |
| | Pregnancy |
| ***Missing information*** | Children |
| | Vaccination |
| | Hepatic and renal impairment |
| | Combination therapy including biologic therapy |
| | Elderly subjects |

Source: Bristol Myers Squibb, Risk Management Plan, 2007.[111]

#### *2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP*

At the time of the initial RMP submission, safety risks that were not included in the RMP did not meet the criteria to be designated as an important identified or potential risk. Abatacept's well-characterized safety profile has been consistent across approved indications and reflected in the SmPC under Sections 4.4 and 4.8.

#### *2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Risks considered important for inclusion in the list of safety concerns for the initial RMP[111] from 2007 are provided in Table 2.7.1.2-1.

## Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

| Risk Type | Risk-Benefit Impact |
|---|---|
| ***Important identified risks*** | |
| Infections | The most clinically significant treatment-related ARs associated with abatacept are infection ARs. Severe infection ARs were low in frequency. Serious infections may lead to hospitalization and/or be associated with a fatal outcome. Most infections can be managed by dose interruption and appropriate diagnostic procedures and treatment. |
| Infusion-related reactions | Acute infusional reactions are infrequent. However, life-threatening hypersensitivity reactions may occur. |
| ***Important potential risks*** | |
| Malignancy | No evidence of an increased risk of malignancy. However, malignancies can be associated with a fatal outcome. |
| Autoimmune symptoms and disorders | No evidence for an increased risk of medically significant autoimmunity. The incidence of autoimmune events in RA trials has remained stable over time. Signs and symptoms of autoimmunity should be monitored and managed accordingly. |
| Immunogenicity | Low rates of immunogenicity have been observed with no impact observed on safety or efficacy even following prolonged dose interruptions and rechallenge. |
| Pregnancy | Nonclinical and clinical data do not suggest that abatacept interferes with embryonic development. However, abatacept is not recommended during pregnancy unless the clinical benefit outweighs the potential risk. Controlled clinical studies in pregnant women have not been conducted |
| ***Missing Information*** | |
| Children | Children were excluded from the RA studies for the initial submission. The safety and effectiveness of abatacept in pediatric subjects below the age of 18 years were not established. |
| Vaccination | No controlled data are available on the effects of vaccinations in subjects with active RA receiving abatacept. The warning on the use of live vaccines with abatacept was presented in the SmPC. |
| Hepatic and renal impairment | The use of abatacept in subjects with significant hepatic and renal impairment has not been studied; the Phase II/III core RA studies excluded these subjects. Safety conclusions cannot be established within this population. |
| Combination therapy including biologic therapy | There is insufficient evidence to assess the safety and efficacy of abatacept in combination with anakinra, and abatacept has not been studied in combination with biologic agents that suppress lymphocyte function or deplete lymphocyte count. |
| Elderly patients | Safety data from clinical studies for elderly patients (≥65 years) with RA are limited. While the frequencies of serious infection and malignancy among abatacept-treated patients relative to placebo over age 65 were higher than among those under age 65, these patients still obtain a clinical benefit similar to that observed in patients < 65 years of age. There do not |

**Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

| Risk Type | Risk-Benefit Impact |
|---|---|
| | appear to be any concerns that would preclude the use of abatacept with appropriate caution in elderly subjects. |

## *2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP*

**Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP**

| | |
|---|---|
| **Safety Concern: Immunogenicity in paediatric patients** | |
| **Previously classified as missing information and removed from the list of safety concerns** | The Category 3 planned additional pharmacovigilance activity included a 5-year long-term extension to the Phase 3 IM101301 study in patients with JIA to evaluate safety of long-term exposure of abatacept administered subcutaneously in JIA patients, aged 2-17 years, including the evaluation of immunogenicity. Overall, no new or unexpected safety findings or toxicities were identified for abatacept during the 5-year extension to Study IM101301 in paediatric patients with pJIA on abatacept treatment, aged 2-17, with prior inadequate response to MTX and/or other biologic DMARDs. In all, acknowledging the limitations of the data, the results from the 5-year follow-up extension period were consistent with the results of the previously reported ADA testing during the initial 2-year reporting period of the study IM101301 of paediatric JIA patients ages 2-17 on SC abatacept treatment. CHMP concluded that the findings of the 5-year extension to study IM101301 do not change the previous conclusions on the risk-benefit of abatacept.<br>The ongoing IM101240 is not expected to provide meaningful data on the immunogenicity. The protocol includes blood sampling related to immunogenicity, but owing to very low rates of antibody testing in the cohort and low positivity rates, data collection is being discontinued. As there are no additional pharmacovigilance activities ongoing with only routine risk minimization measures in place, MAH has proposed deleting immunogenicity in pediatric patients as a missing information from list of safety concerns considering the results of the completed study IM101301. |
| **Safety Concern: Malignancies** | |
| **Previously classified as important potential risk and removed from the list of safety concerns** | The safety concern of malignancies has been well characterized based upon cumulative data and is sufficiently described in the EU SmPC. Although the ongoing IM101240 continues to monitor malignancies, it is unlikely to provide significant new insights. There are only routine risk minimization measures in place. In accordance with PRAC advice (Type II variation AR / Procedure EMA/VR/0000287898), the MAH is deleting malignancies as an important potential risk from the list of safety concerns. |

## 2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

### 2.7.3.1 Presentation of Important Identified and Important Potential Risks

**Table 2.7.3.1-1: Important Identified Risk: Infections**

| **Infections** | |
|---|---|
| Potential mechanisms | Abatacept binds to CD80/CD86 receptors on antigen presenting cells, thereby inhibiting their binding to the costimulatory molecule CD28 on T cells. By inhibiting full T-cell activation, abatacept modulates the response of the immune system and may affect host defenses against infections. |
| Evidence source and strength of evidence | In RA clinical trials, there were small increases in the overall incidences of infection, serious infections, and dose interruptions due to infection in the abatacept treatment group compared with the placebo treatment group. Majority of the infections were non-serious. Most serious infections were likely to be bacterial in origin and responded to therapy. Mycobacterial, disseminated viral, or invasive fungal were rare. |
| Characterization of risk | **I. Infections in RA**<br>**Double-blind, Controlled Period - Integrated IV/SC Clinical Safety Database** |

| | **Abatacept Group** | **IR (per 100 p-y)** | **Placebo Group** | **IR (per 100 p-y)** |
|---|---|---|---|---|
| Total Number of Subjects | 2653 | | 1485 | |
| Infection AEs | 1440 (54.3%) | 93.21 | 767 (51.6%) | 93.05 |
| Infection SAEs | 70 (2.6%) | 3.0 | 28 (1.9%) | 2.25 |
| Infections leading to D/C | 26 (1%) | NA | 10 (0.7%) | N/A |
| Infections leading to death | 3 (0.1%) | 0.13 | 3 (0.2%) | 0.24 |

In the double-blind, the most frequently reported (10% of abatacept-treated subjects) infections were upper respiratory traction infection (11.9%, IR 14.3 per 100 p-y) and nasopharyngitis (11.8% IR 14.3 per 100 p-y). The most frequently reported SAEs of infection in abatacept group were pneumonia [0.6%, IR 0.68 per 100 p-y], cellulitis [0.2% IR 0.25 per 100 p-y], bronchitis [0.2%, IR 0.17 per 100 p-y] and urinary tract infection [0.2%, IR 0.17 per 100 p-y].

