SANDOZ

EU Safety Risk Management Plan (RMP) Zessly

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 31 Aug 2023

Date of Final sign off: 22 Nov 2023

Rationale for submitting an updated RMP:

The approved RMP version 3.0 was updated to remove the UKIBD (UK) registry from the additional pharmacovigilance (PV) activities.

The main trigger for the Zessly RMP update is to remove the UKIBD registry as an additional pharmacovigilance activity based on the cumulative evidence regarding safety profile of Zessly and established long-term safety data for Remicade.

In addition, based on the outcome of the previous RMP variation procedure (Procedure No. EMEA/H/C/004647/II/0020), RABBIT and BADBIR registries information was updated as completed. Based on the PRAC recommendation for all infliximab containing products on 24 Jan 2022 (EMEA/H/C/000240/IB/0233), the characterization of the risk "Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab" was updated to include information 'live vaccines is not recommended to infants for at least 12 months following birth after in utero exposure to infliximab.'

The RMP safety concerns (important risks and missing information) and risk minimization activities remain consistent with those of the latest Remicade RMP public summary (Janssen EMA 2022).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v3.0
Part I	Additional monitoring status updated from 'Yes' to 'No'.
Part II	Post-authorization experience updated. Updated the the statement "Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for at least 12 months after birth."
Part III, V and VI	Registry UKIBD (UK) removed from additional pharmacovigilance activities. Part V.1, V.3, Part VI II.B updated the the statement "Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for at least 12 months after birth."
Part VII	Annex 2: Participation end dates and dates of final reports are provided for registries UKIBD (UK), RABBIT (DE) and BADBIR (UK). Annex 3: Registry UKIBD (UK) removed from additional pharmacovigilance activities. Annex 8: Updated with summary of changes. Other: The RMP heading numbers removed from the Summary of the RMP as instructed in the EMA Guidance on the format of the risk management plan in the EU (Rev.2.0.1).

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 3.0

Approved with procedure: EMEA/H/C/004647; Date of approval (opinion date): 05 May 2022

QPPV name: Juergen Maares

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder's QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

6-MP	6-Mercaptopurine
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AS	Ankylosing Spondylitis
ATC	Anatomical Therapeutic Chemical (Classification System)
AZA	Azathioprine
BADBIR	British Association of Dermatologists Biological Interventions Register
BCG	Bacillus Calmette-Guérin
BLA	Biologics License Application
CD	Crohn´s disease
CDR	Complimentary determining region
CHF	Congestive Heart Failure
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CRP	C reactive protein
DDD	Defined daily dose
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FcRn	Neonatal Fc Receptor
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HSR	Hypersensitivity reaction
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory Bowel Disease

IgG / IgG1	Immunoglobulin G / Immunoglobulin G subclass 1
IL	Interleukin
JIA	Juvenile Idiopathic Arthritis
JRA	Juvenile Rheumatoid Arthritis
MAA	Marketing Authorization Application
MCC	medical Cell Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple sclerosis
MTX	Methotrexate
NK	Natural Killer (Cells)
NMSC	Non-Melanoma Skin Cancer
NYHA	New York Heart Association
OI	Opportunistic infection
PK	Pharmacokinetic(s)
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic Arthritis
Ps	Psoriasis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTY	Patient-treatment-years
PUVA	Psoralen And Ultraviolet A
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid Arthritis
RABBIT	Registry Rheumatoid Arthritis: Observation of Biologics Therapy
RMP	Risk Management Plan
ROW	Rest of the world
SAE	Serious adverse event
SCC	Skin cell cancer
SIR	Standardized incidence ratio
SLE	Systemic Lupus Erythematodes
SMQ	Standardized MedDRA Query
SMR	Standardized morbidity ratio
SOC	System organ class

SWIBREG	Swedish Registry for Inflammatory Bowel Disease
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor Alpha
TNF-β	Tumor Necrosis Factor beta (lymphotoxin-alpha)
TK	Toxicokinetic
UC	Ulcerative colitis
UK	United Kingdom
UKIBD	Inflammatory Bowel Disease Registry in the UK
US	United States
UV	Ultraviolet
WHO	World Health Organization

Part I: Product Overview

Table 1 Part I.1 - Product Overview

Active substance (INN or common name)	Infliximab
Pharmacotherapeutic group (ATC Code)	Immunosuppressants, Tumor Necrosis Factor alpha (TNF-α) inhibitors L04AB02
Marketing Authorization Applicant	Sandoz GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zessly
Marketing authorization procedure	Centralized Procedure
Brief description of the product	**Chemical class:** Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α, but not to TNF-ß.
	Summary of mode of action: Infliximab inhibits the functional activity of TNF-α in a wide variety of in vitro bioassays. *In vivo*, infliximab rapidly forms stable complexes with human TNF-α, a process that parallels the loss of TNF-α bioactivity. Elevated concentrations of TNF-α have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. After infliximab treatment, patients exhibited decreased levels of serum IL-6 and CRP, and increased hemoglobin levels in rheumatoid arthritis patients with reduced hemoglobin levels, compared with baseline. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques. In PsA, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin. Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable TNF-α. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing TNF-α and interferon γ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.
	Important information about its composition: Infliximab is produced in

	CHO cells by recombinant DNA technology
Hyperlink to the Product Information	[Zessly SmPC]
Indications in the EEA	**Current:** Rheumatoid arthritis Zessly, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate. • adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated. Adult Crohn's disease Zessly is indicated for: • treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. • treatment of fistulizing, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). Paediatric Crohn's disease Zessly is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy. Ulcerative colitis Zessly is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric ulcerative colitis Zessly is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. Ankylosing spondylitis Zessly is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy. Psoriatic arthritis Zessly is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been

	inadequate. Zessly should be administered: • in combination with methotrexate • or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. Psoriasis Zessly is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** Adults (≥ 18 years): Rheumatoid arthritis 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Zessly must be given concomitantly with methotrexate. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment. Moderately to severely active Crohn's disease 5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion. In responding patients, the alternative strategies for continued treatment are: • Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or • Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

	Fistulizing, active Crohn's disease 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given. In responding patients, the alternative strategies for continued treatment are: • Maintenance: Additional infusions of 5 mg/kg every 8 weeks or • Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking. Ulcerative colitis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. 3 doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. Ankylosing spondylitis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given. Psoriatic arthritis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Psoriasis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given. Re-administration for Crohn's disease and rheumatoid arthritis If the signs and symptoms of disease recur, Zessly can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed HSRs have been uncommon and have occurred after infliximab-free intervals of less than 1 year. The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients. Re-administration for ulcerative colitis The safety and efficacy of re-administration, other than every 8 weeks, has not been established.

	Re-administration for ankylosing spondylitis The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established. Re-administration for psoriatic arthritis The safety and efficacy of re-administration, other than every 8 weeks, has not been established. Re-administration for psoriasis Limited experience from re-treatment with 1 single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen Limited experience from re-treatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment. Re-administration across indications In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended. In this situation, Zessly should be re-initiated as a single dose followed by the maintenance dose recommendations described above. Special populations *Elderly* Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. No dose adjustment is required. *Renal and/or hepatic impairment* Infliximab has not been studied in these patient populations. No dose recommendations can be made. *Paediatric population* *Crohn's disease (6 to 17 years)* 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval. The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. No recommendation on a posology can be made in children younger than 6 years. *Ulcerative colitis (6 to 17 years)* 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment. The safety and efficacy of infliximab have not been studied in children with

	ulcerative colitis below the age of 6 years. No recommendation on a posology can be made in children younger than 6 years. *Psoriasis* The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of psoriasis have not been established. No recommendation on a posology can be made. *Juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis* The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indications of juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis have not been established. No recommendation on a posology can be made. *Juvenile rheumatoid arthritis* The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of juvenile rheumatoid arthritis have not been established. No recommendation on a posology can be made.
	Proposed: Not applicable.
Pharmaceutical form and strengths	**Current:** 100 mg powder for concentrate for solution for infusion (powder for concentrate). The powder is a freeze-dried white pellet.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II Module SII: Non-clinical part of the safety specification

PF-06438179 was designed as a similar biological medicinal product (or biosimilar) to Remicade® (INN: infliximab) by Pfizer. Sandoz has acquired from Pfizer the rights for the development and commercialization of PF-06438179 in the 28 countries that form the EEA. Sandoz assigned the project code GP1111 to the program, and the biosimilar product to Remicade® is referred to by its invented name Zessly throughout this section. Remicade® was authorized to Janssen Biologics B.V., Leiden, The Netherlands in the EU/EEA (EMEA/H/C/000240) via the centralized procedure on 13 Aug 1999 and was licensed to Janssen Biotech, Inc., Spring House, PA (BLA: 103772) in the US on 24 Aug 1998. In this document, Remicade® in general terms, without pointing to any source, is referred to as reference product. To differentiate the sources of Remicade and distinctly point to a specific source when applicable, Remicade sourced from the EU is referred to as infliximab-EU and Remicade sourced from the US is referred to as infliximab-US. Remicade that was used by the innovator in nonclinical testing is referred to as reference product in this document.

