Summary of the risk management plan for Zessly (infliximab)

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

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

This summary of the RMP for Zessly 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).

I. The medicine and what it is used for

Zessly is authorized for the treatment of RA, CD (adult and pediatric), UC (adult and pediatric), AS, PsA, and psoriasis (see SmPC for the full indication). It contains infliximab as the active substance, and it is given by the intravenous route of administration.

Further information about the evaluation of Zessly's benefits can be found in Zessly'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/zessly

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

Important risks of Zessly, together with measures to minimize such risks and the proposed studies for learning more about Zessly's 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 PL and SmPC addressed to patients and HCPs;
- 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.

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

II.A: List of important risks and missing information

Important risks of Zessly 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 Zessly. 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 infection/sepsis Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab Demyelinating disorders Malignancy
Important potential risks	Colon carcinoma/dysplasia (in pediatric ulcerative colitis)
Missing information	None

II B: Summary of important risks

Important identified risk: Serious infection/sepsis

Evidence for linking the risk to the medicine	Serious infection/sepsis, including TB, OIs and HBV reactivation, is listed in section 4.3 Contraindications, section 4.4 special warnings and precautions for use; section 4.8 Undesirable effects of the Remicade SmPC; and section 2 of the Remicade PL. This risk is also listed as an important identified risk in the RMP v19 public summary of the reference product Remicade. Therefore, serious infection/sepsis is considered to be an important identified risk for Zessly.
Risk factors and risk groups	The incidence of infection is high in people with immune impairment. Patients with chronic infection or a history of recurrent infection, including those who use other immunosuppressive medications, such as MTX, are at greater risk of developing an OI during infliximab therapy. Patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, and blastomycosis are widespread, are also at increased risk of developing an OI during infliximab therapy. Patients treated with 10 mg/kg infliximab were at a higher risk of serious infection when compared to the 3 mg/kg infliximab treatment arm.

	In clinical studies, the incidence of serious infections in infliximab-treated patients 65 years of age and older was greater than that seen in those under 65 years of age. As well, more infliximab treated children developed infections compared to infliximab treated adults. Risk factors for septic arthritis in patients with pre-existing joint disease include advanced age, diabetes mellitus, the presence of joint prostheses, skin infections and a diagnosis of RA. The most common risk factors to develop TB include conditions impairing the immune system, such as advanced age, HIV infection, alcohol abuse, malignancy, corticosteroids or other immunosuppressive therapy, connective tissue disease, renal failure, diabetes, and pregnancy. Additional risk factors include contact with a person(s) with active TB infection and having been born in, lived in, or traveled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (eg, hospitals and nursing homes) or high-density institutions (eg, prisons).Risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (chemotherapy, corticosteroids, MTX, AZA, and/or TNF-α antagonist). Other risk factors/conditions that predispose a patient for HBV reactivation include AIDS, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3, 4.4, 4.5, 4.6 and 4.8 PL section 2 Legal status: Prescription only Additional risk minimization measures: Patient reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Participation in UKIBD (UK)

Important identified risk: Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	
Evidence for linking the risk to the medicine	BCG breakthrough infection is listed in section 4.4 Special warnings and precautions of the Remicade SmPC. Agranulocytosis in infants with in utero exposure is listed in section 4.6 fertility, pregnancy and latation, section 4.8 Undesirable effects of the Remicade SmPC, and in section 2 of the Remicade PL. This risk is also listed as an important identified risk in the RMP v19 public summary of the reference product Remicade. Therefore BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab is considered to be an important identified risk for Zessly.
Risk factors and risk groups	Infants exposed to infliximab in utero and receiving BCG vaccine within 6 months after birth. Women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last reference product treatment.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.5, 4.6, and 4.8 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: Patient reminder card (BCG only)
Important identified risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Demyelinating disorders are listed in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the Remicade SmPC and section 2 of the Remicade PL. The risk is also listed as an important identified risk in the RMP v19 public summary of the reference product Remicade. Therefore demyelinating disorders is considered to be an important identified risk for Zessly.
Risk factors and risk groups	The etiology of MS and other autoimmune diseases can be linked to genetic and environmental factors. First-degree relatives of MS patients are 20-40 times more likely to develop MS than the general population. In a twin study, the overall monozygotic-to-dizygotic concordance ratio of 3.0 reflected the heritable nature of MS. Further, the likely polygenic nature of heritability was supported by the finding that ancestry by northern latitude (highest risk in Celtic and Scandinavian) and early diagnosis were independent predictors of concordance among the monozygotic twins.

	Environmental triggers may also be involved in the development of MS. A number of studies have suggested an association between smoking and MS. For example, a Norwegian cross sectional study of 22,312 people found a higher risk of MS in smokers than non-smokers (rate ratio 1.81; 95% Cl 1.1 2.9). Similar results were noted in a case control study from the UK. Another possible risk factor for MS is the month of birth. A large population-based study found that the risk of MS is increased for those born in May and decreased for those born in November, suggesting that the gestational or neonatal environment influences the risk of MS later in life.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8 PL section 2.2 and 4 Legal status: Prescription only Additional risk minimization measures: None
Important identified risk: Malignancy	
Evidence for linking the risk to the medicine	Malignancy is listed in Section 4.4 warnings and precautions for use and section 4.8 Undesirable effects of the Remicade SmPC. The risk is also listed as an important identified risk in the RMP v19 public summary of the reference product Remicade. Therefore malignancy is considered to be an important identified risk for Zessly
Risk factors and risk groups	Caution should be exercised when considering infliximab for patients with a history of malignancy, or patients with Ps and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Caution should also be exercised when considering continuing treatment in subjects who develop a malignancy. Patients with COPD may be at an increased risk of cancer with infliximab treatment.