Tuberculosis was reported in 1 subject in the abatacept group (<0.1%; IR 0.04 per 100 p-y) and 1 subject in the placebo treated group (0.1%; IR 0.08 per 100 p-y).

Herpetic infections were reported in 104 (3.9%; IR: 4.51 per 100 p-y) abatacept-treated subjects and 43 (2.9%; IR: 3.49 per 100 p-y) placebo-treated subjects. In abatacept-treated subjects, herpes simplex, herpes zoster and herpes virus infection occurred with an IR of 2.45, 1.88 and 0.21 per 100 p-y, respectively. Two subjects (0.1%) experienced SAEs of herpes zoster (IR 0.08 per 100 p-y).

## Table 2.7.3.1-1: Important Identified Risk: Infections

| Infections | |
|---|---|

Hepatitis E was reported in 1 abatacept treated subject (IR 0.04 per 100 p-y) in the double-blind controlled period. Four (0.3%) placebo-treated subjects reported hepatitis with an IR of 0.32 per 100 p-y.

Opportunistic infections were reported in 4 (0.2%) abatacept-treated subjects (IR: 0.17 per 100 p-y). Bronchopulmonary aspergillosis, fungal eye infection, pseudomonal pneumonia and tuberculosis were reported in 1 subject each (IR 0.04 per 100 p-y). Seven (0.5%) placebo-treated subjects experienced opportunistic infections (IR: 0.56 per 100 p-y). Fungal oesophagitis, gastrointestinal candidiasis, cryptococcal meningitis, oesophegeal candidiasis, pneumocystis jirovecii pneumonia, respiratory moniliasis and tuberculosis occurred in 1 subject each (IR 0.08 per 100 p-y).

**Cumulative Period - Integrated IV/SC Clinical Safety Database**.

| | Abatacept Group | IR (per 100 p-y) |
|---|---|---|
| Total Number of Subjects | 7044 | |
| Infection AEs | 5018 (71.2%) | 64.51 |
| Infection SAEs | 493 (7%) | 2.40 |
| Infections leading to D/C | 141 (2%) | 0.66 |
| Infections leading to death | 34 (0.5%) | 0.16 |

The IR of infections during the cumulative period was lower compared to the IR in the double-blind placebo controlled period in the abatacept treatment group (64.51 versus 93.21 per 100 p-y respectively). During the cumulative period, the most frequently reported (>15% of subjects) infections were pathogen unspecified infections (65%; IR: 49.90 per 100 p-y), upper respiratory tract infection (21.5%; IR: 8.60 per 100 p-y), pneumonia (19.3%; IR:7.45 per 100 p-y), nasopharyngitis (18.5%; IR: 7.38 per 100 p-y), urinary tract infection (16.1%; IR: 6.09 per 100 p-y), and bronchitis (15.2%; IR: 5.69 per 100 p-y). The most frequently reported infection SAEs were pneumonia [1.6%, IR 0.54 per 100 p-y], and urinary tract infection [0.6%, IR 0.18 per 100 p-y].

Tuberculosis (combined) occurred in 17 (0.2%) subjects with an IR per 100 p-y of 0.08. Three (<0.1%) subjects with pulmonary tuberculosis SAEs and 1 subject (<0.1%) with a peritoneal tuberculosis SAE were hospitalized.

Herpes infections (combined) were reported for 584 (8.3%) subjects with an IR of 2.94 per 100 p-y. The most frequently reported herpes infections were herpes zoster (4.0%; IR 1.38 per 100 p-y), oral herpes (3.3%; IR 1.13 per 100 p-y) and herpes simplex (0.9%; IR 0.28 per 100 p-y). The most frequently reported herpes infection SAE was herpes zoster, which occurred in 9 (0.1%) subjects (IR 0.04 per 100 p-y). Most of the serious herpes zoster infections required hospitalization [8 (0.1%) subjects, IR 0.04 per 100 p-y]. Most herpes infections were mild or moderate in severity. Severe herpes infections were infrequent - severe herpes zoster infections were reported in 22 (0.3%) subjects; very severe herpes zoster infections was reported in 1 subject. Herpes infections that led to discontinuation during the

**Table 2.7.3.1-1: Important Identified Risk: Infections**

| Infections | |
|---|---|
| | cumulative period included 5 subjects with herpes zoster, 1 subject with herpes virus infection and 1 subject with oral herpes infection.<br>Hepatitis was reported in 8 (0.1%) abatacept-treated subjects (IR 0.04 per 100 p-y) in the cumulative (N=7044) period. AE of chronic hepatitis and toxic hepatitis was each reported in 3 subjects (<0.1%) (IR 0.01 per 100 p-y). There were no hepatitis B reactivation events reported.<br>Opportunistic infections occurred in 45 (0.6%) subjects with an IR of 0.21 per 100 p-y. The most frequently reported opportunistic infections were oesophageal candidiasis, pulmonary tuberculosis, fungal eye infections and ophthalmic herpes simplex infection.<br>Post-marketing Epidemiology Studies<br>The incidence rates of hospitalized infection were 4.19 per 100 p-y in Study IM101045A[112], 1.63 per 100 p-y in IM101045B,[113] 4.27 per 100 p-y in Study IM101125,[114] and 3.79 per 100 p-y in IM101127.[115] The most recent incidence rate of serious infection for study IM101212 was reported as 1.03 per 100 p-y.[116] The most recent rate of hospitalized infection for Study IM101213 was reported as 5.57 per 100 p-y.[117]<br>For TB, 17 cases were identified in Study IM101045A (0.43 per 100 p-y);[112] these cases were identified via administrative claims and were not verified. One case of TB was reported in IM101127.[115] Nine cases of TB were reported in IM101213.[117] No cases were reported in Studies IM101045B[113] and IM101125.[114] In Study IM101212, TB data was not reported.[116]<br>For herpetic infections, 74 cases of herpes zoster were identified via administrative claims in Study IM101045A (1.90 per 100 p-y).[112] Two cases of herpes zoster (0.09 per 100 p-y) and no cases of herpes simplex were noted in Study IM101045B,[113] and no cases that have been classified as serious were reported in Studies IM101125, IM101127, or IM101212.<br>In the post-marketing epidemiology studies, 1 case of hepatitis C was noted in IM101045B.[113]<br>Study IM101045B noted 3 opportunistic infections (0.13 per 100 p-y).[113] Study IM101045A reported 31 opportunistic infections (excluding herpes zoster) (0.78 per 100 p-y).[112] There were 2 cases of opportunistic infection reported in Study IM101125,[114] and 1 case reported in Study IM101127.[115] No cases of opportunistic infection were reported in IM101212.[116]<br>**II. Infections in PsA** |

## Table 2.7.3.1-1: Important Identified Risk: Infections

**Infections**

In **Study IM101332**, most infections were mild or moderate in severity.

| IM101332 | Double-Blind | | Cumulative Abatacept Period | |
|---|---|---|---|---|
| | ST Period | | ST+OL up to Year 1 | ST+OL+LTE up to Year 2 |
| | N=213 (aba) | N=211 (pbo) | N=398 | N=398 |
| Infection AEs | 57 (26.8%) | 63 (29.9%) | 162 (40.7%) IR 61.62 per 100p-y | 209 (52.5%) IR 75.91 per 100 p-y |
| Infection SAEs | 3 (1.4%) | 2 (0.9%) | 7 (1.8%) | 10 (2.5%) |
| Infections leading to D/C | 3 (1.4%) | 0 | 4 (1%) | 7 (1.8%) |
| Infections leading to death | 0 | 0 | 0 | 0 |

aba=abatacept; IR = incidence rate; OL= open-label; LTE=long-term extension; PBO = placebo, ST = short-term.