Consistent with Regulatory Authority Guidance (e.g. EMA's general guidance EMEA/CHMP/BMWP/42832/2005 Rev. 1 on the non-clinical and clinical development of biosimilars, EMA's guidance EMA/CHMP/BMWP/403543/2010 on the non-clinical and clinical development of biosimilar products containing monoclonal antibodies, and the FDA Guidance for Industry Scientific considerations in demonstrating biosimilarity to a reference product (2015), and the WHO Guidelines on evaluation of similar biotherapeutic products), the goal for the development of Zessly was to demonstrate its similarity to the reference product and not to re-investigate the non-clinical pharmacology, PK, and toxicity of infliximab that had previously been characterized by the reference product sponsor. Since structural and functional characterization of Zessly, infliximab-EU and infliximab-US showed similarity between the 3 products, all the data generated by reference product sponsor for infliximab can be extrapolated to Zessly, and only limited non-clinical testing was considered necessary to support the similarity between Zessly and infliximab.

Thus, a single-dose IV TK/tolerability study (Study GP11-001 (12GR295)) in male rats administered Zessly or infliximab-EU was considered sufficient to address any residual concerns regarding the similarity of Zessly to infliximab-EU and infliximab-US already shown on the physicochemical, biophysical and functional level. This comparative non-clinical study was conducted in rats because of the ethical concerns associated with the use of chimpanzees (the only pharmacologically relevant species for toxicity testing), and the lack of toxicity observed in studies conducted by reference product sponsor in rats, chimpanzees, mice or rabbits.

Although the infliximab-CDR does not bind TNF from animal species other than chimpanzees, the FcRn from animal species, including rats, does recognize the Fc fragment of human IgG, and thus, it is possible to characterize FcRn-mediated/non-target related clearance and TK and to assess Fc-related functionality in rodents (Wallace and Rees 1980, Abdiche et al 2015).

In addition, a non-comparative, 2-week toxicity study in rats administered Zessly was conducted (Study GP11-002 (14GR168)). While non-comparative studies are generally not recommended in the EMA biosimilar guidelines (EMEA/CHMP/BMWP/42832/2005 Rev. 1

and EMA/CHMP/BMWP/403543/2010), the study was conducted based on the specific request from a Regulatory Authority (PMDA meeting outcome/2014). Taking into account the well documented toxicological profile of infliximab obtained during the development of the reference product that allowed for comparability and cross-referencing to historical data, the conduct of a safety study with Zessly alone was considered acceptable. Both studies were conducted in accordance with GLP regulations.

Zessly showed a similar TK and safety profile to that of infliximab-EU. Key safety findings from non-clinical studies conducted with reference product are also presented in Table 2.

Table 2 Part II SII Key safety findings from non-clinical studies and relevance to human usage: toxicology/safety pharmacology

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity The tTK and tolerability of Zessly and infliximab-EU were similar, following a single bolus IV injection of 10 or 50 mg/kg to male rats, followed by an 8-week observation and TK sampling period. No adverse effects were observed with Zessly in a non-comparable 2-week IV toxicity study where male and female rats were administered Zessly once weekly at doses of 10 or 50 mg/kg/dose for a total of 3 doses (Study GP11-002 (14GR168)). In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNF-α, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans (Remicade SmPC). No genotoxicity, carcinogenicity, local tolerance, reproductive and developmental toxicity or other toxicology studies were considered necessary for Zessly.	Data support the non-clinical data known from reference product and show similarity of tolerability and safety between Zessly and reference product
Local tolerance Reference product showed no indication of local irritation following intravenous administration in rabbits (Remicade SmPC).	Regarding injection site reactions, see Section 7, Module SVII.
Genotoxicity and carcinogenicity Reference product was not genotoxic in *in vitro* assays. Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNF-α demonstrated no increase in tumors when challenged with known tumor initiators and/or promoters (Remicade SmPC).	No safety concern. Regarding carcinogenicity, see Section 7, Module SVII.
Reproductive toxicity and key safety findings (from nonclinical studies) Studies were conducted in mice using a monoclonal antibody against mouse TNF-α (cV1q). In these experiments, it was demonstrated that cV1q crossed the placenta but there was no indication of impairment of reproductive function, embryotoxicity or teratogenicity (Remicade	Although the relevance of these findings for humans is unknown, it was concluded that women of childbearing potential treated with infliximab should use adequate contraception to prevent pregnancy.

Key Safety findings (from non-clinical studies)	Relevance to human usage
SmPC). In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females (Remicade SmPC).	Furthermore, administration of infliximab during pregnancy is not recommended.

There were no important identified risks, important potential risks or missing information.

Part II Module SIII Clinical trial exposure

Zessly/GP1111 is an infliximab-containing biosimilar drug product approved by the EC on 18 May 2018. The reference product Remicade received its first marketing authorization in the US in August 1998 for the treatment of CD. In August 1999, the reference product was approved in the EU for treating CD; subsequent marketing authorizations were granted for treatment of RA, adult and pediatric ulcerative colitis, pediatric CD, AS, PsA, and Ps in various markets.

One PK study (study GP11-101) has been conducted with GP1111 in healthy subjects to demonstrate comparable PK with EU-authorized and US-licensed reference product (henceforth termed infliximab-EU and infliximab-US) and to assess the safety and immunogenicity of GP1111.

One confirmatory efficacy and safety study (study GP11-301) was conducted to demonstrate equivalent efficacy and to compare safety and immunogenicity of GP1111 and infliximab-EU in patients with moderate to severe active RA who have had an inadequate response to MTX.

Part II Module SIII Clinical trial exposure

Clinical study exposure to GP1111 comprises:

- Study GP11-101 in 49 healthy subjects using a single dose of 10 mg/kg body weight administered intravenously over a period of not less than 2 hours using a calibrated infusion pump
- Study GP11-301 in patients with moderately to severely active RA using multiple doses of 3 mg/kg body weight administered intravenously at Weeks 0, 2, and 6, followed by a maintenance administration every 8 weeks until Week 70. Patients were followed up until Week 78. One-time dose escalation to 5mg/kg body weight was allowed from Week 14 onwards. A total of 592 patients received at least 1 dose of GP1111.

In the following tables, treatment groups are defined as follows:

- Patients with prior exposure to the Remicade (Infliximab-EU) (switching arm) include patients who received Infliximab-EU in TP1 of GP11-301 and were re-randomized to GP1111 at Week 30 or patients who received Infliximab-EU in TP1 and TP2 and were switched to GP1111 at Week 54
- Total patients receiving GP1111 include patients who were exposed to GP1111 from: (1)TP1 - all subjects in GP1111 arm; (2)TP2 - all subjects in GP1111 continuous arm (GP1111/GP1111); (3)TP2 - all subjects in Infliximab-EU/GP1111 arm (on or after the date of re-randomization at Week 30); (4)TP3 - all subjects in GP1111 continuous arm (GP1111/GP1111/GP1111); (5)TP3 - all subjects in Infliximab-EU/GP1111/GP1111 arm (TP3 data, on or after the date of switch at Week 30); (6)TP3 - all subjects in Infliximab-EU/Infliximab-EU/GP1111 arm (TP3 data, on or after the date of switch at Week 54)

Table 3 Part II SIII Duration of exposure to GP1111 in Study GP11-301 (in patients with disease rheumatoid arthritis (safety population)) up to EOS at Week 78

	Remicade (Infliximab-EU) Naïve Patients		Patients with prior exposure to the Remicade (Infliximab-EU) (switching arm)		Total patients receiving GP1111	
	Patients	Patient time (patient-years)	Patients	Patient time (patient-years)	Patients	Patient time (patient-years)
≤ 14 weeks	14	2.71	16	2.50	30	5.21
Between 14-30 weeks (> 14 weeks and ≤ 30 weeks)	19	6.99	127	57.73	146	64.72
Between 30-54 weeks (> 30 weeks and ≤54 weeks)	31	23.74	126	114.98	157	138.72
More than 54 weeks (> 54 weeks)	259	382.52	0	0	259	382.52
Total person time (≥ 1 dose)	323	415.96	269	175.20	592	591.17

Duration of exposure and person time calculations include 8 weeks exposure after the last administration of GP1111

Table 4 Part II SIII Exposure to GP1111 by age group and gender

Age	Sex	Remicade (Infliximab-EU) Naïve Patients		Patients with prior exposure to the Remicade (Infliximab-EU) (switching arm)		Total patients receiving GP1111	
		Patients	Patient time (patient-years)	Patients	Patient time (patient-years)	Patients	Patient time (patient-years)
18-44 years	Male	19	25.63	15	10.65	34	36.28
	Female	65	80.56	51	33.16	116	113.71
45-64 years	Male	31	43.39	27	16.30	58	59.70
	Female	144	189.48	126	83.38	270	272.67
≥65 years	Male	15	18.82	11	6.18	26	25.00
	Female	49	58.08	39	25.73	88	83.81

Duration of exposure and person time calculations include 8 weeks exposure after the last administration of GP1111.

Table 5 Part II SIII Exposure to GP1111 in Study GP11-301 by dose

	Remicade (Infliximab-EU) Naïve Patients		Patients with prior exposure to the Remicade (Infliximab-EU) (switching arm)		Total patients receiving GP1111	
Dose	**Patients**	**Patient time (patient-years)**	**Patients**	**Patient time (patient-years)**	**Patients**	**Patient time (patient-years)**
3 mg/kg	323	320.79	192	123.03	515	443.82
5 mg/kg	113	95.50	93	52.23	206	147.73

Duration of exposure and person time calculations include 8 weeks exposure after the last administration of GP1111.

