SANDOZ A Novartis Division

Chief Medical Office & Patient Safety

GP2017 (INN: adalimumab) 20 mg/0.4 mL and 40 mg/0.8 mL Solution for Injection

GP2017

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Adalimumab
Product(s) concerned (brand name(s)):	Hyrimoz
Document status:	Final
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Disclaimer:

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 Hyrimoz 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 Hyrimoz in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Sandoz Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Hyrimoz.

Summary of the risk management plan for Hyrimoz (adalimumab)

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

Hyrimoz SmPC and Hyrimoz Labelling and Package Leaflet give essential information to healthcare professionals and patients on how Hyrimoz should be used.

This summary of the RMP for Hyrimoz 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 the RMP for Hyrimoz.

I. The medicine and what it is used for

Hyrimoz is authorized for use in rheumatoid arthritis (RA), juvenile idiopathic arthritis (Polyarticular juvenile idiopathic arthritis and Enthesitis-related arthritis), axial spondyloarthritis (Ankylosing spondylitis and Axial spondyloarthritis without radiographic evidence of AS), Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Hidradenitis suppurativa (HS), Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis, Paediatric uveitis, and Paediatric ulcerative colitis (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of the benefits of Hyrimoz can be found in the respective EPARs, including its plain-language summary, available on the EMA website, under the medicines' webpages:

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Hyrimoz together with measures to minimize such risks and the proposed studies for learning more about these 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.

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 analyzed regularly, 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 Hyrimoz is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Hyrimoz 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 Hyrimoz. 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

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 Hyrimoz
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 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 JIA 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 ulcerative colitis

II B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and considered to be an important identified risk of the reference product Humira. Serious infections are therefore considered as an important identified risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	Serious infections were reported in both adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors. Patients with RA had a 2-fold increased adjusted risk of hospitalized infections compared to those without RA concluded from a retrospective cohort. Current prednisone use > 7.5 mg/day, previous infections and previous hospitalized infections increased the risk of hospitalized infections as well as probably RA disease activity.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric
Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	TB is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and is considered to be an important identified risk of the reference product Humira. TB is therefore considered as an important identified risk of Hyrimoz, a biosimilar to Humira.

Risk factors and risk groups	Tuberculosis has been reported in both adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. Routine risk minimization activities recommending specific clinical measures to address the risk: Before initiation of therapy with Hyrimoz, all patients must be evaluated for both active and inactive ("latent") TB infection. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric
Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Malignancies (including lymphoma, HSTCL, leukemia, NMSC, melanoma, Merkel cell carcinoma, and other malignancies) are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and are considered to be an important identified risk of the reference product Humira. Malignancies are therefore considered as an important identified risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	**Lymphoma** For Hodgkin lymphoma age at diagnosis is a strong risk factor for survival, for non-Hodgkin lymphoma gender with a higher survival rate in males. The most commonly used prognostic system for Hodgkin lymphoma is the International Prognostic System, which uses the following factors: serum albumin less than 4 g/dL, hemoglobin less than 10.5 g/dL, male sex, age ≥45, stage IV disease, WBC count >15,000/µL, absolute lymphocyte count <600/µL or <8% of the total WBC count or both.

HSTCL

A moderate risk factor is immune-mediated disease, concomitant azathioprine, and possibly TNF inhibitor treatment.

Leukemia

General risk factors are gender and age. Men are more likely to develop CML, CLL and AML than women. The risk of most leukemias, with the exception of ALL, typically increases with age.
Genetics: For most leukemias there is no clear link. First degree relatives of CLL patients or identical twins of AML or ALL patients are at increased risk.

Lifestyle: Smoking cigarettes increase risks for AML.
Exposures: High-energy radiation, long term exposure to chemicals such as pesticides or industrial chemicals like benzene are considered a risk.

Previous treatment: Certain types of chemotherapy and radiation therapy for other cancers are considered leukemia risk factors.

NMSC

BCC: white skin type, male sex, sunlight exposure - patient geographic location affects the risk of developing skin cancer. A latency period of 20-50 years is typical between the time of ultraviolet damage and clinical onset of cancer, gene mutations, X-ray, immunosuppressed patients, previous non-melanoma skin cancer.