In **Study IM101158**, infections were reported in 34.9% -35.6% and 35% of subjects in three abatacept groups, respectively, and 35.7% of subjects in the placebo group during the ST period. A total of 100 abatacept-treated subjects (62.1%) reported at least one event of infection during the combined ST + LT period up to 35 months. During the ST period of Study IM101158, SAEs of infection were reported in 2 abatacept-treated subjects and 0 placebo-treated subjects. During the ST + LT period, serious infection were reported in 6 (3.7%) subjects. Infections leading to discontinuation were reported in 2 (1.2%) subjects during ST+LT period. Most of the infections were mild or moderate in intensity except 2 infectious events assessed as severe in intensity during the cumulative ST+OL period. There were no serious infections with fatal outcomes.

There were no cases of TB in Study IM101332 or IM101158.

Herpes infections occurred at a low frequency in the PsA studies. During the cumulative abatacept period to Year 2 in Study IM101332, 6 (1.5%) subjects reported oral herpes (incidence rates per 100 p-y of 1.10) and 7 (1.8%) subjects reported herpes zoster (IR per 100 p-y of 1.27). In the LT period of Study IM101158, oral herpes was reported in 5 (3.4%), herpes zoster in 3 (2.0%) and herpes simplex in 2 (1.4%) subjects treated with abatacept.

No subjects reported hepatitis in Study IM101332 (cumulative up to Year 1) or IM101158. During the cumulative abatacept period up to Year 2 in Study IM101332, 1 subject reported hepatitis A, which led to discontinuation.

During the cumulative abatacept period of Study IM101332 up to Year 2, and LT period of Study IM101158, potential opportunistic infection events reported in abatacept treated subjects included

## Table 2.7.3.1-1: Important Identified Risk: Infections

| Infections | |
|---|---|
| | pneumocystis jirovecii lung infection and oropharyngeal candidiasis (1 case each in IM101332), oral herpes (6 in IM101332; 5 in IM101158), herpes zoster (3 in each study), and herpes simplex (2 in IM101158, none in IM101332). No other opportunistic infections were reported.<br><br>**III. Infections in JIA**<br><br>During Period C of **Study IM101033**, 120 (78.4%) subjects reported at least 1 AE in the Infections and infestations SOC. Most of these infections were bacterial and viral. There were 10 (6.5%) subjects who experienced an SAE in the Infection and Infestations SOC during Period C of IM101033. The incidence rate was 1.72 per 100 p-y. Most of the reported infections of interest were mild or moderate in intensity and 'unlikely' or 'unrelated' to the study drug according to the investigator. These infections were consistent with those commonly seen in outpatient pediatric populations and resolved with treatment without significant clinical sequelae.<br><br>In the cumulative period of Study IM101301, a total of 40 (87.0%, IR 164.97 per 100 p-y) subjects in the 2-5 year old cohort experienced AEs in the Infections and Infestations SOC. The most frequently reported infections were nasopharyngitis (37.0%, IR 26.96 per 100 p-y ), upper respiratory traction infection (21.7%, IR 15.04 per 100 p-y), rhinitis (17.4%, IR 10.79 per 100 p-y), conjunctivitis (13.0%, IR 8.00 per 100 p-y), pharyngitis (13.0%, 7.55 per 100 p-y), and gastroenteritis (13.0%, 7.83 per 100 p-y). Two subjects (IR 2.38 per 100 p-y) experienced SAEs of infection in the cumulative period (abscess limb and cellulitis). All infections were mild to moderate in severity except one subject (2.2%) who experienced a severe event of limb abscess. One subject discontinued due to an infection (rhinitis; non-serious AE).<br><br>In the cumulative period for the 6-17 year old cohort, a total of 118 (68.2%, IR 79.81 per 100 p-y) subjects experienced AEs in the Infections and Infestations SOC. The most frequently reported infections were nasopharyngitis (30.1%, IR 20.87 per 100 p-y) and upper respiratory tract infection (18.5%, IR 12.13 per 100 p-y). Four subjects (IR 1.30 per 100 p-y) experienced SAEs of infection in the cumulative period (appendicitis, pneumonia, pyelonephritis, and sepsis). All infections were mild to moderate in severity except one subject (0.6%) who experienced a severe event of sepsis. One subject discontinued due to an infection (sepsis, SAE).<br><br>There were no cases of TB, hepatitis or opportunistic infections reported in IM101033. During Period C of IM101033, herpes infections by PT included varicella (6 subjects; incidence rate: 1.03 per 100 p-y), herpes zoster (5 subjects; incidence rate: 0.84 per 100 p-y), oral herpes (3 subjects; incidence rate: 0.50 per 100 p-y), herpes opthalmic (1 subject; incidence rate: 0.17 per 100 p-y), and herpes simplex (1 subject; incidence rate: 0.17 per 100 p-y). Two were serious (herpes zoster, varicella).<br><br>In the cumulative period of IM101301 for the 6-17 year old cohort, there was one event of latent TB diagnosed by positive quantiferon test and normal chest image (IR 0.6 per 100 p-y). Two subjects had |

## Table 2.7.3.1-1: Important Identified Risk: Infections

| **Infections** | |
|---|---|
| | infections that fit the criteria for potential opportunistic infection: herpes zoster and candida infection (thrush). Both occurred during the ST period and were classified as mild in intensity. No events of hepatitis were reported. In the 2-5 year old cohort, no TB or opportunistic infections were reported. |
| Risk factors and risk groups | Age, extra-articular manifestations of RA, leukopenia, use of corticosteroids, and comorbidities has been identified as predictors of infection in RA subjects. Abatacept use with anti-TNFs may increase the risk of infections. Risk groups for TB include persons with prior or current exposure to others with TB, and persons living in poverty with limited access to medical care, adequate housing, and nutrition. |
| Preventability | Most infections can be managed by dose interruption and appropriate diagnostic procedures and treatment. Infections can be minimized by appropriate subject selection by considering factors such as previous history of infections, assessment of risks for chronic or latent infections, and age. While transitioning from TNF blocking agent therapy to abatacept therapy, subjects should be monitored for signs of infection. Active or latent TB should be evaluated by standard medical practice. This may include tuberculin skin testing or quantiferon and chest x-ray. Abatacept should not be administered to subjects who have evidence of active TB. |
| Impact on the risk-benefit balance of the product | Abatacept is an immunomodulator and can increase the risk of infections. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The Patient Alert Card, alerts professionals and patients to these risks and their appropriate management guidelines. |
| Public health impact | All available data suggest that abatacept has a consistent AE profile across all indications. The majority of AEs observed have been managed successfully by dose interruption and appropriate diagnostic procedures and treatment. |
| MedDRA terms | MedDRA SOC - Infections and Infestations |