Table 6 Part II SIII Exposure to GP1111 in Study GP11-301 by race

	Remicade (Infliximab-EU) Naïve Patients		Patients with prior exposure to the Remicade (Infliximab-EU) (switching arm)		Total patients receiving GP1111	
Race	**Patients**	**Patient time (patient-years)**	**Patients**	**Patient time (patient-years)**	**Patients**	**Patient time (patient-years)**
White	257	336.85	202	132.61	459	469.45
Black	5	4.46	8	5.55	13	10.01
Asian	46	58.01	38	23.38	84	81.39
Other	15	16.65	21	13.66	36	30.31

Duration of exposure and person time calculations include 8 weeks exposure after the last administration of GP1111

Part II Module SIV: Populations not studied in clinical trials

Since this MAA has been submitted for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC, as amended, an abbreviated clinical program was justified.

RA is considered a sensitive indication that can be used to detect differences between treatments. Therefore, the confirmatory efficacy and safety study GP11-301 was done in patients with moderate to severe RA who had an inadequate response to MTX based on scientific discussions with EMA. The design, conduct, and within-group response rates of study GP11-301 were generally similar to those characteristics in historical clinical studies that demonstrated relatively large and consistent treatment effects of infliximab over placebo. Therefore, the totality of available information supports the sensitivity of study GP11-301. Other patient populations were not studied in GP1111 development program.

Part II Module SIV.1. Exclusion criteria in pivotal clinical studies within the development program

Most exclusion criteria applied in the clinical studies with GP1111 as well as in the clinical studies of the reference product aimed for optimization of study conduct and minimization of bias and confounding of study results and are not related to safety concerns.

As a standard precautionary measure to avoid potential harm of study subjects to the extent reasonably possible, pregnant or breastfeeding women as well as patients with underlying diseases that might deteriorate during treatment with infliximab were also excluded from the clinical studies with GP1111 and clinical studies of the reference product (e.g. patients with significant liver disease, malignancy, or demyelinating disease). The disorders listed in Table 7 were all classified as important risks of the reference product at the time of study conduct. However, careful assessment of the available data led to the conclusion that contraindicating the use of infliximab in these patients was not warranted.

Table 7 Part SIV.1. Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to the active substance or to any of the excipients (allergy, infusion reaction, anaphylaxsis)	Contraindications	No	Risk of severe and even fatal HSR on exposure. Patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients are listed in section 4.3 of the Remicade SmPC.
Active infections, including: Serious infection (e.g., hepatitis,	Contraindications	No	Resolution or control of infection prior to infusion is required because of immunosuppressive

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
pneumonia, pyelonephritis); Active or latent TB; Opportunistic infection (OI) (e.g., cytomegalovirus, pneumocystis carinii, aspergillosis, histoplasmosis, or myocbacteria other than TB); Chronic or recurrent infectious disease			action. Patients with TB or other severe infections such as sepsis, abscesses, and opportunistic infections are listed in section 4.3 of the Remicade SmPC.
Moderate to severe CHF (NYHA class III/IV), including medically controlled, asymptomatic patients.	Contraindications	No	Risk–benefit and potential to exacerbate underlying CHF disease is not known. Patients with moderate or severe heart failure (NYHA class III/IV) are listed in section 4.3 of the Remicade SmPC.

Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Clinical study experience with GP1111 comprises 592 patients with moderately to severely active RA. 323 patients of the 592 patients were exposed to GP1111 with no previous exposure to infliximab-EU. 269 patients were exposed to GP1111 who previously were exposed to infliximab-EU. 259 patients received GP1111 for more than 54 weeks (Table 3). In addition, 49 healthy subjects received 1 single dose of GP1111. This clinical experience may be insufficient to detect rare adverse reactions, adverse reactions with a long latency to onset or due to cumulative effects, or adverse reactions specific to target populations other than patients with RA. The existing clinical study experience also may be insufficient to detect rare differences in adverse reactions between GP1111 and the reference product.

GP1111 showed a similar PK and safety profile to that of the reference product as directly shown the in GP1111 nonclinical program and when comparing with available literature data for the reference product Memorandum to BLA 98-0012, Remicade EPAR – Scientific Discussion, and the Remicade monograph. GP1111 also showed a similar PK and safety profile to the reference product in the GP1111 clinical development program. Thus, it is justified to build upon the extensive clinical study experience that has accumulated for the reference product. The number of patients exposed to GP1111 (592 patients) is considered sufficient to detect adverse reactions to the reference product with a true frequency greater than 1 in 100 with a high statistical power (> 99%).

Rare adverse drug reactions with a frequency of 1 in 1,000 or lower would have a lower statistical power. Due to the relatively small number of patients exposed to GP1111, detection of rare events remains limited. Some of the limitations of the GP1111 clinical study program

can be considered to be offset by the extensive experience with the marketed product (estimated post-authorization exposure between first marketing in EU in 1999 and August 2013 approximately 4.2 million patient-years).

Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Although specific clinical experience with GP1111 in some patient populations is limited, there is sufficient information or the information is equally limited on use of the reference product in these patients. Based on biosimilarity between GP1111 and the reference product, the same considerations for clinical use apply to GP1111.

Table 8 Part II SIV.3. Exposure of special populations included or not in clinical study development programs

Type of special population	Exposure
Children	No pediatric clinical study was performed with GP1111. However, the safety of the reference product was studied in 120 pediatric subjects (4 to 17 years of age) with active JRA despite MTX; in 112 pediatric subjects (6 to 17 years of age) with moderate to severe, active CD, and in 60 pediatric subjects (6 to 17 years of age) with moderate to severe UC. The reference product has indications in pediatrics in these diseases. The safety of the reference product in pediatric patients (<18 years of age) with Ps, JIA, PsA, or AS, and in pediatric patients with CD <6 years of age has not been established (Remicade SmPC) for supporting the initial marketing authorization of these indications.
Elderly (≥ 65 years)	Clinical study experience with GP1111 in the elderly is limited and no PK data are available from this population. Specific studies of the reference product in elderly patients have not been conducted with the reference product, as reflected in the Remicade SmPC (section 4.2 Posology and method of administration). In clinical studies with the reference product, a total of 6,438 subjects were treated with the reference product. Of these subjects, 496 were □65 years old (193 male, 303 female). In addition, of these 496 subjects, 55 were □75 years old (13 male and 42 female). No major age-related differences in clearance or volume of distribution were observed in clinical studies with the reference product and no dose adjustment is required.
Pregnant women or breastfeeding women	Pregnant or breastfeeding women were not specifically studied in the GP1111 clinical development program. There were 2 GP1111 exposed pregnancies reported during the TP1 of study GP11-301. One of these pregnancies resulted in induced abortion; the other pregnancy resulted in live birth of a healthy male baby. No adverse outcomes were reported. There are no studies of either GP1111 or the reference product in pregnant women ("missing information"). Subjects who were pregnant, nursing, or planning pregnancy (women or men) were not eligible to participate in clinical studies. Therefore, safety of GP1111 and the reference product in pregnant or lactating women has not been established, as reflected in the Remicade SmPC. Although prohibited by protocol, exposure to GP1111 and the reference product during pregnancy occurred. Use of drug during lactation is considered missing

Type of special population	Exposure
	information.
Patients with relevant comorbidities: • Patients with hepatic impairment	No formal clinical studies with GP1111 and the reference product in subjects with hepatic impairment have been conducted; therefore, the effects of hepatic impairment on GP1111 and the reference product disposition are unknown. The Remicade SmPC indicates that the reference product has not been studied in these patient populations and no dose recommendations can be made ("missing information").
• Patients with renal impairment	No formal clinical studies with the reference product in subjects with renal impairment have been conducted; therefore, the effects of renal impairment on the reference product disposition are unknown. The Remicade SmPC indicates that the reference product has not been studied in these patient populations and no dose recommendations can be made ("missing information").
• Patients with a disease severity different from inclusion criteria in clinical studies	No safety concerns specific to treatment of patients with a disease severity different from the inclusion criteria in the clinical study population are known.
• Patients with cardiovascular impairment	These populations were not included in the clinical development program.
• Immunocompromised patients	
• Patients with other relevant co-morbidity	Clinical experience with GP1111 and the reference product, in patients with hepatitis C virus or HIV infection is limited.
Population with relevant different ethnic origin	The reference product clinical studies have been conducted across the globe with multiple clinical studies conducted in a variety of ethnic groups. The majority of subjects in the reference product clinical studies were white. However, no apparent differences between racial or ethnic groups were observed with regard to efficacy or safety. Use in different ethnic origins is formally classified as "missing information". In addition, no racial differences in the PK of the reference product would be expected based on findings from comparative PK assessments IgG1-based monoclonal antibodies between Caucasians and Asians (Zhou et al 2012).
Subpopulations carrying relevant genetic polymorphisms	No relevant polymorphisms are known at this point.

Part II Module SV: Post-authorization experience

The DDD of infliximab is provided by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo with 3.75 mg. The DDD for infliximab is based on the treatment of RA. The actual administered dose may vary based on the indication for use, however, the WHO DDD will be used to estimate the exposure in PTY. Post-authorization estimate exposure is calculated using the following formula:

Estimated exposure in PTYs = Total number of mg sold /daily defined dose × 365 days/year.

Part II Module SV.1. Post-authorization exposure

The estimated exposure is provided in the following table.

Table 9 Part II SV.1. Estimated post-marketing (nonclinical study) exposure

Formulation	**Cumulative until 31 Aug 2023***	
	Amount sold (mg)	**Estimated exposure (PTY)**
Parenteral 100 mg	395,799,700	289,169
Total (mg sold)	**395,799,700**	**289,169**

*sale of Zessly started in Nov-2018

Since the sales were only noted for the EEA region, no separate region-wise sales are provided.

