Summary of the Risk Management Plan (RMP)

Hulio® (adalimumab)

Solution for Injection

Marketing Authorisation Holder: Mylan Pharma GmbH

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Based on EU RMP, version 4.0,

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Hulio® (adalimumab)

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

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

This summary of the RMP for Hulio® 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 Hulio®'s RMP.

I. The medicine and what it is used for

Hulio® is authorised for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, psoriatic arthritis, plaque psoriasis in adults and children, hidradenitis suppurativa, Crohn's disease in adults and children, ulcerative colitis, and non-infectious uveitis in adults and children (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 Hulio®'s benefits can be found in Hulio®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events 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 Hulio® is not yet available, it is listed under 'missing information' below.

In the case of Hulio®, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of important risks and missing information

Important risks of Hulio® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. 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 Hulio®. 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/use in special patient populations etc.);

Table 1 Part VI: Summary of safety concerns

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 Hulio®
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

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 Crohn's disease (CD) • Episodic treatment in psoriasis, ulcerative colitis and juvenile idiopathic arthritis (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 1: Serious infections	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). In the clinical studies conducted with Hulio® to date, the most common treatment-related infections included bronchitis, nasopharyngitis and urinary tract infection, although the overall number of patients experiencing any serious infection was small (20 subjects [3.0%] receiving Hulio®). Serious infections have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute

Important identified risk 1: Serious infections	
	risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh et al, 2015). Other risks associated with serious infections include: very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 where patients with severe infections are contraindicated SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis* *SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where patients with active tuberculosis or other severe infections are contraindicated* *PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for infections* *PL section 4 listed as side effects* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Reminder Card*

Important identified risk 1: Serious infections	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). TESAEs that occurred in more than 1 patient were: disseminated TB (2 patients, 1 [0.2%] in each treatment group) and latent TB (2 patients [0.3%], both with FKB327). No case of pulmonary TB was reported on FKB327 compared to 2 cases [0.4%] on Humira®. Tuberculosis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh et al, 2015). Other risks associated with serious infections include: very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin

Important identified risk 2: Tuberculosis (TB)	
	integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 where patients with active tuberculosis are contraindicated* *SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis* *SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed as adverse reactions* *PL section 2 where patients with active tuberculosis are contraindicated* *PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for TB* *PL section 4 listed as side effects* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Reminder Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 3: Malignancies	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, malignancies have been reported

Important identified risk 3: Malignancies	
	to occur commonly (≥ 1/100 to < 1/10) to uncommonly (≥ 1/1,000 to < 1/100). One case (0.2%) of basal cell carcinoma (BCC) was reported in the clinical studies conducted with FKB327, with one case (0.2%) of squamous cell carcinoma (SCC) reported in the Humira® treatment group. There have been one case (0.2%) breast cancer and one case (0.2%) cervix carcinoma in the FKB327 treatment group but none in Humira treatment group in the clinical studies conducted with Hulio® to date. There have been no treatment-related cases of hepatosplenic T-cell lymphoma, leukaemia, melanoma, Merkel cell carcinoma in the clinical studies conducted with Hulio® to date. One treatment-related case of lymphoma in the FKB327 treatment group was reported as post-study event. Malignancies have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Patients with RA have a 10 % increase in overall malignancy risk compared with the general population. Furthermore, the SIR estimates for patients with RA continued to show an increased risk of lymphoma and lung cancer as previously observed. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk among patients with RA compared with the general population.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given about malignancies in patients treated with a TNF antagonist* *SmPC section 4.8 where a description of malignancies observed in adalimumab clinical trials is provided* *SmPC section 4.8 listed several malignancies* *PL section 2 where a warning is given that Hulio® can increase*

Important identified risk 3: Malignancies	
	the risk of getting cancer *PL section 4 listed as a side effect* *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Reminder Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis [ON])	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, demyelinating disorders have been reported to occur rarely (≥ 1/10,000 to < 1/1,000). There have been no treatment-related cases coded as a recognised demyelinating disorder, although one (0.2%) treatment-related adverse event of hypoaesthesia was reported in the clinical studies conducted with Hulio®. Demyelinating disorders have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors associated with an increased risk for MS are a combination of genetic susceptibility (HLA-DR15 haplotype) and environmental exposures (including latitude, vitamin D deficiency, season of birth, Epstein Barr virus infection, and smoking behaviour) (O'Gorman et al, 2012). These factors appear to act synergistically and the risk of MS is increased in individuals exposed to more than one factor (Disanto et al 2012). Being Caucasian and female increases risk, as does having a family