## Table 2.7.3.1-2: Important Identified Risk: Infusion Related Reactions (IV Abatacept)

| **Infusion Related Reactions** | |
|---|---|
| Potential mechanisms | Infusion related reactions can be observed during treatment with any protein products administered intravenously including abatacept. Because abatacept is a fully human protein, the risk of serious infusion-related reactions was considered to be low. |
| Evidence source and strength of evidence | In RA clinical trials, there were small increases in the incidences of infusional events and dose interruptions due to acute infusional adverse events in the abatacept treatment group compared with the placebo treatment group. Most acute infusional events were mild or moderated in severity. The most frequently reported infusional |

## Table 2.7.3.1-2: Important Identified Risk: Infusion Related Reactions (IV Abatacept)

| Infusion Related Reactions | |
|---|---|
| | events were dizziness, nausea and flushing. Serious infusion related reactions were rare. Premedications were not used during clinical trials with abatacept. |
| Characterization of risk | **I. Infusion Related Reactions (IV Abatacept) in RA**<br>In the double-blind, controlled period of 7 IV studies, acute infusional events (infusional AEs reported within 1 hour following the start of infusion) in abatacept-treated subjects occurred in 152 (6.4%, n=2367) with an IR of 7.66 per 100 p-y, compared with in 64 placebo-treated subjects (4.7%, n=1352) with an IR of 5.82 per 100 p-y. The most frequently reported acute infusional events in the abatacept treatment group were dizziness (2.1%) nausea (0.9%) and flushing (0.6%). One subject experienced a SAE of dizziness, and one subject experienced an SAE of nausea in abatacept-treated subjects. Prespecified peri-infusional events (infusional AEs reported within 24 hours following the start of infusion) during the double-blind controlled period occurred in 353 (14.9%) abatacept-treated subjects compared with in 180 (13.3%) placebo-treated. The most frequently reported peri-infusional events in the abatacept-treatment group were dizziness (4.4%), nausea (4.3%) and flushing (0.9%). Four SAEs of peri-infusional events were reported in 3 subjects, including chest pain, dizziness, throat tightness, and infusion related reaction.<br>During the cumulative period (N=6104) of 10 studies in which IV abatacept was administered, acute infusional AEs were reported in 348 (5.7%) subjects with an IR of 1.95 per 100 p-y. The most frequently reported acute infusional AEs were dizziness (1.4%), nausea (0.8%) and infusion site extravasation (0.7%). Prespecified peri-infusional events during the cumulative period occurred in 861 (14.1%) subjects. The most frequently reported peri-infusional events were nausea (3.6%) dizziness (3.2%) and rash (0.7%, IR 0.24 per 100 p-y). Anaphylactic reaction (3 subjects) and anaphylactic shock (1 subject) have been reported during the cumulative period of the studies.<br>In the abatacept post-marketing epidemiology studies, Study IM101045A has identified 1 anaphylactic reaction as detected by hospital/ER or physician visit claims (0.05 per 100 p-y).[112] Study IM101045B has reported an incidence rate of 1.48 per 100 p-y of severe infusion reactions,[113] and Study IM101127 has reported an incidence rate of 0.62 per 100 p-y of infusion or injection site reactions in patients receiving abatacept.[115]<br><br>**II Infusion Related Reactions (IV Abatacept) in PsA**<br>During the ST period of Study IM101158, a total of 16 abatacept-treated subjects had an acute infusional or a peri-infusional event; however, all 16 subjects recovered within 24 hours. None were serious and 2 subjects discontinued the study drug due to the event |

## Table 2.7.3.1-2: Important Identified Risk: Infusion Related Reactions (IV Abatacept)

| **Infusion Related Reactions** | |
|---|---|
| | During the LT period of Study IM101158, acute infusional AEs were reported by 4 (2.7%) treated subjects. Peri-infusional AEs were reported by 11 (7.5%) subjects. None were serious or led to study discontinuation.<br><br>**III Infusion Related Reactions in JIA**<br>In Study IM101033 acute infusional AEs were reported in a total of 6 (3.9%) subjects treated in Period C. Of the 6 subjects, 5 had received abatacept in double-blind phase Period B (ie, Period B Abatacept cohort), and 1 subject had received placebo (Period B-Placebo cohort), indicating that there was no increase in the rate of acute infusional AEs following the reintroduction of abatacept during Period C. Peri-infusional AEs were reported for 22 (14.4%) subjects treated with abatacept in Period C; dizziness, nausea and vomiting were the most commonly reported events. One of the acute infusional AEs reported in Period C was serious (hypersensitivity on Day C954). This SAE was considered probably related to study treatment. |
| Risk factors and risk groups | None. No specific risk factors for serious infusional events have been identified. |
| Preventability | Pretreatment with anti-histamines and/or steroids may decrease the risk of severe infusional events; pretreatment was not used in the clinical trials. Patients should be educated on the symptoms of hypersensitivity, and should be instructed to call their healthcare provider or to go to the emergency room should they develop these symptoms. |
| Impact on the risk-benefit balance of the product | Serious infusion related reactions are rare, but they could be life-threatening or even fatal. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The Patient Alert Card, alerts professionals and patients to these risks and their appropriate management guidelines. |
| Public health impact | No public health impact outside of the treated patient population. Severe infusion reactions, including high-grade hypersensitivity reactions, following administration of abatacept are uncommon. |
| MedDRA terms | BMS Modified SMQ (Annex 7)<br>Periinfusional IM101 |

## Table 2.7.3.1-3: Important Identified Risk: Injection Reactions (SC Abatacept)

| **Injection Site Reactions** | |
|---|---|
| Potential mechanisms | Injection reactions include both local injection site reactions (pre-specified) and systemic injection reactions (pre-specified, occurring with 24 hours following abatacept SC administration). All subcutaneously administered therapies have the potential to |