Source of data: Sandoz worldwide sales volume

Distribution by formulation and region is shown in the following table.

Table 10 Part II SV.1 Cumulative exposure* from marketing experience

	EEA	**USA and Canada**	**Japan**	**ROW**
Parenteral (PTY)	289,169	Not applicable	Not applicable	Not applicable

ROW: Rest of World; USA: United States of America; EEA: European Economic Area
Source of data: Sandoz worldwide sales volume

*sale of Zessly started in Nov-2018

Part II Module SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Drugs with abuse potential generally include drugs that affect the CNS, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change (FDA Guidance for Industry Assessment of abuse potential of drugs (2017)). Based on structure and mechanism of action, infliximab is not anticipated to have a potential abuse and/or dependence potential. There is no known potential for misuse for illegal purposes.

Part II Module SVII: Identified and potential risks

Part II Module SVII.1: Identification of safety concerns in the initial RMP submission

This section is not applicable as the RMP was already approved.

Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The current RMP safety concerns (important risks and missing information) as listed in Table 18 are in alignment with the latest RMP public summary for the reference product Remicade (Janssen EMA 2022). No changes to the current safety concerns are proposed.

Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Serious infection/sepsis

Incidence, severity and outcome of treatment-emergent AEs of serious infection/sepsis are summarized in Table 11 for all patients receiving GP1111 and for Remicade (infliximab-EU) naive patients treated with GP1111. Other details are presented in Table 12. No serious infection/sepsis occurred in healthy subjects exposed to GP1111 in study GP11-101.

Table 11 Part II SV.3.1 Clinical study data of serious infection/sepsis (all patients receiving GP1111)

	All patients receiving GP1111 N=592 [2] n (%)	**Remicade (infliximab-EU) naïve patients treated with GP1111 N=323 n (%)**
Number of patients with at least 1 event [1]	14 (2.4%)	9 (2.8%)
SAEs	14 (100.0%)	9 (100.0%)
Maximum severity		
Mild (Grade 1-2)	1 (7.1%)	1 (11.1%)
Moderate (Grade 3)	13 (92.9%)	8 (88.9%)
Severe (Grade 4-5)	0	0
AE outcome		
Fatal	0	0
Resolved	12 (85.7%)	9 (100.0%)
Present	2 (14.3%)	0

[1] Percentage based on the total number of subjects

	All patients receiving GP1111 N=592 [2] n (%)	Remicade (infliximab-EU) naïve patients treated with GP1111 N=323 n (%)

[2] Includes AEs reported during GP1111 use from: (1)TP1 - all subjects in GP1111 arm; (2)TP2 - all subjects in GP1111 continuous arm (GP1111/GP1111); (3)TP2 - all subjects in Infliximab-EU/GP1111 arm (on or after the date of re-randomization at Week 30); (4)TP3 - all subjects in GP1111 continuous arm (GP1111/GP1111/GP1111); (5)TP3 - all subjects in Infliximab-EU/GP1111/GP1111 arm (TP3 data, on or after the date of switch at Week 30); (6)TP3 - all subjects in Infliximab-EU/Infliximab-EU/GP1111 arm (TP3 data, on or after the date of switch at Week 54).

Includes all data collected since the first infusion of GP1111.

Search strategy: SAEs only, SOC: Infections and infestations HLGT: Microbiology and serology investigations.

Patients are counted only once in each row regardless of number of events per patient per row.

Severity counts are based on the maximum severity or grade of events. For multiple events of same severity, outcome counts are based on the most recent events.

CTCAE v4.3 applied. MedDRA (v20.0) coding dictionary applied.

Serious Adverse Events (SAEs) - according to the investigator's assessment.

Percentages are calculated based on the number of patients that had at least 1 event.

Agresti-Coull confidence limit for the binomial proportion is calculated.

Table 12 Part II SV.3.1 Important identified risk serious infection/sepsis: Other details

Serious infection/sepsis	Details
MedDRA terms for spontaneous post-marketing data	SAEs only, SOC: Infections and infestations HLGT: Microbiology and serology investigations
Potential mechanisms	TNF-α regulates important biological functions related to host defense such as maintenance of lymphoid microarchitecture, amplification of inflammatory responses by innate immune cells, and generation of optimal cellular, humoral and phagocytic responses, especially for intracellular pathogens (Hehlgans and Pfeffer 2005). Inhibition of TNF may thus increase the potential for infections including TB, OIs and HBV reactivation. Sepsis constitutes a systemic response to infection characterized by cytokine-mediated pro-inflammatory responses and anti-inflammatory responses. In animal models of abdominal sepsis such as cecal ligation and puncture, the injection of TNF can be beneficial by preventing a bacterial superinfection. Hence inhibition of TNF by infliximab may potentiate bacterial infections to become systemic (Hehlgans and Pfeffer 2005).
Evidence source(s) and strength of evidence	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 Remicade RMP public summary (Janssen EMA 2022) of the reference product Remicade. Therefore, serious infection/sepsis is considered to be an important identified risk for Zessly.

Serious infection/sepsis	Details
Characterization of the risk:	Studies with GP1111: Serious infection/sepsis was not reported in healthy subjects receiving GP1111 (Study GP11-101). In patients with moderately or severely active RA, serious infection/sepsis was reported in 14 patients receiving at least 1 dose of GP1111, most of which (13 patients) were Grade 3, including 3 cases of pneumonia in TP1 and 1 case of TB in TP3. No cases of HBV reactivation were reported. No Grade 4-5 events occurred during the study. Patients with RA: Among 584 patients with RA, 252 had ≥1 serious infection (646 total infections; 9.1 per 100 person-years). In a validation cohort, 55 patients had ≥1 serious infection (166 total infections; 7.2 per 100 person years) (Crowson et al 2012). The crude incidence of OI per 100,000 patient-years in patients with RA treated with anti-TNF agents is 192 in the UK (2006), 152 in France (2006), and 3000 the US (2010) (Winthrop 2012). Furthermore, a systematic review of patients with RA and TB found that the risks of TB was increased 2 to 10 fold in patients with RA unexposed to TNF-α antagonists, and 2 to 4 fold in those exposed to TNF-α antagonists compared to the general population (Baronnet et al 2011). A meta-analysis of 468 HBsAg-negative and anti-HBc-positive patients with RA found HBV reactivation in 8 (1.7%) patients who were undergoing anti-TNF treatment (Lee et al 2013). Patients with CD and/or UC: In the UK, 42 out of 202 (20.8%) patients with IBD undergoing anti-TNF treatment had an infectious event, with 24 serious infectious events occurring in 20 (9.9%) patients. Two patients experienced sepsis-related complications (colonic perforation and facial cellulites) (Lees et al 2009). The annual incidence of active TB in a retrospective cohort study in subjects with IBD was 20/100,000 compared to 9/100,000 in control subjects, yielding an unadjusted relative risk for active TB of 2.36 (95% confidence interval, 1.17-4.74). Adjusting for confounders, corticosteroid use and smoking, the odds ratio for active TB in IBD was 1.88 (95% confidence interval, 0.68-5.20) (Aberra et al 2007). Patients with Ps: In a cohort of 25,742 patients with Ps and controls, the likelihood of infectious diseases in patients with Ps was twice higher than in the control population (908 vs. 438 events per 100,000 person years, crude HR: 2.08, 95% Cl: 1.96-2.22), with respiratory tract, abdominal, and skin infections occurring most frequently (Wakkee et al 2011). Furthermore, 163 of 793 (20.5%) patients with Ps exposed to biological treatment were diagnosed with latent TB infection, with an active TB rate of 145 cases per 100,000 patient-years (95% Cl: 54-389). No cases of TB were found in the control group (Sanchez-Moya et al 2013). Patients with AS: A systematic review comprising 3345 patients given placebo or NSAIDs (n=2202) found 14 serious infections in patients receiving anti-TNF treatment (14/966, 0.7%) versus 2 serious infections observed in patients treated with placebo (2/500, 0.4%). A meta-analysis of the RCTs showed that the increase in serious infections with TNF blockers compared with placebo was not significant (risk difference=0.4%) (Fouque-Aubert et al 2010).

Serious infection/sepsis	Details
	The impact of these risks on the individual patient can be potentially significant. Patients who are exposed to and subsequently infected with an infectious agent may have a more severe course due to use of the product. This risk needs to be carefully weighed against the benefit conferred by use of the medication. Discontinuation of infliximab therapy should be considered in patients with confirmed serious infection/sepsis.
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 infection 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 (Cunnane et al 2003). 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 (e.g., hospitals and nursing homes) or high-density institutions (e.g., 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 (Ocama et al 2005).
Preventability	Infliximab is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and OIs (section 4.3 Contraindications of the Remicade SmPC). Patients developing a new infection during the treatment with infliximab should be closely monitored and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Patients should avoid exposure to potential risk factors for infections as appropriate. If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted and the benefit/risk balance of infliximab therapy should be carefully considered. Anti TB therapy should be considered before initiating infliximab if inactive (‘latent’) TB is diagnosed, patients with a

Serious infection/sepsis	Details
	negative test for latent TB present risk factors for TB, or an adequate course of treatment in patients with a history of latent or active TB cannot be confirmed (Section 4.4 Special Warnings and Precautions for Use of the Remicade SmPC). An invasive fungal infection in infliximab-treated patients should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. (section 4.4 Special warnings and precautions for use of the Remicade SmPC). Patients should be tested for HBV infection before initiating treatment with infliximab. HBV-positive patients must consult with a physician with expertise in the treatment of HBV. HBV carriers requiring treatment with infliximab should be closely evaluated and monitored for signs and symptoms of active HBV infection throughout therapy and for several months following therapy termination. Infliximab should be stopped in patients who develop HBV reactivation and effective antiviral therapy with appropriate supportive treatment should be initiated (section 4.4 Special warnings and precautions for use of the Remicade SmPC).
Impact on the benefit-risk balance of the product	Based on analytical, nonclinical, and clinical results, Sandoz concludes that biosimilarity of GP1111 and the reference product Remicade has been successfully demonstrated in accordance with applicable EMA guidance. Benefits and risks are assumed to be similar to those established for Remicade.
Public health impact	In post marketing spontaneous reporting, infections are the most common SAE in patients treated with infliximab. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. Impact is low to moderate with prompt and appropriate treatment.

