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.

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 minimization* measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly 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 • Infusion-related reactions (IV abatacept only) • Injection reactions (SC abatacept only)
Important potential risks	• Malignancies • Autoimmune symptoms and disorders • Infections associated to immunization with live vaccines
Missing information	• Long-term safety in 2-5 year old patients with JIA • Immunogenicity in paediatric patients

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 minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4, and 4.8

Important identified risks

	Additional risk minimization measures: Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Postmarketing epidemiology studies: • IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis 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 minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8. Additional risk minimization measures: Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies • IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis 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 minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4, and 4.8 Additional risk minimization measures: Patient Alert Card

Important potential risks

Malignancies	
Evidence for linking the risk to the medicine	In the nonclinical studies, lymphoma and mammary gland tumors were identified in a mouse carcinogenicity study. The findings appeared to be secondary to suppression of host defense with reactivation of latent oncogenic viruses specific to the mouse. The clinical significance of this observation is unknown. In a one-year toxicity study in cynomolgus monkeys, abatacept was not associated with any significant toxicity. In the RA clinical studies double-blind, controlled period, IR of malignancies in abatacept-treated subjects was comparable to placebo-treated subjects; the IR of malignant AEs during the cumulative period decreased relative to the IR in the double-blind placebo controlled period in abatacept treatment group
Risk factors and risk groups	Risk factors for malignancy are dependent on malignancy type. No RA specific risk factors for overall malignancy have been identified.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4 and 4.8
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies • IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis • IM101816: A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Sweden Using the ARTIS Register • IM101803: A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Denmark Using the DANBIO Register
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 minimization measures	Routine risk minimization measures: Sections 4.4 and 4.8 of the SmPC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies: • 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. No other risk factors in the treated populations have been characterized.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4, 4.5 and 4.6.

Important potential risks

	Additional risk minimization measures: Patient Alert Card

Missing information

Long-term safety in 2-5 year old patients with JIA	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • IM101240 An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis • IM101301: A Phase 3 Study of Abatacept in Patients with Juvenile Idiopathic Arthritis
Immunogenicity in paediatric patients	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8. Additional pharmacovigilance activities: • IM101301: A Phase 3 Study 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
IM101301: A Phase 3 Study of Abatacept in Patients with Juvenile Idiopathic Arthritis	To evaluate safety of long-term exposure of abatacept administered subcutaneously in JIA patients (including patients aged 2-5 years) and evaluate immunogenicity in paediatric patients.
IM101816: A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Sweden Using the ARTIS Register	To identify and estimate the incidence (frequency) of pre-specified events (overall malignancies, melanoma, NMSC [basal cell carcinoma, squamous cell carcinoma]) among patients treated with abatacept (overall and stratified by RA and PsA indications).
IM101803: A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Denmark Using the DANBIO Register	To identify and estimate the incidence (frequency) of pre-specified events (overall malignancies, melanoma, NMSC [basal cell carcinoma, squamous cell carcinoma]) among patients treated with abatacept (overall and stratified by RA and PsA indications).