| | |
|---|---|
| | cause local injection site reactions. The mechanism of action for abatacept injection site reactions has not been formally studied. For other biologics used to treat RA, injection site reactions are believed to be T-lymphocyte-mediated, Type I hypersensitivity reactions, which decrease in intensity over time possibly due to induced tolerance. Systemic reactions are hypersensitivity reactions that can be observed during treatment with any injectable protein, including abatacept. |
| Evidence source and strength of evidence | In RA clinical trials with abatacept SC administration, there were increases in the incidences of local injection site reactions in the abatacept treatment group compared with the placebo treatment group. Almost all the local injection site reactions were mild to moderate intensity and nonserious; serious local injection site reactions were very rare (<0.01%). Systemic injection reactions were reported in clinical studies and postmarketing experience. Most of the systemic injection reactions were of mild or moderate intensity. Serious systemic injection reactions (i.e., serious hypersensitivity or anaphylaxis) were rare, but can be life-threatening or fatal. |
| Characterization of risk | **I. Injection Reactions (SC Abatacept) in RA**<br>In the double-blind controlled period of 2 SC studies (IM101226, IM101063), pre-specified injection site reactions were reported in 15 (5.2%, n=286) abatacept-treated subjects with an IR of 5.60 per 100 p-y. One subject in the placebo group experienced a pre-specified injection site reaction. The most frequently reported injection site reactions in the abatacept group were injection site swelling, and injection site pain. Pre-specified systemic injection reactions were reported in 28 (9.8%, n=286) abatacept-treated subjects with an IR of 10.93 per 100 p-y. The most frequently reported systemic injection reactions in the abatacept group (≥1% abatacept recipients) were nausea (4.9%), dizziness (1.4%), and flushing (1%). There were no SAEs of systemic injection reactions reported.<br>In the cumulative period (N=2538) of 7 SC studies (IM101226, IM101235, IM101173, IM101167, IM101174, IM101063, IM101185), pre-specified injection site reactions were reported in 116 (4.6%) subjects with an IR of 1.32 per 100 p-y. The most frequently reported injection site reactions were injection site erythema, injection site pain, and injection site pruritus. Pre-specified systemic injection reactions were reported in 249 (9.8%) subjects with an IR of 2.92 per100 p-y. The most frequently reported systemic injection reactions in the abatacept group (≥1% abatacept recipients) were nausea (2.7%) and dizziness (1.5%). Five SAEs of pre-specified systemic injection reaction were reported, including nausea, chest pain (2 events), arthralgia, and dyspnea. There were no anaphylactic reaction or other serious allergic reactions reported during the cumulative period.<br>In the abatacept post-marketing epidemiology studies, no anaphylactic reactions were identified following abatacept SC administration in Study IM101045A. In Study IM101045B, as of 20-Oct-2016, there were 1,496 patients who reported exposure to abatacept. Lower reactions to injection were found as compared to other BDM groups, even if severity was taken into consideration |

| | |
|---|---|
| | (severe reaction to injection: 0.57 per 100 p-y,versus 1.87 per 100 p-y for other BDMs).[113]<br>In the post-marketing experience, rare cases of serious hypersensitivity, including anaphylactic reactions, have been reported following SC administration of abatacept.<br>**II. Injection Reactions (SC Abatacept) in PsA**<br>During the ST period of IM101332, 2 subjects (1 in the abatacept group and 1 in the placebo group) had an injection site reaction. During the cumulative abatacept period up to Year 1 (ST+OL), pre-specified local injection site reactions were reported in 5 (1.3%) abatacept-treated subjects, with an overall IR of 1.75 per 100 patient-years.<br>**III. Injection Reactions (SC Abatacept) in JIA**<br>During the cumulative period in IM101301, 2 (4.3%) subjects in the 2-5 year old cohort and 12 (6.9%) subjects in the 6-17 year old cohort had an injection site reaction. All local injection site reactions were mild or moderate in intensity. No injection site reactions led to discontinuation of study drug. No serious systemic reactions were reported. |
| Risk factors and risk groups | Although risk factors for injection-site reactions have not been formally explored, several have been hypothesized, including poor self-injection technique, repeated use of the same site, medication type, dose and prior duration of therapy. No specific risk factors for systemic injection reactions have been identified. |
| Preventability | To minimize or reduce the risk for any potential local injection site reaction, prior to initiating SC abatacept, the patient should receive training on the correct way to inject abatacept. Patients should be educated on the symptoms of systemic injection reactions, and should be instructed to call their healthcare provider or to go to the emergency room should they develop these symptoms. |
| Impact on the risk-benefit balance of the product | Serious systemic injection reactions are rare, but they could be life-threatening or fatal. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. The Patient Alert Card, alerts professionals and patients to these risks and their appropriate management guidelines. |
| Public health impact | There is no public health impact outside of the treated patient population. |
| MedDRA terms | Injection site reactions MedDRA HLTs:<br>HLT: Injection site reactions<br>HLT: Administration site reactions NEC<br>HLT: Application and instillation site reactions<br>Systemic injection reactions: BMS Modified SMQ (Annex 7) |

**Table 2.7.3.1-4: Important Potential Risk: Autoimmune Symptoms and Disorders**

| **Autoimmune Symptoms and Disorders** | |
|---|---|
| Potential mechanisms | Anti-CTLA4 antibodies (due to immunogenicity) have a potential to block the endogenous regulatory activity of CTLA-4 and increase autoimmunity. |
| Evidence source and strength of evidence | Assessment of the risk for autoimmune disorders is of importance due to anti-CTLA4 antibodies causing autoimmune phenomenon, and the observations of certain autoimmune disorders associated with other biologic treatments, particularly the TNF-antagonist agents. Currently there is no evidence for an increased risk of medically significant autoimmunity in patients with abatacept treatment. |
| Characterization of risk | **I Autoimmune Symptoms and Disorders in RA**<br>During the double-blind, controlled period, pre-specified autoimmune events were reported in 198 (7.5%) abatacept-treated subjects with an IR of 8.77 per 100 p-y of exposure compared with 115 (7.7%) placebo-treated subjects (IR of 9.60 per 100 p-y). The most common autoimmune disorders in abatacept-treated subjects was rheumatoid arthritis (162 [6.1%] subjects) and rheumatoid nodule (16 [0.6%] subjects). In abatacept-treated subjects, SLE was reported in 2 (0.1%) subjects (IR 0.08 per 100 p-y), and psoriasis was reported in 11 (0.4%) subjects (IR 0.47 per 100 p-y). In placebo-treated subjects, psoriasis was reported in 2 (0.1%) subjects. No cases of MS were observed in abatacept- or placebo-treated subjects.<br><br>During the cumulative period (N=7044) pre-specified autoimmune events occurred in 745 (10.6%) subjects with an IR of 3.84 per 100 p-y. Most autoimmune disorders were in the musculoskeletal and connective tissue disorder SOC (603 [8.6%]; IR: 3.07 per 100 p-y) - rheumatoid arthritis occurred in 475 (6.7%) and rheumatoid nodule occurred in 88 (1.2%). SLE, psoriasis and MS occurred in 8 (0.1%) subjects (IR: 0.04 per 100 p-y), 100 (1.4%; IR: 0.54 per 100 p-y) and 2 (<0.1%; IR: 0.01 per 100 p-y) respectively.<br><br>In the post-marketing epidemiology in RA program, Study IM101045A identified, via administrative claims, 33 cases of SLE (1.22 per 100 p-y), 49 cases of psoriasis (1.83 per 100 p-y) and 6 cases of MS (0.21 per 100 p-y).[112] Study IM101045B reported 1 case of MS (0.04 per 100 p-y), 15 cases of psoriasis (0.66 per 100 p-y), and 1 case of SLE (0.04 per 100 p-y).[113] The diagnosis was not validated by medical records for any of the cases in either study. Study IM101125 reported 29 cases of psoriasis (0.68 per 100 p-y), 2 cases of SLE (0.05 per 100 p-y), and 3 cases of MS (0.07 per 100 p-y).[114] Study IM101127 reported 17 cases of psoriasis (0.66 per 100 p-y), 1 case of SLE (0.04 per 100 p-y), and 0 cases of MS.[115] No cases were reported in Study IM101212.[116]<br><br>**II Autoimmune Symptoms and Disorders in PsA** |