Important identified risk: Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab

No AEs relevant to BCG breakthrough infection have been reported either in healthy subjects or patients exposed to GP1111 so far.

Table 13 Part II SV.3.1 Important identified risk BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab: Other details

BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	Details
MedDRA search terms for spontaneous post-marketing data	PT Disseminated Bacillus Calmette-Guerin infection; PT Vaccine breakthrough infection; SMQ Agranulocytosis Note: Manual review for agranulocytosis to select cases where age < 1 year and in utero exposure to infliximab
Potential mechanisms	The immunosuppressive properties of infliximab potentially cause BCG Breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab:

BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	**Details**
	TNF regulates and enhances inflammatory, innate and adaptive immune responses to pathogenic organisms (Hehlgans and Pfeffer 2005). TNF inhibition by infliximab may thus suppress these beneficial activities of TNF and increase the potential for infection. The causal relationship between TNF inhibitors and agranulocytosis is poorly understood. Bone marrow suppression has been reported, albeit rarely, in patients after treatment with etanercept (Hyrich et al 2004). Infliximab crosses the placenta and has been detected up to 12 months in the serum of infants born to women treated with infliximab during pregnancy. After in utero exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection, that can become fatal.
Evidence source(s) and strength of evidence	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 lactation, 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 Remicade RMP public summary (Janssen EMA 2022) 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.
Characterization of the risk:	The impact of this risk on an infant exposed to infliximab in utero is significant. Women of childbearing potential should be carefully monitored during administration of infliximab to avoid pregnancy. No AEs relevant to BCG breakthrough infection have been reported either in healthy subjects or patients exposed to GP1111 so far.
Risk factors and risk groups	Infants exposed to infliximab in utero and receiving BCG vaccine within 12 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.
Preventability	Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for at least 12 months after birth. Infants up to 6 months of age exposed in utero to Infliximab should be closely monitored by pediatricians for signs of infection or low white blood cell count such as persistent fever. Administration of infliximab is not recommended during pregnancy because it crosses the placenta and has been detected in the serum of up to 12 month infants born to patients treated with infliximab during pregnancy. Consequently, these infants may be at increased risk of infection and caution is advised in the administration of live vaccines to them (section 4.6 Fertility, pregnancy and lactation of the Remicade SmPC).
Impact on the benefit-risk balance of the product	Based on analytical, nonclinical, and clinical results, Sandoz concludes that biosimilarity of GP1111 and the reference product Remicade has been successfully demonstrated in accordance with applicable EMA guidance. Benefits and risks are assumed to be similar to those established for Remicade.
Public health impact	Impact is low if labelled recommendations are followed.

Important identified risk: Demyelinating disorders

No AEs relevant to demyelinating disorders have been reported either in healthy subjects or patients exposed to GP1111.

Table 14 Part II SV.3.1 Important identified risk demyelinating disorders: Other details

Demyelinating disorders	Details
MedDRA search terms for spontaneous post-marketing data	SMQ Demyelination (Broad)
Potential mechanisms	The immunomodulator role played by TNF suggests that TNF blockade may promote the development of drug-induced neuropathies by augmenting the number of activated peripheral T cells, thus enhancing autoimmune responses by altering antigen presenting cell function, potentiating T-cell receptor signaling, 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 (Stubgen 2008). A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective (Taoufik et al 2011). Since TNF inhibitors can neutralize both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF.
Evidence source(s) and strength of evidence	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 Remicade RMP public summary (Janssen EMA 2022) of the reference product Remicade. Therefore demyelinating disorders is considered to be an important identified risk for Zessly.
Characterization of the risk:	Between June 2005 and April 2008, 1800 French rheumatologists and internists were contacted to report cases of demyelinating disorders in patients treated with anti-TNF-α. After a median of 10.2 months of treatment, 33 patients developed demyelinating disorders: 22 had CNS and 11 had peripheral nervous system involvement. Underlying disease were RA (n= 16), AS (n= 11), PsA (n=4) (Seror et al 2013). Patients with CD or UC: A systematic review of the literature found 4 studies on the risk of demyelinating disease in IBD. One study revealed an observed prevalence of MS at onset of IBD at 3.7 times the expected (95% Cl: 0. 8-10. 8). In a subsequent analysis of a Danish IBD cohort treated with anti-TNF cohort, 4 out of 651 patients developed demyelinating disorders after anti-TNF-α treatments. An SMR of 4.2 (95% CI: 0.1-23. 0) was found (Andersen et al 2008). Patients with RA, PsA, Ps, or AS: Published data by indication are not available for these indications. No AEs relevant to demyelinating disorders have been reported either in healthy subjects or patients exposed to GP1111 so far. The impact of these risks on the individual patient can vary from minimal to significant. Patients with pre-existing or recent onset of demyelinating disorders may have a more severe course due to use of the product. This risk needs to be carefully weighed against the benefit conferred by use of the medication.

Demyelinating disorders	Details
	Discontinuation of infliximab therapy should be considered in patients with confirmed demyelinating disorders.
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 (Magnano et al 2004). 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 (Islam et al 2006). Environmental triggers may also be involved in the development of MS. A number of studies have suggested an association between smoking and MS (Franklin and Nelson 2003). 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) (Riise et al 2003). Similar results were noted in a case control study from the UK (Hernan et al 2005). 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 (Willer et al 2005).
Preventability	Predictability and preventability of the development of demyelination is not known. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of infliximab treatment should be carefully considered before initiation of infliximab therapy and discontinuation of infliximab therapy should be considered if signs or symptoms of demyelinating disorders develop (section 4.4 Special warnings and precautions for use section of the Remicade SmPC).
Impact on the benefit-risk balance of the product	Based on analytical, nonclinical, and clinical results, Sandoz concludes that biosimilarity of GP1111 and the reference product Remicade has been successfully demonstrated in accordance with applicable EMA guidance. Benefits and risks are assumed to be similar to those established for Remicade.
Public health impact	Impact is low to moderate with prompt and appropriate treatment.

Important identified risk: Malignancy

Incidence, severity and outcome of treatment-emergent AEs of malignancy are summarized in Table 15 for all patients receiving GP1111 and for Remicade (infliximab-EU) naive patients treated with GP1111. Other details are presented in Table 16. No malignancies occurred in healthy subjects exposed to GP1111 in study GP11-101.

Table 15 Part II SV.3.1 Clinical study data of malignancy (all patients receiving GP1111)

	All patients receiving GP1111 N=592 [2] n (%)	**Remicade (infliximab-EU) naïve patients treated with GP1111 N=323 n (%)**
Number of patients with at least 1 event[1]	5 (0.8%)	4 (1.2%)
SAEs	3 (60.0%)	2 (50.0%)
Maximum severity		
Mild (Grade 1-2)	2 (40.0%)	1 (25.0%)
Moderate (Grade 3)	3 (60.0%)	3 (75.0%)
Severe (Grade 4-5)	0	0
AE outcome		
Fatal	0	0
Resolved	1 (20.0%)	1 (25.0%)
Present	4 (80.0%)	3 (75.0%)

[1] Based on the total number of subjects

[2] Includes AEs reported during GP1111 use from: (1)TP1 - all subjects in GP1111 arm; (2)TP2 - all subjects in GP1111 continuous arm (GP1111/GP1111); (3)TP2 - all subjects in Infliximab-EU/GP1111 arm (on or after the date of re-randomization at Week 30); (4)TP3 - all subjects in GP1111 continuous arm (GP1111/GP1111/GP1111); (5)TP3 - all subjects in Infliximab-EU/GP1111/GP1111 arm (TP3 data, on or after the date of switch at Week 30); (6)TP3 - all subjects in Infliximab-EU/Infliximab-EU/GP1111 arm (TP3 data, on or after the date of switch at Week 54).

Includes all data collected since the first infusion of GP1111.

Search strategy: SMQ: Malignancies.

Patients are counted only once in each row regardless of number of events per patient per row.

Severity counts are based on the maximum severity or grade of events. For multiple events of same severity, outcome counts are based on the most recent events.

CTCAE v4.3 applied. MedDRA (v20.0) coding dictionary applied.

Serious Adverse Events (SAEs) - according to the investigator's assessment.

Percentages are based on the number of subjects with at least 1 event

Agresti-Coull confidence limit for the binomial proportion is calculated.

