**Fresenius Kabi (Schweiz) AG**

Am Mattenhof 4
CH-6010 Kriens
T +41 (0)41 552 70 00
info.ch@fresenius-kabi.com
www.fresenius-kabi.ch

TÜV-zertifiziert
nach ISO 9001

# Swiss Summary of the Risk Management Plan (RMP) for Idacio® (Adalimumab)

**Version 1, März 2020**

**EU Risk Management Plan 4.0, 28.02.2019**

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Idacio® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Idacio® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Fresenius Kabi (Schweiz AG) is fully responsible for the accuracy and correctness of the content of the published summary RMP of Idacio®.

**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).

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).
https://www.ema.europa.eu/en/medicines/human/EPAR/idacio

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 rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (from the age of 13 years), psoriatic arthritis, ankylosing spondylitis (Bechterew's disease), Crohn's disease, ulcerative colitis, psoriasis and hidradenitis suppurativa (acne inversa) (see Swiss product information for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

## 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 pharmaco-vigilance 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 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 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**

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| Important Identified Risk | Serious infections, Tuberculosis, Malignancies<br>Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis),<br>Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to Idacio |
| Important Potential Risk | Progressive multifocal leukoencephalopathy<br>Reversible posterior leukoencephalopathy syndrome<br>Colon cancer in ulcerative colitis patients |
| Missing Information | Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease<br>Patients with immune-compromised conditions<br>Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis<br>Long-term safety data in the treatment of adults and children with uveitis |

## II.B Summary of Important Risks

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| **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. |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC:<br>Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections.<br>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.<br>Warning regarding a higher risk of infections in the elderly Population ≥65 years.<br>Section 4.8: Diverticulitis is listed as an adverse reaction.<br>In order to inform patients of these risks, corresponding text is also present in the package leaflet.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>To remind patients about the risk of serious infections associated with the use of Idacio:<br>• Patient Reminder Card. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Monitoring as an event of special interest in registry studies. 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. |

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| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC:<br>Section 4.3: Contraindications for active TB<br>Section 4.4: Warnings regarding active TB<br>In order to inform patients of these risks, corresponding text is also present in the package leaflet.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>To remind patients about the risk of TB associated with the use of Idacio:<br>· Patient Reminder Card. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Monitoring as an event of special interest in registry studies.<br>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). 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. 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.<br><br>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, medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic. Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis.<br><br>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 |

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| | immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles. 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. |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC:<br>Section 4.4: Warning regarding lymphoma, HSTCL, leukaemia, NMSC, melanoma, MCC, and malignancies in the adult and paediatric population.<br>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.<br>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.<br>In order to inform patients of these risks, corresponding text is also present in the package leaflet.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>To remind patients about the risk of malignancies associated with the use of Idacio:<br>• 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). Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age. Subjects with intermediate uveitis have a high prevalence of demyelination. |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC:<br>Section 4.4: Warnings on demyelinating disorders are included.<br>Further details for the uveitis patient population are also included.<br>Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in post-marketing surveillance. |

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| | In order to inform patients of these risks, corresponding text is also present in the package leaflet.<br>Prescription only medicine.<br>Additional risk minimization measures:<br>To remind patients about the risk of demyelinating disorders associated with the use of Idacio.<br>• 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:<br>Text in the SmPC: Section 4.4 of the SmPC has section on vaccinations.<br>Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet.<br>Prescription only medicine.<br>Additional risk minimization measures:<br>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:<br>• 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 an identified 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. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS. 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. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases. |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC: |

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| | 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.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>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 an identified 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%). |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC: None.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>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 an identified 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, diet, and cigarette smoking. |
| Risk minimization measures | Routine risk minimization measures:<br>Text in SmPC: None.<br>Prescription only medicine.<br><br>Additional risk minimization measures:<br>None. |

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| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>Monitoring as an event of special interest in registry studies.<br><br>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:<br><br>Text in SmPC:<br><br>Section 4.4: Warnings regarding patients with immune compromised conditions are included.<br><br>There is currently no information on subjects with a history of clinically significant drug or alcohol abuse listed in the SmPC.<br><br>In order to inform patients of these risks, corresponding text is also present in the package leaflet.<br><br>Prescription only medicine.<br><br>Additional risk minimization measures:<br><br>None. |
| **Missing information:** Episodic treatment in Ps, UC and JIA | |
| Risk minimization measures | Routine risk minimization measures:<br><br>Text in SmPC: None.<br><br>Prescription only medicine.<br><br>Additional risk minimization measures:<br><br>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:<br><br>Text in the SmPC: None.<br><br>Prescription only medicine.<br><br>Additional risk minimization measures:<br><br>None. |
| **Missing information:** Long-term safety information in the treatment of adults and children with uveitis | |
| Risk minimization measures | Routine risk minimization measures:<br><br>Text in SmPC:<br><br>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. |

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| | Prescription only medicine.<br><br>Additional risk minimization measures:<br>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-**A prospective, observational cohort study (sample size of at least 300 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.

**Objective**: The purpose of the study is 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.

**II.C.2.2**

**Observational registry (IBD UK) Study #2-**A prospective, observational cohort study (sample size of at least 300 subjects foreseen) to facilitate continuous improvement in IBD patient care and access to care across the UK, improve understanding of long-term outcomes for IBD patients from care and Support IBD research.

**Objective**: The purpose of the study is 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.