## Table 2.7.3.1-4: Important Potential Risk: Autoimmune Symptoms and Disorders

| **Autoimmune Symptoms and Disorders** | |
|---|---|
| | During the ST period in IM101332, no prespecified autoimmune disorders were reported in abatacept-treated subjects. During the cumulative abatacept period up to Year 1, 1 (0.3%) uveitis was reported in abatacept-treated subject; additional 5 subjects reported 3 SAEs and 2 AEs of psoriasis related events. Pre-specified autoimmune events were reported in 3/398 (0.8%) abatacept-treated subjects during the cumulative abatacept period up to Year 2, with an overall IR of 0.54 per 100 patient years.<br>In the ST period of Study IM101158, 3 abatacept-treated subjects had worsening psoriasis or psoriatic arthritis. No other autoimmune events were reported. During the LT period, autoimmune disorders were reported in 5 (3.4%) subjects. All of these events were psoriasis.<br><br>**III Autoimmune Symptoms and Disorders in JIA**<br>In Study IM101033, 7 subjects had pre-specified autoimmune disorders reported during Period C (cutaneous vasculitis, psoriasis, vitiligo, uveitis, type 1 diabetes, MS and Raynaud's phenomenon).<br>During the cumulative period of Study IM101301, 3 subjects reported an autoimmune event (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, psoriasis and Takayasu's arteritis; IR 0.8 per 100 p-y). All events were mild or moderate in intensity and observed in the 6-17 year old cohort. No autoimmune events were reported in the 2-5 year old cohort. All subjects in the 2 through 5 year age cohort had negative anti-GAD and anti-TPO values at baseline, 2 positive anti-GAD results were reported post-baseline, and none of the subjects had a positive anti-TPO value post-baseline. Positive anti-GAD was not associated with any autoimmune thyroid-related events or autoimmune type I diabetes. In the 6-17 year old cohort, most subjects had negative anti-GAD and anti-TPO results at baseline; 6 single positive anti-GAD or anti-TPO antibody values were observed on-treatment relative to baseline. One subject had a positive anti-TPO result relative to baseline after the last dose. Positive anti-GAD and positive anti-TPO were not associated with any autoimmune thyroid-related events or Type I diabetes. |
| Risk factors and risk groups | Risk factors for autoimmune disorders include gender, ethnicity, genetic predisposition, family history, infections and some environmental factors. |
| Preventability | Although not preventable, signs and symptoms of autoimmunity should be monitored and managed accordingly. Assessment of direct causality with abatacept should be considered. |
| Impact on the risk-benefit balance of the product | Based on the potential for varying severities of autoimmune disease, the effect on quality of life would vary. Currently there is no evidence for an increased risk of medically significant autoimmunity. The incidence of autoimmune events associated with RA and psoriasis has remained stable over time. |

### Table 2.7.3.1-4: Important Potential Risk: Autoimmune Symptoms and Disorders

| **Autoimmune Symptoms and Disorders** | |
|---|---|
| Public health impact | There is no public health impact outside of the treated patient population. |
| MedDRA terms | BMS Modified SMQ (Annex 7):<br>Autoimmune disorders |

### Table 2.7.3.1-5: Important Potential Risk: Infections Associated to Immunization with Live Vaccines

| **Infections Associated to Immunization with Live Vaccines** | |
|---|---|
| Potential mechanisms | Infection is an identified risk with abatacept due to its immunomodulatory effect. Vaccination of a person on immunosuppressant therapy with a live vaccine raises a concern that the patient may develop an infection from the vaccine. Abatacept may cross the placenta into the serum of infants born to women treated with abatacept during pregnancy. Consequently, these infants may be at increased risk of infection. The safety of administering live vaccines to infants exposed to abatacept in utero is unknown. |
| Evidence source and strength of evidence | There is no data of infections associated to live vaccine immunization identified from abatacept clinical studies and postmarketing experience. Data have suggested that other biological DMARDS that are used to treat RA or other diseases may affect the safety of live vaccines in newborns and infants exposed to these drugs in utero. |
| Characterization of risk | A review of the BMS Safety Database (including clinical trial and post-marketing reports) revealed no reports of infections associated to immunization with live vaccine, in adults, newborns or infants born to women who were treated with abatacept during pregnancy. |
| Risk factors and risk groups | All immunosuppressant therapies have the potential to cause infections associated to immunization with live vaccines. Patients who are immunocompromised are at an increased risk of infection. |
| Preventability | Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. Administration of live vaccines to infants exposed to abatacept *in utero* is not recommended for 14 weeks following the mother's last exposure to abatacept during pregnancy. |
| Impact on the risk-benefit balance of the product | Immunosuppressant therapy has the potential to cause infections associated to immunization with live vaccines. Serious infections may lead to hospitalization and/or be associated with a fatal outcome. |
| Public health impact | Infections pose a major health risk primarily to the treated patient. No data are available on the secondary transmission of infection from persons receiving liver vaccines to patients |

**Table 2.7.3.1-5: Important Potential Risk: Infections Associated to Immunization with Live Vaccines**

| Infections Associated to Immunization with Live Vaccines | |
|---|---|
| | receiving abatacept. There is no public health impact outside of the treated patient population. |
| MedDRA terms | Vaccinia virus infection; Vaccine virus shedding; Vaccine breakthrough infection; Varicella; Varicella post vaccine; Yellow fever; Yellow fever vaccine-associated viscerotropic disease; Yellow fever vaccine-associated neurotropic disease; Adenovirus infection; Herpes zoster; Herpes zoster infection neurological; Influenza; Mumps; Rubella; Rubella in pregnancy; Rubella infection neurological; Measles; Measles post vaccine; Smallpox; Bovine tuberculosis |

### *2.7.3.2 Presentation of the Missing Information*

**Table 2.7.3.2-1: Missing Information**

| Missing Information | Is the safety profile expected to be different from the general target population? |
|---|---|
| **Population in need of further characterisation:** | |
| Long-term safety in 2-5 year old patients with JIA | Safety data from the clinical study for long-term use of abatacept in JIA patients aged 2-5 years are limited. The immune system in younger children is not as mature as in the older paediatric patient group and there may still be gaps in knowledge of long-term safety of abatacept in the younger age group. |

## 2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

**Table 2.8-1: Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | • Infections<br>• Infusion-related reactions (IV abatacept only)<br>• Injection reactions (SC abatacept only) |
| Important potential risks | • Autoimmune symptoms and disorders<br>• Infections associated to immunization with live vaccines |
| Missing information | • Long-term safety in 2-5 year old patients with JIA |

# 3 PART III: PHARMACOVIGILANCE PLAN

The pharmacovigilance plan provides details of pharmacovigilance studies that are intended to proactively identify and/or characterize safety concerns and will inform risk mitigation strategies for the identified and potential risks.

## 3.1 Routine Pharmacovigilance Activities

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. Questionnaires (including those for pregnancy follow-up) are used to obtain event-specific follow-up as part of routine pharmacovigilance practices. These questionnaires are not specific to abatacept and are used to obtain standard event-specific follow-up information for all products.