Table 16 Part II SV.3.1 Important identified risk malignancy: Other details

Malignancy	**Details**
MedDRA search terms for spontaneous post-marketing data	SMQ Malignancies
Potential mechanisms	TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumor cell lines (Mocellin et al 2005). In particular, TNF is

Malignancy	Details
	capable of directly triggering apoptosis through the TNF-Rl receptor by activation of the caspase cascade (Eberle et al 2007). TNF was shown to kill tumor cells in vitro, depending upon the tumor cell line, and therefore it is possible that the neutralization of TNF by infliximab could promote the growth of tumor cells normally lysed by TNF (Mocellin et al 2005). Immunosuppression, either from treatment with a TNF inhibitor or other immunosuppressive drugs such as MTX and thiopurines, is associated with an increased risk of lymphoma (Subramaniam et al 2013), possibly due to reduced tumor surveillance. Immunosuppression in general may unfavorably affect the risk for the occurrence or progression from HPV infection to invasive cervical cancer. Whether TNFα blockers increase the risk of virus-associated malignancies, such as cervical cancer, is not known.
Evidence source(s) and strength of evidence	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 Remicade RMP public summary (Janssen EMA 2022) of the reference product Remicade. Therefore malignancy is considered to be an important identified risk for Zessly
Characterization of the risk:	The impact of this risk on the individual patient can vary from minimal to potentially significant. Patients with a history of malignancy or who develop malignancy may have a more severe course due to the use of infliximab. This risk needs to be carefully weighed against the benefit conferred by use of the medication. Studies with GP1111: Malignancy was not reported in healthy subjects receiving GP1111 (Study GP11-101). In patients with moderately to severely active RA, malignancy was reported in 5 patients receiving at least 1 dose of GP1111, 3 of which reported SAEs (Grade 3 laringeal squameous cell carcinoma, Grade 2 ocular lymphoma, both in TP2, and Grade 3 bladder cancer in TP3) and discontinued from the study due to these events (Study GP11-301). The other 2 patients reported non-serious AEs of grade 1-2 cell marker increased and Grade 3 colon cancer. Patients with RA: Epidemiological studies have estimated the frequency of various cancers in patients with RA to range from 2 to 15%. Out of 84,475 patients with RA observed for 405,540 person-years, 5,533 incidence cancers were diagnosed (Parikh-Patel et al 2009). Another study reported an overall cancer incidence in RA as 99.2 cases per 10,000 PY (95% Cl: 80.0 to 121.7) (Franklin et al 2007). An approximately 2-fold increased incidence of lymphoma has been observed in the RA patient population compared with the non-RA population (Ekstrom et al 2003). The reason for this increased incidence is unclear. A study comparing disease activity with the risk of developing lymphoma in patients with RA revealed that patients with medium overall disease activity had an 8-fold increased risk, whereas patients with high overall disease activity had a 70-fold increased risk of lymphoma (Baecklund et al 2006). Another study of RA patients showed only 1 case of cervical cancer during a total 2,260 person-years, leading to an incidence rate of 6 per 10,000 patient-years (Abásolo et al 2008). Insurance data from the US comprising 58,979 women with RA showed an incidence rate of high-grade cervical dysplasia and cervical cancer of 83.3 per 100,000 person-years. The risk of high-grade cervical dysplasia and

Malignancy	Details
	cervical cancer was 1.5 times greater in RA patients (HR: 1.49; 95% CI: 1.11-2.00) than in those without systemic inflammatory diseases (Kim et al 2015). Increased incidence ratios for skin cancer in patients with RA have been observed in an anti-TNF cohort (1.72, 95% Cl: 1.43-2.04) compared with the English population. In patients without previous skin cancer, basal cell carcinoma incidence per 100,000 patients-years was 342 (95% Cl: 290-402) after anti-TNF (Mercer et al 2012). Patients with CD/UC: The cancer incidence in UC patients has been calculated as 14 per 1,000 PY (95% Cl: 5.0 to 34) (Thomas et al 2007). CD patients with at least 30% of the colon affected may have an increased risk of colorectal dysplasia and cancer. Using meta analytical techniques, RR of small bowel cancer compared with the general population was 28.4 (95% Cl: 14.46 to 55.66) and colorectal cancer 2.4 (95% Cl: 1.56 to 4.36).There was significant association between the anatomic location of the diseased bowel and the risk of cancer in that segment (von Roon et al 2007). However, several lines of evidence indicate that IBD is not associated with an increased risk of lymphoma. UC patients from 8 population-based cohort studies, comprising 17,052 IBD patients, were found to have a significantly increased risk of leukemia (2. 00, 95% CI: 1.31-3. 06; Pedersen et al 2010). In a Danish national cohort of women, 28 patients with UC developed cervical cancer compared with 1,918 control patients, with no significant difference in risk (incidence rate ratio: 0.78; 95% CI: 0.53-1.13), whereas 26 patients with CD developed cervical cancer compared with 940 controls, with a 53% increased risk in patients with CD (incidence rate ratio: 1.53; 95% CI: 1.04-2.27) (Rungoe et al 2015). Similar findings were reported in another population-based cohort study from Denmark (Jess et al 2013). Insurance data from the US comprising 25,176 women with IBD showed that the incidence rate of high-grade cervical dysplasia and cervical cancer was 110.3 per 100,000 person-years and the adjusted hazard ratio of high grade cervical dysplasia and cervical cancer was 1.07 (95% CI: 0. 79-1.45) in women with IBD compared to those without systemic inflammatory diseases (Kim et al 2015). A systematic data search encompassing 172,837 patients with IBD reported a pooled crude incidence rate of melanoma in patients with IBD of 27.5 cases per 100,000 person-years. Overall, IBD was associated with a 37% increase in risk of melanoma (RR, 1.37, 95% Cl: 1.10-1. 70). The risk was increased among patients with CD (7 studies: RR: 1.80, 95% Cl: 1.17-2.75) and UC (7 studies: RR; 1.23, 95% Cl: 1.01- 1.50). Patients with Ps/PsA: Patients with severe Ps are at an increased risk of developing a malignancy, especially NMSC and lymphoma. An observational study conducted in the UK GPRD showed that 1,703 out of 67,761 patients had cancer, of which 54% had a history of Ps.The incidence rate for all cancers was 5.83 per 1000 person years, with an incidence of leukemia and myeloproliferative disorders of 33 per 100,000 patients (95% CI: 25 - 43), and an incidence of melanoma of 18 per 100,000 person-years (95% Cl: 13-26) (Brauchli et al 2009). An increased overall cancer incidence was observed in a cohort of hospitalized patients with Ps (SIR l.3; 95% Cl: l.2 to 1.4), with the highest estimated RR for Hodgkin's disease (SIR 3.3; 95% Cl: I.4 to 6.4), squamous cell skin carcinoma (SIR

Malignancy	Details
	3.2; 95% Cl: 2.3 to 4.4), non- Hodgkin's lymphoma (SIR 2.2; 95% Cl: 1.4 to 3.4), and laryngeal cancer (SIR 2.9; 95% Cl: 1.5 to 5.0) (Hannuksela-Svahn et al 2000). Analyses of cancer risk in women with autoimmune diseases have shown an SIR for cervical cancer of 1.16 (95% CI: 0. 76-1. 70) for patients with Ps (Hemminki et al 2012). Insurance data from the US comprising 34,665 women with Ps revealed an incidence rate of high-grade cervical dysplasia and cervical cancer of 82.2 per 100,000 person-years (Kim et al 2015). Furthermore, a study conducted in Europe and Canada with over 1,200 patients with Ps found that malignancies were diagnosed in 3.8% of patients, 49% of which were skin malignancies, mostly squamous cell carcinoma (Paul et al 2003). An increased risk for skin carcinoma was also observed in a study of Swedish patients hospitalized for Ps, with a SIR for squamous cell carcinoma of the skin of 2.46 (95% Cl: 1.82-3.27) (Boffeta et al 2001). Patients with AS: A large national cohort of patients with AS from Sweden comprising 6,621 patients found no overall increase in cancer risk (SIR 1.05; 95% Cl: 0.94 to 1.17) (Feltelius et al 2003). Similarly, a case-control study of the risk for malignant lymphoma in AS revealed no increased risk of lymphoma (Askling et al 2006). Analyses of cancer risk in women with autoimmune diseases, conducted using Swedish national datasets, showed a SIR for cervical cancer of 1.34 (95% CI: 0.53-2.78) for patients with AS (Hemminki et al 2012).
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 (Navarro et al 2003; Mittal et al 2006). Based on published series of cases, young men appear to be at a higher risk for HSTCL (Belhadj et al 2003). 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 (Beauparlant et al 1999; Ljung et al 2004). 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 (Wolfe and Michaud 2007).

Malignancy	Details
	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 (American Cancer Society 2017a). 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 (Jess et al 2013). 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 (Wu et al 2016). 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 (Stern and Lunder 1998; Nijsten and Stern 2003; Curtin et al 2005). Risk factors for the development of melanomas can be categorized as environmental or host factors (American Cancer Society 2017b). 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 (American Cancer Society 2017b). 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%; Duprat et al 2011, Wang et al 2011). The incidence of MCC was found to be higher in areas with a greater solar UVB radiation index (Nicolaidou et al 2012). 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 (Duprat et al 2011). Patients with other tumors, such as squamous cell carcinoma and chronic lymphocytic leukemia, also have an increased risk of MCC (Wang et al 2011).
Preventability	Caution should be exercised when considering TNF-□-antagonist therapy for patients with a history of malignant disease, or when considering continuing treatment in patients who develop any form of malignancy (section 4.4 Special warnings and precautions for use of the Remicade SmPC). Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits of continued therapy to the individual patient should be carefully considered by the clinician (section 4.4 Special warnings and precautions for use of the Remicade SmPC). Caution should also be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking (section 4.4 Special warnings and precautions for use of the Remicade SmPC).