Squamous cell carcinoma: Patient related risk factors are organ transplantation, hematologic malignancy, long-term immunosuppressive therapy, HIV infection or AIDS.

Merkel cell carcinoma

The following factors are associated with increased risks: Whites / fair skin, UV radiation, age, long-term immunosuppression (risk 15 times increased compared to general population), RA, autoimmune disorders, organ transplantation, HIV, arsenic exposure, Merkel cell polyomavirus.

Melanoma

Important tumor specific risk factors are depth of invasion, the presence or absence of ulceration, and the nodal status at diagnosis. Patient factors are white skin, age, sun exposure.

	TNF seems to be a negative prognostic factor in melanoma surgery and correlates with chemotherapy resistance. However, high intra-tumor levels of TNF might be beneficial for immunotherapy. **Other malignancies** No specific risk groups or risk factors are known within the population of patients treated with adalimumab.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric

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	Demyelinating disorders are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and considered to be an important identified risk of the reference product Humira. Demyelinating disorders are therefore considered as an important identified risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	Potential risk factors may include subjects with pre-existing or recent onset central demyelinating disorders. MS: Genetic susceptibility and presumed non-genetic trigger such as viral infection or low vitamin D levels. GBS: Preceding gastrointestinal infection, older age, and upper extremity muscle strengths. ON: Young adults, female, Caucasian.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, where recommendations are done to perform a neurologic evaluation in patients with non-infectious intermediate uveitis prior to the initiation, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric

Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz	
Evidence for linking the risk to the medicine	BCG disease following live BCG vaccination in infants with in utero exposure to Humira is considered to be an important identified risk of the reference product Humira and is therefore considered as an important identified risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	Adalimumab treatment may be required to maintain disease stability for women during pregnancy. Adalimumab may cross the placenta, leading to in-utero exposure, impairing the development of the immune system. A prolonged half-life of adalimumab in infants may prolong this exposure, and hence lead to a compromised immunosystem. Therefore, the risk is potentially related to the maternal dose of adalimumab and how late into the pregnancy adalimumab treatment continued. The practice for BCG vaccine of neonates also differs across countries depending on national guidelines and the risk of TB exposure for the infant.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use; and 4.6 Fertility, pregnancy and lactation PL sections 2 Legal status: Prescription only Routine risk minimization activities recommending specific clinical measures to address the risk: Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. **Additional risk minimization measures:** Patient Reminder Card – adult and pediatric
Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	PML mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. PML is considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz, a biosimilar to Humira.

Risk factors and risk groups	The development of PML has been most extensively studied with natalizumab (1.78 per 1000 for patients treated more than 2 years). Contributors to the risk to develop PML under natalizumab, rituximab or efalizumab and possibly also infliximab are the combined application and sequential application of immunomodulatory/ immunosuppressive compounds and the duration and exposure of treatment.
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only

Important potential risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Evidence for linking the risk to the medicine	RPLS mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. RPLS considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	Risk factors are probably comorbid conditions (e.g. autoimmune disorders).
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only.

Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients

Evidence for linking the risk to the medicine	It is not known if adalimumab treatment influences the risk for adenocarcinoma of the colon. Adenocarcinoma of colon in UC patients is considered to be an important potential risk of the reference product Humira and is therefore considered to be an important potential risk of Hyrimoz, a biosimilar to Humira.
Risk factors and risk groups	Risk factors for colorectal cancer in UC patients include young age at diagnosis, longer duration, greater anatomical extent of colonic involvement, the degree of inflammation, family history of colorectal cancer, and presence of primary sclerosing cholangitis.
Risk minimization measures	**Routine risk minimization measures:**

	Guidance is provided in the section 4.4 Special warnings and precautions for use of the SmPC, where it is recommended that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC 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. PL section 4. Legal status: Prescription only.
Missing information: Patients with immune-compromised conditions	
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: Section 4.2 Posology and method of administration, Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties. PL sections 2 and 4. Legal status: Prescription only
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:** Guidance is provided in the following sections of the SmPC: Section 4.2 Posology and method of administration PL section 2. Legal status: Prescription only
Missing information: Episodic treatment in Ps, UC, and JIA	
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only
Missing information: Long-term safety information in the treatment of children with uveitis	
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only
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:** Legal status: Prescription only

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 Hyrimoz.

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

There are no studies required for Hyrimoz.