## 3.2 Additional Pharmacovigilance Activities

A summary of ongoing post-authorization safety study protocols/activities in the abatacept pharmacovigilance plan is provided in Table 3.2-1.

**Table 3.2-1: Post-Authorization Safety Studies Short Name Summary**

| Study short name and title | Rationale and study objectives | Study design | Study population | Milestone(s) | Due Date(s) |
|---|---|---|---|---|---|
| IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis | To characterize and evaluate the safety of abatacept in JIA in routine clinical practice: infections, malignancy, autoimmune disorders | This study is an observational, multi-center registry. | JIA patients (including patients 2-5 years of age) | 1. Recruiting Update | Annually each February beginning in 2011 |
| | | | | 2. Interim data | 30- Jun- 2014<br>30- Jun- 2019<br>30- Jun- 2024 |
| | | | | 3. Final Study Report | 30-Jun-2029 |

## 3.3 Summary Table of Additional Pharmacovigilance Activities

**Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities**

| Study / Status | Summary of objectives | Safety concerns addressed | Milestone(s) | Due Date(s) |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis<br>Ongoing | To characterize and evaluate the safety of abatacept in JIA in routine clinical practice: infections, malignancy, autoimmune disorders | Infections, infusion-related reactions, autoimmune disorders, long-term safety of abatacept in JIA patients 2-5 years of age | 1. Recruiting Update<br>2. Interim data<br><br><br>3. Final Study Report | Annually each February beginning in 2011<br>30-Jun- 2014<br>30-Jun- 2019<br>30- Jun- 2024<br>30-Jun- 2029 |

# 4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no post-authorization efficacy studies which are specific obligations or conditions of MA.

# 5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## 5.1 Routine Risk Minimisation Measures

**Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| Infections | Routine risk communication:<br>The SmPC includes a contraindication (Section 4.3) for Severe and uncontrolled infections such as sepsis and opportunistic infections. Specific subsections on infections and/or ADRs in subjects with COPD in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable Effects) of the SmPC.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be screened for latent tuberculosis and viral hepatitis prior to initiating abatacept. The available medical guidelines should also be taken into account.<br>Other routine risk minimisation measures beyond the Product Information: None. |
| Infusion-related reactions (IV Abatacept) | Routine risk communication:<br>The SmPC includes a contraindication (Section 4.3) for Hypersensitivity to the active substance or to any of the excipients. Specific subsections on allergic or infusion-related reactions in Sections 4.4 and 4.8 of the SmPC.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: If any serious allergic or anaphylactic reaction occurs, intravenous abatacept therapy should be discontinued immediately and appropriate therapy initiated - the use of ORENCIA should be permanently discontinued.<br>Other routine risk minimisation measures beyond the Product Information: None. |
| Injection Reactions (SC Abatacept) | Routine risk communication:<br>The SmPC includes a contraindication (Section 4.3) for Hypersensitivity to the active substance or to any of the excipients. Specific subsections on allergic or injection reactions in Sections 4.4 and 4.8 of the SmPC.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: If any serious allergic or anaphylactic reaction occurs, subcutaneous abatacept therapy should be discontinued immediately and appropriate therapy initiated - the use of ORENCIA should be permanently discontinued. |

**Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| | Other routine risk minimisation measures beyond the Product Information: None. |
| Autoimmune symptoms and disorders | Routine risk communication:<br>Specific subsections on autoimmune disease or autoantibodies in Sections 4.4 and 4.8 of the SmPC.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br>Other routine risk minimisation measures beyond the Product Information: None. |
| Infections Associated to Immunization with Live Vaccines | Routine risk communication:<br>SmPC specific subsections in sections 4.4, 4.5 and 4.6 on vaccinations.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. Administration of live vaccines to infants exposed to abatacept *in utero* is not recommended for 14 weeks following the mother's last exposure to abatacept during pregnancy.<br>Other routine risk minimisation measures beyond the Product Information: None. |
| Long-term safety in 2-5 year old patients with JIA | Routine risk communication:<br>Statements on long-term safety of abatacept in JIA patients aged 2-5 years in Section 4.8 of the SmPC.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br>Other routine risk minimisation measures beyond the Product Information: None. |

## 5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of additional risk minimisation activities are provided in Annex 6.

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| Additional Risk Minimisation:<br>o Patient Alert Card | **Objectives:**<br>To further raise awareness of patients and healthcare professionals on important identified risks of infection, infusion related reactions (IV abatacept), injection reactions (SC abatacept) and potential risk of infections associated to immunization with live vaccines and their appropriate management.<br>**Rationale for the additional risk minimisation activity:**<br>Opportunity for reinforcing key messages to early recognition and appropriate management of important identified risks of infection, infusion related |

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| | reactions (IV abatacept), injection reactions (SC abatacept) and potential risk of infections associated to immunization with live vaccines to maintain favorable benefit/risk of abatacept in market use.<br><br>**Target audience and planned distribution path:**<br><br>Patients/Caregivers<br><br>**Plans to evaluate the effectiveness of the interventions and criteria for success:**<br>Routine pharmacovigilance activities and post-marketing epidemiology studies will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PSUR).<br><br>A HCP/patient cross-sectional survey and retrospective chart review (PASS study IM101537) was conducted to evaluate the effectiveness of the Patient Alert Card for both IV and SC abatacept in a sample of EU countries. Protocol IM101537 was submitted in October 2014. Final study report approved in January 2018. Based on the results of this study, the MAH did not propose to make any modifications to the content of the Patient Alert Card, which seemed to be effective. |

## 5.3 Summary Table of Risk Minimisation Measures

**Table 5.3-1: Summary of Risk Minimisation Measures**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Infections | Routine risk minimisation measures:<br>SmPC Sections 4.3, 4.4 and 4.8 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None |
| | Additional risk minimisation measures: Patient Alert Card: Highlights the need for an adequate history and screening related to infections, such as TB and hepatitis, prior to treatment with abatacept, as well as the need to seek immediate medical attention when symptoms of infections occur during treatment. | Additional pharmacovigilance activities:<br>Postmarketing epidemiology study: IM101240 |
| Infusion-related reactions (IV abatacept only) | Routine risk minimisation measures: SmPC Sections 4.3, 4.4 and 4.8 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None |
| | Additional risk minimisation measures: Patient Alert Card: highlights risk of hypersensitivity after use of | Additional pharmacovigilance activities: Postmarketing |

| | | |
|---|---|---|
| | abatacept and instructs patients to seek immediate medical attention should symptoms of serious allergic reactions develop. | pharmacoepidemiology study: IM101240 |
| Injection reactions (SC abatacept only) | Routine risk minimisation measures: SmPC Sections 4.3, 4.4 and 4.8<br>Additional risk minimisation measures: Patient Alert Card: highlights risk of hypersensitivity after use of abatacept and instructs patients to seek immediate medical attention should symptoms of serious allergic reactions develop. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br>Additional pharmacovigilance activities:<br>None. |
| Autoimmune symptoms and disorders | Routine risk minimisation measures: SmPC Sections 4.4 and 4.8<br>Additional risk minimisation measures: None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br>Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study: IM101240 |
| Infections associated to immunization with live vaccines | Routine risk minimisation measures: SmPC Section 4.4, 4.5 and 4.6 on vaccinations.<br>Additional risk minimisation measures: Patient Alert Card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to abatacept in utero | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br>Additional pharmacovigilance activities: None |
| Long-term safety in 2-5 year old patients with JIA | Routine risk minimisation measures: SmPC Section 4.8.<br>Additional risk minimisation measures: None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.<br>Additional pharmacovigilance activities: Post-marketing pharmacoepidemiology study: IM101240 |

# 6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ORENCIA (abatacept)

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

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

This summary of the RMP for ORENCIA 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 ORENCIA's RMP.

