SAMSUNG BIOEPIS

Swiss Summary of Risk Management Plan (RMP)

for

Imraldi® (Adalimumab)

Samsung Bioepis CH GmbH

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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 Imraldi® 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 Imraldi® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Samsung Bioepis CH GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Imraldi®.

SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR IMRALDI

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

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

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

I. The medicine and what it is used for

Imraldi is authorised for rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), enthesitis-related arthritis, ankylosing spondylitis (AS), axial spondyloarthritis without radiographic evidence of AS (nr-axSpA), psoriatic arthritis (PsA), psoriasis (PsO), paediatric plaque PsO, hidradenitis suppurativa (HS), crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, uveitis and paediatric uveitis (see SmPC for the full indication). It contains adalimumab as the active substance for subcutaneous injection.

Further information about the evaluation of Imraldi's benefits can be found in Imraldi'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/imraldi

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

Important risks of Imraldi, together with measures to minimise such risks and the proposed studies for learning more about Imraldi'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 (e.g. with or without prescription) can help to minimise its risks.

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

In the case of Imraldi, 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 Imraldi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Imraldi 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 Imraldi. 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-Barré syndrome [GBS] and optic neuritis); BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi
Important potential risks	Progressive multifocal leukoencephalopathy (PML); Reversible posterior leukoencephalopathy syndrome (RPLS); Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	Patients with immune-compromised conditions; Episodic treatment in PsO, UC and juvenile idiopathic arthritis (JIA); Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; Long-term safety information in the treatment of children with uveitis Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

II.B Summary of important risks

II.B.1 Important identified risk

Serious infections	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.

Serious infections	
Risk factors and risk groups	Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.3, 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: Anti-rheumatic Therapies In Sweden (ARTIS), Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) See section II.C of this summary for an overview of the post-authorisation development plan.

Tuberculosis	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Factors that increase the risk of infection include steroids or other medications that suppress the immune system, such as anti-rejection drugs for a transplanted organ, Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), certain types of cancer or other disorders that affect the immune system, implanted medical devices, malnutrition, and increased age.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.3, 4.4; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: Anti-rheumatic Therapies In Sweden (ARTIS), Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) See section II.C of this summary for an overview of the post-authorisation development plan.

Malignancies	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; and referenced scientific publications
Risk factors and risk groups	Lymphoma There is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease.

Malignancies	
	Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease. In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma. Factors that increase the risk of HL include age (from 15 to 30 years as well as older than 55 years), a family history of lymphoma, being a male, previous Epstein-Barr virus infection, and a weakened immune system (such as from HIV/AIDS or certain medications after organ transplant). Factors that may increase the risk of NHL include medications that suppress the immune system, infections with certain viruses and bacteria (such as HIV, Epstein-Barr virus, ulcer-causing Helicobacter pylori), and older age (60 years or older) Hepatosplenic T-cell lymphoma (HSTCL) Some of these HSTCLs with adalimumab have occurred in young adult patients on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) used for IBD. The potential risk with the combination of AZA or 6-MP and adalimumab should be carefully considered. Additionally, thiopurine therapy in patients with IBD, combined immunosuppression, age groups from 10 to 35 years, and the male sex are considered to be risk factors of HSTCL. Leukaemia Patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after treatment with a TNF-antagonist. Caution should also be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease. Factors with an increased risk of leukaemia include previous chemotherapy and radiation therapy, certain genetic disorders (such as Down syndrome), exposure to certain chemicals (such as benzene), smoking, and a family history of leukaemia. Non-melanoma skin cancer (NMSC) Risk factors of skin cancer include radiation (sunlight or radiation therapy), personal or family history of melanoma, fair skin (having less melanin), certain medical conditions that suppress the immune system, certain medicines (such as some antibiotics, hormones, or antidepressants), and exposure to arsenic at work. In addition, actinic keratosis and HPV infection are also risk factors of skin cancer. Melanoma

