Summary of Risk Management Plan for Yuflyma®

Active substance:	Adalimumab
Dosage strength:	40mg/0.4ml
Pharmaceutical form:	Solution for injection
Version number of RMP summary	1.0
Name of Marketing Authorisation Holder:	iQone Healthcare Switzerland SA
Date:	30 June 2022
Reference RMP	EU RMP version 1.0 (CHMP positive opinion dated 11 February 2021)

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 Yuflyma® 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 Yuflyma® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. iQone Healthcare Switzerland SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Yuflyma®.
In the following summary, Yuflyma® is referenced with the trade name Yuflyma™, as approved in the EU.

Part VI: Summary of the risk management plan

Summary of risk management plan for Yuflyma™ (Adalimumab)

This is a summary of the Risk Management Plan (RMP) for Yuflyma. The RMP details important risks of Yuflyma, how these risks can be minimised, and how more information will be obtained about Yuflyma risks and uncertainties (missing information).

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

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

I. The medicine and what it is used for

Yuflyma is authorised for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), axial spondyloarthritis (axial SpA) – ankylosing spondylitis (AS) and axial SpA without radiographic evidence of AS, psoriatic arthritis (PsA), psoriasis (Ps), paediatric plaque Ps, hidradenitis suppurativa (HS) (including adolescents from 12 years of age), Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), uveitis (UV), and paediatric UV (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Yuflyma's benefits can be found in Yuflyma's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/yuflyma

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

Important risks of Yuflyma, together with measures to minimise such risks and the proposed studies for learning more about Yuflyma'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 PL 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 Yuflyma, 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 Periodic Safety Update Report (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 Yuflyma is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Yuflyma 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 Yuflyma. 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 [ON]) • BCG disease following live BCG vaccination in infants with in utero exposure to Yuflyma
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 Crohn's disease (CD) • Episodic treatment in psoriasis (Ps), ulcerative colitis (UC), and juvenile idiopathic arthritis (JIA) • Long-term safety information in the treatment of children with uveitis

II.B Summary of important risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	In patients treated with adalimumab, respiratory tract infections have been reported to occur very commonly, whereas, intestinal infections, skin and soft tissue infections, reproductive and urinary tract infections etc. have been commonly reported. Meningitis and brain infections, TB and eye infections are uncommon (Humira® Summary of Product Characteristics [SmPC]). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	Risk factors for infection, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, acquired immune deficiency syndrome (AIDS), or large burns or severe trauma.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.8 • PL section 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card

Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	TB, including reactivation and new onset of TB, has been reported in patients receiving adalimumab. There have been pulmonary as well as extra-pulmonary TB (Humira® SmPC). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	Risk factors for TB, in general, include very young people and elderly people, immunosuppressive medications (such as transplant recipients), including steroids; treatment with chemotherapy drugs or radiation; removal of the spleen; long-standing diabetes, AIDS, malnutrition, alcoholism, or large burns or severe trauma.
Risk minimisation measures	<u>Routine risk minimisation measures:</u>

	• SmPC sections 4.2, 4.3, 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card

Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Malignancies (some fatal) have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents including adalimumab in the post marketing setting. Approximately half the cases were lymphomas and rarely, hepatosplenic T-cell lymphoma have been also reported in patients treated with adalimumab (Humira® SmPC). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC) and clinical trials of Yuflyma.
Risk factors and risk groups	History of malignancy, immunosuppressant therapy (e.g., chemotherapy or steroids), and/or AIDS or human immunodeficiency virus (HIV) infection may increase the risk of malignancy. Exposure to sunlight is the main risk factor for most skin cancers. Phototherapy for Ps also increases the risk of skin cancer. UC is associated with a higher risk of colon cancer.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card

Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])	
Evidence for linking the risk to the medicine	TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system (CNS) demyelinating disease including MS and ON, and peripheral demyelinating disease, including GBS. The role that TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced

	neuropathies by augmenting the number of activated peripheral T-cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T–cell receptor signalling, and/or decreasing apoptosis of autoreactive T-cells. These autoreactive T-cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens. A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective. Since TNF inhibitors can neutralise both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF. Furthermore, an increasing number of neurologic side effects with the use of TNF-α Blockers have been reported in the literature, consisting of central and peripheral nervous system demyelinating events (Kemanetzoglou E *et al.*, 2017). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Patients with a history of demyelinating disorders, or a family history may be at greater risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections 4.4 and 4.8. • PL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient reminder card.

Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Yuflyma	
Evidence for linking the risk to the medicine	Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	No epidemiological data available.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC section 4.4 and 4.6 • PL section 2 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u>

	Patient reminder card.

Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	PML is a reported complication of a variety of autoimmune rheumatic diseases (ARDs) and is associated with both synthetic and biologic immunosuppressive agents (Molloy and Calabrese, 2012). Although John Cunningham (JC) virus antibodies are present in about 80% of adults, PML occurs primarily in immunocompromised individuals and is thought to be caused by JC virus reactivation. As a result, PML has been reported primarily in patients with underlying immunosuppressive conditions (i.e., HIV infection, AIDS, malignancies) and immunosuppressive medications. In addition, results from a study of a national hospital discharge database also suggested that rheumatic diseases, including Systemic Lupus Erythematosus (SLE) and RA, are associated with a higher rate of PML compared to the background population (Kothary *et al.*, 2011). PML has also been reported with TNF inhibitors in the setting of autoimmune diseases (Molloy and Calabrese, 2012). Since, TNF-α plays a critical role in recruiting and activating macrophages, NK cells, T-cells, and antigen presenting cells, depletion of TNF by treatment with TNF-α blockade may facilitate reactivation of JC virus infection and progression to PML (Sammut *et al.*, 2016). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients (e.g., due to chemotherapy, or HIV/AIDS). An analysis of PML cases 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 malignancies of the lymphoid (immune) system. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, and some rheumatic diseases.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> None

Important potential risk: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Two cases (Mahévas T *et al.*, 2015, Nwafo N, 2018) have reported an association between RPLS and adalimumab. RPLS has also been reported in subjects treated with other medicines similar to adalimumab (Kastrup and Diene,r 2008, Zamvar *et al.*, 2008, Haddock R *et al.*, 2011, Garg N *et al.*, 2013). Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Risk factors include high blood pressure (BP) (including high BP in pregnancy) and use of medicines known as calcineurin inhibitors.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> None

Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	In a review of published studies concerning the risk of colon cancer in UC patients, the yearly incidence rate of colon cancer ranged from approximately 0.006% to 0.16%. Yuflyma is a biosimilar medicinal product to the reference product Humira®. The evidence of the above mentioned risk is derived from known information of Humira® (Humira® SmPC).
Risk factors and risk groups	Factors associated with an increased risk of colon cancer include age greater than 50 years, presence of colon polyps, personal or family history of some cancers, duration of UC, extent and severity of UC, diet, and cigarette smoking.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC section 4.4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> None

Missing information: Patients with Immune Compromised conditions	
Risk minimisation measures	Routine risk communication: • SmPC section 4.4. • PL section 2.

	Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Episodic treatment in psoriasis (Ps), ulcerative colitis (UC), and juvenile idiopathic arthritis (JIA)	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Prescription only medicine Additional risk minimisation measures: None

Missing information: Long-term safety information in the treatment of children with uveitis	
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2 Legal status: Prescription only medicine Additional risk minimisation measures: None

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 Yuflyma.

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

There are no studies required for Yuflyma.