## I. The medicine and what it is used for

ORENCIA is authorised for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis (see SmPC for the full indication). It contains abatacept as the active substance and it is given by either intravenous infusion or subcutaneous injection.

Further information about the evaluation of ORENCIA’s benefits can be found in ORENCIA’s 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/orencia

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

Important risks of ORENCIA, together with measures to minimise such risks and the proposed studies for learning more about ORENCIA'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 and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

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

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

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

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

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

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

**List of important risks and missing information**

| | |
|---|---|
| ***Important identified risks*** | • Infections<br>• Infusion-related reactions (IV abatacept only)<br>• Injection reactions (SC abatacept only) |
| ***Important potential risks*** | • Autoimmune symptoms and disorders<br>• Infections associated to immunization with live vaccines |
| ***Missing information*** | • Long-term safety in 2-5 year old patients with JIA |

## *II.B Summary of important risks*

**Important identified risks**

| **Infections** | |
|---|---|
| Evidence for linking the risk to the medicine | In RA clinical trials, there were small increases in the overall incidences of infection, serious infections, and dose interruptions due to infection in the abatacept treatment group compared with the placebo treatment group. Majority of the infections were non-serious. Most serious infections were likely to be bacterial in origin and responded to therapy. Mycobacterial, disseminated viral, or invasive fungal were rare. |
| Risk factors and risk groups | Age, extra-articular manifestations of RA, leukopenia, use of corticosteroids, and comorbidities has been identified as predictors of infection in RA subjects. Abatacept use with anti-TNFs may increase the risk of infections. Risk groups for TB include persons with prior or current exposure to others with TB, and persons living in poverty with limited access to medical care, adequate housing, and nutrition. |
| Risk minimisation measures | Routine risk minimisation measures: SmPC Sections 4.3, 4.4, and 4.8 |
| | Additional risk minimisation measures: Patient Alert Card |

## Important identified risks

| | |
|---|---|
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Postmarketing epidemiology studies:<br>• IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis<br><br>See section II.C of this summary for an overview of the post-authorization development plan. |
| **Infusion related reactions (IV Abatacept)** | |
| Evidence for linking the risk to the medicine | In RA clinical trials, there were small increases in the incidences of infusional events and dose interruptions due to acute infusional adverse events in the abatacept treatment group compared with the placebo treatment group. Most acute infusional events were mild or moderate in severity. The most frequently reported infusional events were dizziness, nausea and flushing. Serious infusion related reactions were rare. Premedications were not used during clinical trials with abatacept. |
| Risk factors and risk groups | None. No specific risk factors for serious infusional events have been identified. |
| Risk minimisation measures | Routine risk minimisation measures: SmPC Sections 4.3, 4.4 and 4.8.<br><br>Additional risk minimisation measures: Patient Alert Card |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies<br>• IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis<br>See section II.C of this summary for an overview of the post-authorization development plan. |
| **Injection reactions (SC Abatacept)** | |
| Evidence for linking the risk to the medicine | In RA clinical trials with abatacept SC administration, there were increases in the incidences of local injection site reactions in the abatacept treatment group compared with the placebo treatment group. Almost all the local injection site reactions were mild to moderated intensity and nonserious; serious local injection site reactions were very rare (<0.01%). Systemic injection reactions were reported in clinical studies and postmarketing experience. Most of the systemic injection reactions were of mild or moderate intensity. Serious systemic injection reactions (i.e., serious hypersensitivity or anaphylaxis) were rare, but can be life-threatening or fatal. |
| Risk factors and risk groups | Although risk factors for injection-site reactions have not been formally explored, several have been hypothesized, including poor self-injection technique, repeated use of the same site, medication type, dose and prior duration of therapy. No specific risk factors for systemic injection reactions have been identified. |
| Risk minimisation measures | Routine risk minimisation measures: SmPC Sections 4.3, 4.4, and 4.8<br><br>Additional risk minimisation measures: Patient Alert Card |

## Important potential risks

| **Autoimmune symptoms and disorders** | |
|---|---|
| Evidence for linking the risk to the medicine | Assessment of the risk for autoimmune disorders is of importance due to anti-CTLA4 antibodies causing autoimmune phenomenon, and the observations of certain autoimmune disorders associated with other biologic treatments, particularly the TNF-antagonist agents. Currently there is no evidence for an increased risk of medically significant autoimmunity in patients with abatacept treatment. |
| Risk factors and risk groups | Risk factors for autoimmune disorders include gender, ethnicity, genetic predisposition, family history, infections and some environmental factors. |
| Risk minimisation measures | Routine risk minimisation measures: Sections 4.4 and 4.8 of the SmPC. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies:<br>• IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis |
| **Infections associated to immunization with live vaccines** | |
| Evidence for linking the risk to the medicine | There is no data of infections associated to live vaccine immunization identified from abatacept clinical studies and postmarketing experience. Data have suggested that other biological DMARDS that are used to treat RA or other diseases may affect the safety of live vaccines in newborns and infants exposed to these drugs in utero. |
| Risk factors and risk groups | All immunosuppressant therapies have the potential to cause infections associated to immunization with live vaccines. Patients who are immunocompromised are at an increased risk of infection. |
| Risk minimisation measures | Routine risk minimisation measures: SmPC Section 4.4, 4.5 and 4.6.<br><br>Additional risk minimisation measures: Patient Alert Card |

## Missing information

| **Long-term safety in 2-5 year old patients with JIA** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: SmPC Section 4.8. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• IM101240 An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis |

## *II.C Post-authorization development plan*

### II.C.1 Studies which are conditions of the marketing authorization

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

### II.C.2 Other studies in post-authorization development plan

## Category 3 on-going and planned additional pharmacovigilance activities

| Study short name and title | Rationale and study objectives |
|---|---|
| IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis | To characterize and evaluate the safety of abatacept in JIA in routine clinical practice: infections, malignancy, autoimmune disorders |

## ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

# Annex 6: Details of Proposed Additional Risk Minimization Activities (If Applicable)

1 page(s) excluding cover page

# ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

The Marketing Authorisation Holder shall ensure that in each Member State where ORENCIA is marketed, all patients who are expected to use ORENCIA have access to the Patient Alert Card (provided within each medicine pack).

- **Patient alert card**:
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using ORENCIA
  - That ORENCIA treatment may increase the risk of infections and allergic reactions.
  - Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
  - Contact details of the ORENCIA prescriber
  - A warning message for patients who have received ORENCIA while pregnant to inform healthcare personnel before any vaccination is given to the baby due to the potential risk of severe infection caused by immunization with live vaccines