Malignancy	Details
	Before initiating or continuing infliximab therapy in patients with chronic IBD receiving an immunosuppressant such as AZA or 6-mercaptopurine, the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant treatment must be carefully assessed (section 4.4 Special warnings and precautions for use of the Remicade SmPC). Cervical cancer prevention requires a multipronged approach, including primary prevention employing HPV vaccination, secondary prevention through early screening of precancerous lesions by an efficient screening technique, and tertiary prevention by securing effective treatment of precancerous lesions. A combination of these approaches can help to reduce the burden of cervical cancer and its antecedent morbidity and mortality, but all of these measures are not feasible in all settings due to resource and allocation constraints (Aggarwal 2014). Although most cervical screening programs stop screening at the age of 65, this age threshold is being questioned (Andrae et al 2008, Rustagi et al 2013, Sherman et al 2015). For women taking infliximab including those over 60 years of age, doctors may recommend to continue regular screenings for cervical cancer (section 4.4 Special warnings and precautions for use of the Remicade SmPC). The most important preventive measures against MCC and melanoma are to limit sun exposure, especially in the middle of the day (between the hours of 10 am and 4 pm), to use sunscreen, and to wear protective clothing and hats to limit exposure to UV light. Periodic skin examinations are also recommended for those at risk for skin cancer (Section 4.4 Special Warnings and Precautions for Use section of the Remicade SmPC).
Impact on the benefit-risk balance of the product	Based on analytical, nonclinical, and clinical results, Sandoz concludes that biosimilarity of GP1111 and the reference product Remicade has been successfully demonstrated in accordance with applicable EMA guidance. Benefits and risks are assumed to be similar to those established for Remicade.
Public health impact	Impact is low to moderate with prompt and appropriate treatment.

Important potential risk: Colon carcinoma/dysplasia (in pediatric ulcerative colitis)

There is no data for GP1111 in pediatric ulcerative colitis.

Table 17 Part II SV.3.1 Important potential risk colon carcinoma/dysplasia (in pediatric ulcerative colitis): Other details

Colon carcinoma/dysplasia (in pediatric UC)	Details
MedDRA search terms for spontaneous post-marketing data	HLT Anal canal neoplasm malignant; HLT Colorectal and anal neoplasms malignancy unspecified; HLT Colorectal neoplasms malignant ; PT Colon dysplasia Note: Manual review to select cases <18 years of age and UC in indication or medical history
Potential mechanisms	TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumor cell lines (Mocellin et al 2005). Low doses of TNF can increase tumor blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumor cells (Balkwill 2009). Therefore the neutralization of TNF by infliximab may allow some types of tumor cells to survive.

Colon carcinoma/dysplasia (in pediatric UC)	**Details**
Evidence source(s) and strength of evidence	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 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 (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 Remicade RMP public summary (Janssen EMA 2022) of the reference product, colon carcinoma/dysplasia (in pediatric ulcerative colitis) is considered to be an important potential risk for Zessly.
Characterization of the risk	Patients with CD/UC: A population-based cohort 20-year follow-up study in Finland of patients with IBD was conducted. Colorectal cancer was found in 21 patients, the SIR being 1.83 (95% Cl: 1.13-2.79) for IBD. Colorectal cancer risk was 3/09 (95% CI: l.50-5.75) for extensive UC (Manninen et al 2013). No AEs relevant to colon carcinoma/dysplasia (in UC) have been reported either in healthy subjects or patients exposed to GP1111 so far. The impact of this risk on the individual patient can vary from minimal to potentially significant. Patients with a history of colon carcinoma/dysplasia or who develop colon carcinoma/dysplasia may have a more severe course due to use of the product. This risk needs to be carefully weighed against the benefit conferred by use of the medication.
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).
Preventability	All patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g., patients with longstanding 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 (section 4.4 Special warnings and precautions for use of the Remicade SmPC). This evaluation should include colonoscopy and biopsies per local recommendations. Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits to the individual patients must be carefully reviewed and consideration should be given to discontinuation of therapy.
Impact on the benefit-risk balance of the product	Based on analytical, nonclinical, and clinical results, Sandoz concludes that biosimilarity of GP1111 and infliximab Remicade has been successfully demonstrated in accordance with applicable EMA guidance. Benefits and risks are assumed to be similar to those established for Remicade.
Public health impact	Impact is low to moderate with prompt and appropriate treatment.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II Module SVIII: Summary of the safety concerns

Table 18 Part II SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance plan (including post-authorization safety studies)

Part III.1. Routine pharmacovigilance activities

The Global Pharmacovigilance System ensures the services of a QPPV and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires for following risks

Specific adverse reaction follow-up checklists will be used to collect further data to help further characterizing and/or closely monitoring each of the respective safety concerns specified below:

Title of the Follow-up questionnaire	Important Identified Risk / Important Potential Risk
Malignancy	• Malignancy.
Serious infection	• Serious infection/sepsis.

The specific adverse reaction follow-up questionnaires are provided to the reporters in order to obtain structured information on reported suspected adverse reactions of special interest.

The Targeted Follow-up Checklists are provided in Annex 4.

Other forms of routine pharmacovigilance activities for risks

Follow up of case reports: The minimum desired case information for infliximab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

Part III.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are ongoing or planned for Zessly.

Part III.3. Summary Table of additional pharmacovigilance activities

No additional pharmacovigilance activities are ongoing or planned for Zessly.

Part IV: Plans for post-authorization efficacy studies

Not applicable.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

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

Part V.1. Routine risk minimization measures

Table 19 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Serious infection/sepsis	**Routine risk communication** SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.6 Fertility, pregnancy and lactation, and 4.8 Undesirable effects PL section 2 What you need to know before you use Zessly and section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations to discontinue infliximab treatment if a patient develops a new serious infection or sepsis in SmPC section 4.4 Special warnings and precautions for use Recommendation to inform the doctor on symptoms of infections in PL section 2 What you need to know before you use Zessly **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only
Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	**Routine risk communication** SmPC sections 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.6 Fertility, pregnancy and lactation, and 4.8 Undesirable effects: PL sections 2 What you need to know before you use Zessly and 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation not to concurrently administer live vaccines and for an at least 12 month waiting period following birth before the administration of live vaccines to infants exposed in utero to infliximab in SmPC section 4.4 Special warnings and precautions for use **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only
Demyelinating disorders	**Routine risk communication** SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects: PL sections 2 What you need to know before you use Zessly and 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to**

Safety concern	Routine risk minimization activities
	address the risk: Recommendations to discontinue infliximab if disorders including MS, and peripheral demyelinating disorders, including Guillain-Barré syndrome develop in SmPC section 4.4 Special warnings and precautions for use Recommendation to tell the doctor straight away if the patients get symptoms of a nerve disease which include changes in vision, weakness in arms or legs, numbness or tingling in any part of the body during treatment with Zessly is included in PL section 2 What you need to know before you use Zessly **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only
Malignancy	**Routine risk communication** SmPC sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects, and 5.3 Preclinical safety data PL sections 2 What you need to know before you use Zessly and 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation to consider continuing treatment in patients who develop a malignancy in SmPC section 4.4 Special warnings and precautions for use. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only
Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	**Routine risk communication** SmPC sections 4.4 Special warnings and precautions for use and 5.3 Preclinical safety data **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation to screen patients screened for dysplasia at regular intervals before therapy and throughout their disease course in SmPC section 4.4 Special warnings and precautions for use **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only

Part V.2. Additional Risk minimization measures

Patient reminder card

Objectives:

To minimize the risk for the most critical side effects “Serious infection/sepsis” and “BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab” (BCG only) of Zessly.

Rationale for the additional risk minimization activity:

To minimize the risk of the most critical side effects.

Target audience and planned distribution path:

All HCPs who are most likely to prescribe Zessly to patients with RA, PsA, AS, adult and pediatric CD and adult and pediatric ulcerative colitis are provided with a Patient Reminder Card for distribution to patients receiving Zessly.

Plans to evaluate the effectiveness of the interventions and criteria for success:

AE reports are reviewed on an on-going basis and appropriate action taken as needed. Frequency and severity of AEs related to serious infection/sepsis and BCG breakthrough infection in infants with in utero exposure to infliximab covered by the patient reminder card are the primary indicator. The post-marketing AE profile is compared with the expected AE profile.