Important identified risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis [ON])	
	relative with MS (http://patient.info/doctor/multiple-sclerosis-pro). Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus [Blázquez & Saiz 2016]), vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease) (http://patient.info/doctor/guillain-barre-syndrome-pro, Ansar & Valadi 2015). Risk factors for optic neuritis include female sex, race (more frequent in white Caucasians, genetic mutations (as per MS), bacterial/viral infections, sarcoidosis/lupus and some drugs (e.g. quinine and some antibiotics) (http://www.mayoclinic.org/diseases-conditions/optic-neuritis/symptoms-causes/ - accessed 02Feb2017)
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease* *SmPC section 4.4 where a warning is given to exercise caution in considering the use of Hulio® in patients with pre-existing or recent- onset central or peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop* *SmPC section 4.4 where guidance is given to perform neurologic evaluation in patients with non-infectious intermediate uveitis prior to and during treatment* *SmPC section 4.8 listed as an adverse reaction*

Important identified risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis [ON])	
	PL section 2 where a warning is given for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs
Additional pharmacovigilance activities:	Additional pharmacovigilance activities: *None*

Important identified risk 5: BCG disease following live BCG vaccination in infants with in utero exposure to Hulio®	
Evidence for linking the risk to the medicine	Data from reference product trials, registries and database. Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. 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.
Risk factors and risk groups	Infants who are exposed to adalimumab intrauterine.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4: 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. SmPC section 4.6: Adalimumab may cross the placenta into the

Important identified risk 5: BCG disease following live BCG vaccination in infants with in utero exposure to Hulio®	
	serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. PL section 4: Hulio alters immune response. Administration of live vaccines (e.g., BCG vaccine used to prevent tuberculosis) to your infant exposed to Hulio in-utero is not recommended for 5 months following your last Hulio injection during pregnancy. *Legal status (prescription only medicine)* Additional risk minimisation measures: *Patient Reminder Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 1: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of PML in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of PML in the clinical studies conducted with Hulio® to date. PML has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or

	relapsing–remitting multiple sclerosis patients treated with natalizumab. PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number of cases and together account for less than 10% of all reported PML cases (Pavlovic et al, 2015).
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of RPLS in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of RPLS in the clinical studies conducted with Hulio® to date. RPLS has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Suspected aetiologies 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 et al, 2008).

Important potential risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Risk minimisation measures	Routine risk minimisation measures: *Legal status (prescription only medicine)* Additional risk minimisation measures:
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 3: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. In all RA trials with adalimumab, the rate of ALS was determined as < 0.1 event per 100 patient-years of exposure. Although there have been no treatment-related cases of adenocarcinoma of colon in UC patients in the clinical studies conducted with Hulio® (*studies were conducted in rheumatoid arthritis patients*). However, adenocarcinoma of colon has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for colon cancer include extent and duration of UC, primary sclerosing cholangitis, a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis (Lakatos & Lakatos, 2008). The standardised incidence rate (SIR) for colorectal cancer was 8.6 (95% CI, 3.8 –19.5) in those of young age and 4.8 (95% CI, 3.9 –5.9) in those with extensive colitis. Men with UC had a greater risk of colorectal cancer (SIR, 2.6; 95% CI, 2.2–3.0) than women (SIR, 1.9; 95% CI, 1.5–2.3) (Jess et al, 2012).

Important potential risk 3: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that the risk for developing dysplasia or colon cancer in UC patients is unknown* *SmPC section 4.4 where instruction is given to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Missing information 1: Patients with immune-compromised conditions	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given for physicians to exercise caution when considering the use of Hulio® in patients with underlying conditions which may predispose them to infections, including the use of concomitant immunosuppressive medications* *PL section 2 where a warning is given for the patient to tell their doctor before using Hulio® if they are suffering from another condition which makes them more susceptible to getting infections*

	Legal status (prescription only medicine) Additional risk minimisation measures: *None*

Missing information 2: 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 communication: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine Additional risk minimisation measures: *None*

Missing information 3: Episodic treatment in psoriasis, ulcerative colitis and juvenile idiopathic arthritis (Ps, UC, and JIA)	
Risk minimisation measures	Routine risk minimisation measures: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine Additional risk minimisation measures: *None*

Missing information 4: Long-term safety information in the treatment of children with uveitis	
Risk minimisation measures	Routine risk minimisation measures: None *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Missing information 5: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimisation measures	Routine risk minimisation measures: None *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 Hulio®.

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

FKB327-003: An Open-label Extension Study to Compare the Long term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE).

Study FKB327-003 has been completed and final study report submitted 31 October 2018.

Safety surveillance of Hulio® (FKB327) (adalimumab) using the rheumatoid arthritis RABBIT registry in Germany: long term, prospective, observational study.

Purpose of the study:

This observational post-authorisation safety study aims to characterise the safety profile of the adalimumab biosimilar formulation Hulio®, and to describe the effectiveness and response to the treatment in RA patients in a real life environment, using already existing data from the German Biologics Registry (RABBIT). In particular, this registry will address the long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune hepatitis, and CHF/MI.