Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Idacio (adalimumab)

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

Idacio's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Idacio should be used.

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

I. The Medicine and What it is used for

Idacio is authorized for use in adults in the treatment of:

- Rheumatoid Arthritis (RA),
- Psoriatic Arthritis (PsA)
- Axial Spondyloarthritis (Axial SpA)
- Crohn's Disease (CD),
- Psoriasis,
- Ulcerative Colitis (UC),
- Hidradenitis Suppurativa, and
- Uveitis.

Idacio is authorised for use in paediatrics for the treatment of:

- Polyarticular Juvenile Idiopathic Arthritis (pJIA),
- Paediatric Enthesitis-related Arthritis (pedERA);
- Pediatric Crohn's Disease (pedCD);
- Pediatric Psoriasis (pedPs);
- Adolescent Hidradenitis Suppurativa (HS);
- Paediatric Uveitis (pedUV)
- Paediatric Ulcerative Colitis

Refer to SmPC for the full indications. It contains adalimumab as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of Idacio’s benefits can be found in Idacio’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/idacio

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Idacio, together with measures to minimize such risks and the proposed studies for learning more about Idacio’s risks, are outlined below.

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

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

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including 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 Idacio is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

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

List of important risks and missing information	
Important identified risks	• Serious infections • Tuberculosis (TB); • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS], and optic neuritis [ON]) • BCG disease following live BCG vaccination in infants with in utero exposure to Idacio
Important potential risks	• Progressive multifocal leukoencephalopathy (PML); • Reversible posterior leukoencephalopathy syndrome (RPLS); and • Adenocarcinoma of colon in ulcerative patients (UC) patients
Missing information	• Patients with immune-compromised conditions;

List of important risks and missing information
• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; • Episodic treatment in Ps, UC, and juvenile idiopathic arthritis (JIA); • Long-term safety data in the treatment of adults and children with uveitis • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

II.B Summary of Important Risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Serious infections has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly Population ≥65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Idacio: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest through registry study. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Tuberculosis has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures: Text in SmPC:

	Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Idacio: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest through registry study. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Malignancies has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01 - 13.9) (Beaugerie 2009). Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks may or may not be applicable to HSTCL which is rare (Kotlyar 2011, Parakkal 2011). Risk factors for leukemia depend on the type of leukemia. In general, factors associated with an increased risk of leukemia include smoking, exposure to certain chemicals such as benzene, exposure to radiation, past treatment with chemotherapy or radiation therapy, having certain inherited or genetic disorders, having certain blood disorders, and having a family history of leukemia (National Cancer Institute 2014). Factors associated with an increased risk of skin cancer include radiation (e.g., sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants, thiopurines [Peyrin-Biroulet 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic (National Cancer Institute 2011b). Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis (National Cancer Institute 2011b). Factors associated with an increased risk of melanoma include UV radiation (e.g., sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles (National Cancer Institute 2011b). Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g., organ transplant, HIV), other cancers (e.g., squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure (Becker 2010a).

Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Warning regarding lymphoma, HSTCL, leukaemia, NMSC, melanoma, MCC, and malignancies in the adult and paediatric population. Section 4.8: Information on incidence rates from clinical trials in lymphoma, NMSC, and melanoma. Information on incidence rates from postmarketing surveillance in HSTCL, leukaemia, and MCC. The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of AZA or 6-MP, and that the potential risk combination of AZA or 6-MP and Idacio should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Idacio: • Patient Reminder Card.
Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON])	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON]) has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (e.g., HLA-DR2 [HLA-DRB1*15], ethnic origin [being white], female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors) (Ramagopalan 2010). Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age (Sejvar 2011). Subjects with intermediate uveitis have a high prevalence of demyelination (Burkholder 2012, Zein 2004, Llorenc 2012, Messenger 2015).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in postmarketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of demyelinating disorders associated with the use of Idacio. • Patient Reminder Card.
Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Idacio	

Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. BCG disease following live BCG vaccination in infants with in utero exposure to Idacio has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	No epidemiological data available.
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: Section 4.4 of the SmPC has section on vaccinations. Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of live vaccines associated with the use of Idacio and the risk of live vaccines in infants exposed to Idacio in utero: • Patient Reminder Card.
Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Progressive Multifocal Leukoencephalopathy has been classified as a potential risk for Idacio in accordance with the reference product
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. A descriptive analysis of PML cases identified through claims found approximately 40% of patients were aged 40 to 49 years and 75% were male (Eng 2006). Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS (Weber 2008). Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukaemia (Carson 2009). Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases (Eng 2006, Carson 2009, Calabrese 2007, Bartt 2006, Govindappa 2007).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Important potential risk: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Reversible Posterior Leukoencephalopathy Syndrome has been classified as a potential risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Suspected etiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee 2008).

Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Adenocarcinoma of colon in ulcerative colitis (UC) patients has been classified as a potential risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid PSC (Van Assche 2013), diet, and cigarette smoking (National Cancer Institute 2006).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest through registry study. See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Patients with Immune Compromised conditions	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Warnings regarding patients with immune compromised conditions are included. There is currently no information on subjects with a history of clinically significant drug or alcohol abuse listed in the SmPC. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Episodic treatment in Ps, UC and JIA	

Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Long-term safety information in the treatment of children with uveitis	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.2: Statement that the benefit and risk of continued long-term Idacio treatment in this population should be evaluated on a yearly basis. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine. Additional risk minimization measures: None.

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 the invented name.

II.C.2 Other Studies in the Post-Authorization Development Plan

Observational registry (RABBIT) Study #1 ((Study Identifier: FKS0-000-RAB)-A prospective, observational cohort study (sample size of at least 150 subjects foreseen) whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumor necrosis factor-inhibitor therapies in the treatment of RA.

Purpose of the study: To contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.