	Patients with UC at increased risk for dysplasia or colon carcinoma (e.g., patients with long-standing UC or primary sclerosing cholangitis), or with prior history of dysplasia or colon carcinoma, should be screened (colonoscopy, biopsy) for dysplasia at regular intervals before therapy and throughout their disease course. All reported cases of HSTCL in patients treated with infliximab have occurred in patients with CD or UC and the majority was reported in adolescent or young adult males. All of these patients had received treatment with AZA or 6 MP concomitantly with or immediately prior to infliximab. Cases of HSTCL have been reported in CD and UC patients receiving these drugs who were not treated with infliximab. Based on published series of cases, young men appear to be at a higher risk for HSTCL. Risk factors for HSTCL appear to be immunocompromised patients and patients undergoing solid organ transplantation. Subjects with RA, particularly with highly active disease and/or chronic exposure to immunosuppressive agents, are at a higher risk for lymphoma disorders, even in the absence of TNF-□-antagonist therapy. Epidemiological studies have generally shown that skin cancers are increased in patients with RA, and immunosuppression may potentiate this risk by shortening the latency period to expression of malignancy. Immunosuppression is an important risk factor for cervical cancer; hence drugs that suppress immune response, such as those taken for autoimmune diseases, can increase cervical cancer risk. A Danish study observed that an increased cervical cancer risk in women with CD could be correlated with young age at diagnosis, smoking, 5-aminosalicylic acid, and thiopurine exposure. The risk factors for SCC include chronic UVA and UVB exposure, increasing age, arsenic exposure, genetic predisposition, therapeutic radiation exposure, and immunosuppression. The risk factors for basal cell carcinoma include all those for SCC in addition to basal cell nervous syndrome. With respect to Ps patients, a higher risk of NMSC is seen in those with prior coal tar, UVB therapy, PUVA, retinoids, and cyclosporine therapy.

	Risk factors for the development of melanomas can be categorized as environmental or host factors. Exposure to UV light, especially in patients with a fair complexion, history of sunburns, and poor ability to tan, is the most strongly correlated environmental risk factor with the development of melanoma. Patients with xeroderma pigmentosum who do not have the ability to repair UV light-induced DNA damage are particularly susceptible. Other environmental risk factors include living on or near the equator or higher elevations, exposure to petroleum products, industrial chemicals, and ionizing and non-ionizing radiation. Family or personal histories of melanoma and/or mutations in CDK N2A or CDK4 genes are strong host risk factors. Additional host risk factors include the presence of 5 or more dysplastic nevi, large number of nevi or giant congenital nevus. Patients with conditions that are associated with immune suppression (i.e., HIV, organ transplantation) are at a higher risk of developing melanomas Risk factors associated with the development of MCC include exposure to UV radiation, immunosuppression, and possible viral etiology. MCC occurs most frequently among elderly white patients, and affects males (61%) more commonly than females (39%). The incidence of MCC was found to be higher in areas with a greater solar UVB radiation index. Immunosuppression increases the relative risk of MCC with an approximate 13-fold increase in patients with HIV, and a 10-fold increase in solid-organ transplant patients. Patients with other tumors, such as squamous cell carcinoma and chronic lymphocytic leukemia, also have an increased risk of MCC.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.8, and 5.3 PL section 2 and 4 Legal status: Prescription only Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Participation in UKIBD (UK)

Important potential risk: Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	As per Remicade SmPC, with current data, it is not known if infliximab treatment influences the risk for developing dysplasia or colon cancer. However all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis 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 (see section 4.4 Special warnings and precautions for use of the Remicade SmPC). As this risk is also listed as an important potential risk in the RMP v19 public summary of the reference product Remicade, colon carcinoma/dysplasia (in pediatric ulcerative colitis) is considered to be an important potential risk for Zessly.
Risk factors and risk groups	Patients with long-standing UC or primary sclerosing cholangitis, or who had a prior history of dysplasia or colon carcinoma are at a higher risk for developing colon cancer or dysplasia. Other risk factors for development of colorectal dysplasia and cancer in patients with UC include extent of disease, family history of colorectal cancer, young age at diagnosis, and the presence of backwash ileitis (ileal inflammation in the context of UC).
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 5.3 Legal status: Prescription only Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Participation in UKIBD (UK)

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 Zessly.

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

Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
UKIBD (UK): Inflammatory Bowel Disease (IBD) Registry	The UKIBD Registry provides the first ever UK-wide repository of anonymized IBD adult and pediatric patient data for prospective audit and research purposes. Bringing this data together for the first time will: • Drive continuous improvement in patient care and access to care across the UK • Inform commissioning and service design • Improve our understanding of long term outcomes • Provide local & national data in order to better define the pattern of ulcerative colitis and CD • Support IBD research