Part V.3. Summary of risk minimization measures

Table 20 Part V.3. Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infection/sepsis	**Routine risk minimization measures:** SmPC section 4.3; 4.4 where recommendations are given to discontinue infliximab treatment if a patient develops a new serious infection or sepsis; 4.5, 4.6 and 4.8 PL section 2 where recommendation is given to the patient to inform the doctor on symptoms of infections **Legal status:** Prescription only **Additional risk minimization measures:** Patient reminder card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific AE targeted follow-up questionnaire for serious infections **Additional pharmacovigilance activities:** None
Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	**Routine risk minimization measures:** SmPC section 4.4 where recommendation is given not to concurrently administer live vaccines and for an at least 12 month waiting period following birth before the administration of live vaccines to infants exposed in utero to infliximab; 4.5, 4.6, and 4.8 PL sections 2 and 4 **Legal status:** Prescription only **Additional risk minimization measures:** Patient reminder card (BCG only)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Demyelinating disorders	**Routine risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC section 4.4 where recommendation is given to discontinue infliximab if disorders develop; and 4.8 PL section 2.2 where recommendation is given to the patient to tell the doctor straight away if the patients gets symptoms of a nerve disease during treatment with Zessly; and 4 **Legal status:** Prescription only **Additional risk minimization measures:** None	None **Additional pharmacovigilance activities:** None
Malignancy	**Routine risk minimization measures:** SmPC section 4.4 where recommendation is given to exercise caution when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy; 4.8, and 5.3 PL section 2 and 4 **Legal status:** Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific AE targeted follow-up questionnaire for malignancy **Additional pharmacovigilance activities:** None
Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	**Routine risk minimization measures:** SmPC section 4.4 where recommendation to screen patients screened for dysplasia at regular intervals before therapy and throughout their disease course; and 5.3 PL section: none **Legal status:** Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific AE targeted follow-up questionnaire for malignancy **Additional pharmacovigilance activities:** None

Part VI: 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).

Important new concerns or changes to the current ones will be included in updates of Zessly's RMP.

Part VI: 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.

Part VI: 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*.

Part VI – 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).

Table 21 Part VI II.A 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

Part VI – II.B: Summary of important risks

Table 22 Part VI II.B 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 Remicade RMP public summary (Janssen EMA 2022) 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: None

Table 23 Part VI II.B 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 Remicade RMP public summary (Janssen EMA 2022) 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 12 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)

Table 24 Part VI II.B 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 Remicade RMP public summary (Janssen EMA 2022) 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

Table 25 Part VI II.B 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 Remicade RMP public summary (Janssen EMA 2022) 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: None

Table 26 Part VI II.B 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 Remicade RMP public summary (Janssen EMA 2022) 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: None

Part VI – 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

There are no studies ongoing or planned for Zessly.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

4a. Targeted Follow-up Questionnaire “Malignancy” (Version 1.0, Oct 2016)

4b. Targeted Follow-up Questionnaire “Serious infections” (Version 1.0, Nov 2016)

4a. Targeted Follow-up Questionnaire “Malignancy” (Version 1, Oct 2016)

SANDOZ

Manufacture Receipt Date (dd/mm/yyyy):
_____/_____/_____

Local case ID: _____
Batch number: _____

Targeted Follow-up Questionnaire
Malignancy

In addition to collecting routine information for these adverse events, please ensure the following additional information is provided and/or confirmed.

Date(s) of Zessly administration:

Start: _____ Stop: _____ Duration: _____

Indication: _____

Dose per kg body weight: _____

Malignancy Follow-Up Questions	
Please provide additional details on a separate page if needed, and reference the question number	
Age and Date of Birth:	**Gender:** ☐ Female ☐ Male
Race / Ethnicity:	
☐ Asian	☐ Black or African American
☐ White or Caucasian	☐ Hispanic or Latino
☐ Hawaiian Native or Pacific Islander	☐ American Indian or Native American
☐ Other	☐ Unknown
Indication(s) for Infliximab Use:	
☐ Rheumatoid Arthritis	☐ Ankylosing Spondylitis
☐ Juvenile Idiopathic Arthritis or Juvenile Rheumatoid Arthritis	☐ Psoriasis
☐ Psoriatic Arthritis	☐ Other *(please specify):*
Infliximab Dosing Information:	
Infliximab Dose/Interval:	Duration of Use (months or years):
Age at First Exposure to Infliximab:	Number of Doses (Received to Date):
Date of First Exposure to Infliximab:	
Status of Infliximab Usage	
☐ Continued or Ongoing	
☐ Temporarily Discontinued, provide stop and restart dates:	
☐ Permanently Discontinued, provide stop date:	
☐ Switched to another treatment *(provide product/dose/frequency/start date):*	
Did the patient receive another TNF-α inhibitor?	
☐ No	

Malignancy Follow-Up Questions

☐ Yes, please specify and provide start and stop dates:

Prior exposure to, or concomitant use of, immunosuppressant Drugs, including glucocorticosteroids and anti-neoplastics, or other drugs which have a risk for malignancy stated in their label (please provide start and stop dates for each):

_____

__

_____

Concomitant Medications with Infliximab other than those already listed above (please provide start and stop dates for each):

_____

__

_____

Malignancy Event Information

Date of Malignancy Diagnosis:			
Is this a new primary malignancy?	☐ Yes	☐ No	☐ Unknown
If no, is this a recurrence of a previous malignancy?	☐ Yes	☐ No	☐ Unknown
Time (in months or years) from start of infliximab treatment to malignancy diagnosis:			
Time (in months or years) from start of other TNF-α inhibitor treatment to malignancy Diagnosis (if applicable):			
Histopathologic diagnosis as stated on the original diagnostic pathology report:			
Copy of Pathology Report Included?	☐ Yes	☐ No	
Copy of Definitive Surgical Report Included?	☐ Yes	☐ No	

Describe the malignancy staging and findings that supported specified staging, including system used:

_____

_____

Presenting Symptoms:

_____

_____

Please provide the status of any relevant viral infections (e.g., Epstein-Barr virus, HPV, hepatitis B) prior to or concurrent with TNF blocker exposure including date of diagnosis and treatment:

_____

Malignancy Follow-Up Questions

List any relevant risk factors for malignancy from the patient's medical history, tobacco use (provide pack-years), exposures, or medications:

_____

_____

List any preventive measures take specific for malignancy, if any, including, mammograms, Pap smears, of HPV vaccine:

_____

_____

Family history of malignancy

☐ No

☐ Yes, please specify relationship and type of malignancy:

Describe Primary Treatment for Malignancy:

_____

_____

Outcome of Event:

☐ Patient recovered and event resolved

☐ Event resolved with sequelae

☐ Event ongoing

☐ Fatal

If fatal outcome, please provide cause of death and relationship to the malignancy:

_____

_____

(Targeted follow-up questionnaire for Malignancy, version 1.0, Effective Date: DD Oct 2016).

4b. Targeted Follow-up Questionnaire “Serious infections” (version 1, Nov 2016)

SANDOZ

Manufacture Receipt Date (dd/mm/yyyy):
_____/_____/_____

Local case ID: _____
Batch number: _____

Targeted Follow-up Questionnaire
Serious Infections

In addition to collecting routine information for these adverse events, please ensure the following additional information is provided and/or confirmed.

Date(s) of Zessly administration:

Start: _____ Stop: _____ Duration: _____

Indication: _____

Dose per kg body weight: _____

Infections Follow-Up Questions				
Please provide additional details on a separate page if needed, and reference the question number				
Concomitant medications				
Medication	Indication	Total Daily Dose	Start Date [dd-MMM-yyyy]	Stop Date [dd-MMM-yyyy]
List relevant medical history or any known risk factors for acquiring the specific infection in question				
_____ _____				
Is the patient considered immunocompromised? If so, please provide details (underlying diagnoses, immunosuppressive therapy, etc.)				
_____ _____				
Diagnosis (list symptoms and signs, specific diagnosis and how event was diagnosed)				
Date of first symptoms:	[dd-MMM-yyyy]			
Date of diagnosis:	[dd-MMM-yyyy]			
Laboratory and radiology data (List all relevant laboratory data below. Include culture results if available. Attach additional pages if needed))				
Laboratory test	**Date [dd-MMM-yyyy]**	**Results**		

Infections Follow-Up Questions		
Treatment and response (List patient treatment regimen and outcome of event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant)		
_____ _____		
Did the event resolve? ☐ Yes ☐ No	If yes, list date that event was considered resolved: [dd-MMM-yyyy]	
Was infliximab re-administered after the event? ☐ Yes ☐ No	If yes, did event recur or worsen (list details below)?	
Were there any unusual features of the patient´s presentation or clinical course?		
_____ _____		

(Targeted follow-up questionnaire for Serious infections, version 1.0, Effective Date: DD Nov 2016).

Annex 6 - Details of proposed additional risk minimization activities

Risk minimization activities:

Product Information - SmPC section 4.2 "Posology and method of administration" indicates the following:

Zessly treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of RA, IBD, AS, PsA, or Ps. Zessly should be administered intravenously. Zessly infusions should be administered by qualified HCPs trained to detect any infusion-related issues. Patients treated with Zessly should be given the PL and the special Patient Reminder Card.

In order to minimize the risk for the most critical side effects “Serious infection/sepsis” and “Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab” (BCG only) of Zessly, a **Patient Reminder Card** has been developed. All HCPs who are most likely to prescribe Zessly to patients with RA, PsA, AS, adult and pediatric CD and adult and pediatric UC are provided with a Patient Reminder Card for distribution to patients receiving Zessly. This card provides important safety information for patients, including information relating to infections and to “live vaccination”, e.g. BCG, of babies related to Zessly.

Key elements of the Zessly Patient Reminder Card:

- Free lines for adding additional information: Patient´s name, Doctor’s name and phone number
- Brief introduction to the aim of the Patient Reminder Card
- Request to show the Patient Reminder Card to any treating doctor
- Free lines for adding additional information: results of TB screening, list of allergies, list of concomitant medications
- Instructions for the patient regarding signs of infections
- Instruction for pregnant patients regarding vaccinations of the baby

Request to keep the Patient Reminder Card during and after treatment

Conclusion

The aim of this effort is to enhance patient knowledge regarding the safe use of Zessly, thereby mitigating some of the identified risks associated with Zessly in the treatment of RA, IBD, AS, PsA, and Ps.