Malignancies	
	Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Factors that may increase the risk of melanoma include fair skin (having less melanin), a history of sunburn, a family history of melanoma, excessive ultraviolet (UV) light exposure, many common moles, and a weakened immune system (such as those who have undergone organ transplant). Merkel cell carcinoma (MCC) Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: Anti-rheumatic Therapies In Sweden (ARTIS), Spanish Registry of Adverse Events of Biological Therapies (BIOBADASER) See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis)	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; Imraldi SmPC, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Patients with pre-existing multiple sclerosis (MS) or Guillain-Barré syndrome (GBS) belong to the high-risk group. Additionally, first-degree relatives of patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36. Factors of increased risk of MS include genetic associations (e.g., HLA-DR2 [HLA-DRB1*15]), ethnic origin (e.g., African American men have lower risk than white men), women, Epstein-Barr virus infection, smoking, and latitude/vitamin D. Factors of increased risk of GBS include men, increased age, viral or bacterial infection (particularly *Campylobacter jejuni* infection), and certain vaccines.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card

Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis)	
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

BCG disease following live BCG vaccination in infants with *in utero* exposure to Imraldi	
Evidence for linking the risk to the medicine	Imraldi SmPC, Section 4.6 'Fertility, pregnancy and lactation' and Section 4.4 'Special warnings and precautions for use'
Risk factors and risk groups	Infants who are exposed to Imraldi intrauterine.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4, PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risk

Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Referenced scientific publications
Risk factors and risk groups	Immunosuppressive conditions such as HIV/AIDS are the main risk factors of PML. A study conducted by Eng et al. analysed that approximately 41% of the patients with PML were found in the 40 to 49 years age group and the PML patients were predominantly male with a 75% estimate. HIV infection is the basis of approximately 85% of all PML cases. Before the HIV epidemic, more than 60% of PML cases were found in patients with lymphoproliferative disorders. Other conditions that are risk factors of PML are hematologic malignancies, organ transplants, and chronic inflammatory diseases.
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Study SB5-G31-RA; referenced scientific publications.
Risk factors and risk groups	RPLS etiologies include hypertension, eclampsia, and calcineurin inhibitor use. Comorbid conditions include hypertension, renal disease, dialysis dependency, malignancy, and transplantation.
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Imraldi SmPC, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Concomitant Primary Sclerosing Cholangitis (PSC), post-inflammatory polyps, family history of colorectal cancer.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4 Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

Patients with immune-compromised conditions	
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4; PL section 2 Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None

Patients with immune-compromised conditions	
	See section II.C of this summary for an overview of the post-authorisation development plan.

Episodic treatment in PsO, UC and JIA	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety information in the treatment of children with uveitis	
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.2 Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC	
Risk minimisation measures	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> None See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

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

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
ARTIS - Anti-rheumatic Therapies In Sweden Ongoing	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with adalimumab.	Serious infections; TB; Malignancies; Episodic treatment in PsO and JIA	Protocol submission	2017 1Q
			Study start	Aug 01, 2019
			Study finish	2024 (planned)
			Interim reports	Jun 2020 through 2024
			Final report	2025 (planned)
BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies Ongoing	1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence 2. To identify unexpected adverse events	Serious infections; TB; Malignancies; Episodic treatment in PsO and JIA	Protocol submission	2017 1Q
			Study start	Jan 01, 2019
			Study finish	2024 (planned)
			Interim reports	Jun 2020 through 2024
			Final report	2025 (planned)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	3. To identify relevant adverse events that occur following the suspension of the treatment 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments 5. To identify risk factors for suffering adverse reactions with these treatments 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment			

<ARTIS summary>

Study short name and title: ARTIS - Anti-rheumatic Therapies In Sweden

Rationale and study objectives: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disease patients treated with adalimumab.

Study design: A national prospective, observational, uncontrolled cohort study

Study population: Swedish patients with RA, JIA and other rheumatic diseases who have been treated with adalimumab

Milestones:

- Protocol submission: 2017 1Q
- Study start: Aug 01, 2019
- Study finish: 2024 (planned)
- Interim report: Jun 2020 through 2024
- Final report: 2025 (planned)

<BIOBADASER summary>

Study short name and title: BIOBADASER - Spanish Registry of Adverse Events of

Biological Therapies

Rationale and study objectives: 1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence; 2. To identify unexpected adverse events; 3. To identify relevant adverse events that occur following the suspension of the treatment; 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments; 5. To identify risk factors for suffering adverse reactions with these treatments; 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment

Study design: National observational study

Study population: Spanish patients with rheumatic diseases who are treated with biologics

Milestones:

- Protocol submission: 2017 1Q
- Study start: Jan 01, 2019
- Study end: 2024 (planned)
- Interim report: Jun 2020 through 2024
- Final report: 2025 (planned)