Summary of risk management plan for Libmyris (adalimumab)

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

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

This summary of the RMP for Libmyris 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 Libmyris' RMP.

I. The medicine and what it is used for

Libmyris is authorised for rheumatoid arthritis (RA), psoriasis (Ps), hidradenitis suppurativa, Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, uveitis and paediatric uveitis. Libmyris 40 mg solution is also indicated in juvenile idiopathic arthritis (JIA), axial spondylarthritis, psoriatic arthritis, paediatric plaque Ps (see SmPC for the full indication). It contains adalimumab as the active substance, and it is given by subcutaneous route of administration.

Further information about the evaluation of Libmyris' benefits can be found in Libmyris' 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/libmyris.

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

Important risks of Libmyris, together with measures to minimise such risks and the proposed studies for learning more about Libmyris' 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 Libmyris, 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 Libmyris is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Libmyris 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 Libmyris. 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) • Bacillus Calmette–Guérin (BCG) disease following live BCG vaccination in infants with *in utero* exposure to adalimumab
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

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
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 with advanced age include respiratory infections (e.g. pneumonia, influenza, and tuberculosis), bacteraemia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other

Important identified risk: Serious infections	
	opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population ≥ 65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimisation measures: Patient reminder card.

Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
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), bacteraemia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB In order to inform patients of these risks, corresponding text is also present in the package leaflet. **Prescription only medicine.** Additional risk minimisation measures: Patient reminder card.

Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Data from adalimumab trials. No reports of hepatosplenic T-cell lymphoma (HSTCL) were received from any clinical trial, open-label or controlled. Information from the Humira's post-marketing safety database.
Risk factors and risk groups	A prospective observational cohort study of 19,486 patients with inflammatory bowel disease (IBD), including 7,727 patients with UC or unclassified IBD, found an increased risk for developing

Important identified risk: Malignancies	
	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) [Beaugerie, 2009]. Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks in Section SVII.3 may or may not be applicable to HSTCL which is rare [Kotlyar, 2011, Parakkal, 2011]. Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia 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 leukaemia [National Cancer Institute, 2014]. 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 [Peyrin-Biroulet, 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic [National Cancer Institute, 2011b]. Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis [National Cancer Institute, 2011b]. Factors associated with an increased risk of melanoma include ultraviolet 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 immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles [National Cancer Institute, 2011b]. 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 ultraviolet light exposure [Becker, 2010a].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Sections 4.4: warning regarding patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of PUVA treatment; warning regarding the use of any TNF-antagonist in chronic obstructive pulmonary disease (COPD) patients, as well as in patients with increased risk for malignancy due to heavy smoking; warning regarding patients with UC who are at increased risk for dysplasia or colon carcinoma, or who had a prior history of dysplasia or colon carcinoma

Important identified risk: Malignancies	
	Section 4.8: Malignancies listed as adverse reactions. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimisation measures: Patient reminder card.

Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (e.g. HLA-DR2 [HLADRB1 *15], ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors) [Ramagopalan, 2010]. Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age [Sejvar, 2011]. Subjects with intermediate uveitis have a high prevalence of demyelination [Zein, 2004; Burkholder, 2012; Llorenc, 2012; Messenger, 2015].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.4: Warning on demyelinating disorders included Section 4.8: Demyelinating disorders are also listed as adverse reaction In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient reminder card.

Important identified risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
Risk factors and risk groups	Infants exposed to adalimumab *in utero*.
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC:

Important identified risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	
	Section 4.4 has a section on vaccinations Section 4.6: warning on live vaccines In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient reminder card.

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the Humira's post-marketing safety database.
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. Currently, over 80% of PML cases are diagnosed in patients with HIV/acquired immune deficiency syndrome (AIDS) [Weber, 2008]. 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 [Carson, 2009]. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases [Bartt, 2006; Eng, 2006; Calabrese, 2007; Govindappa, 2007; Carson, 2009].
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Important potential risk: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the Humira's post-marketing safety database.
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, 2008].
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Important potential risk: Adenocarcinoma of colon in UC patients	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials.
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 primary sclerosing cholangitis [Van Assche, 2013], diet, and cigarette smoking [National Cancer Institute, 2006].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. There is a warning in section 4.4 of the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. 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. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: None.

Missing information: Patients with Immune Compromised conditions	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Warnings regarding patients with immune compromised conditions are included. There is currently no information on subjects with a history of clinically significant drug or alcohol abuse listed in the SmPC. 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 CD	
Risk minimisation measures	Routine risk minimisation measures: 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: 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: Section 4.2. Section 4.2 of the SmPC states that it is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. In order to warn patients about this risk, corresponding text is also present in the package leaflet. 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 ulcerative colitis	
Risk minimisation measures	Routine risk minimisation measures: 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 Libmyris.

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

There are no studies required for Libmyris.