REMSIMA

European Medicines Agency

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Remsima
MAH	**MAH**	Celltrion Healthcare Hungary Ktf. 1023 budapest, Regus Obuda Gate Arpad Fejedelem utja 26-28 Hungary
NRA	**Authorisation / Licence number**	EMEA/H/C/002576
MAH	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Manufacturer of the active substance CELLTRION, Inc. 23, Academy-ro, Yeonsu-gu, Incheon, 406-840, Republic of Korea CELLTRION, Inc. (Plant II, CLT2) 20, Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 406-840, Republic of Korea Manufacturer responsible for batch release Biotech Services International Limited Biotec House, Central Park, Western Avenue Bridgend Industrial Estate Bridgend, CF31 3RT United Kingdom
MAH	**Name of the active substance**	Infliximab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB02. Immuno-suppressants, tumour necrosis factor alpha (TNF_{α}) inhibitors
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	Powder for concentrate for solution for infusion (white)
MAH	**Quantitative composition**	100 mg per vial
MAH	**Route of administration**	Intravenous
MAH	**Packaging/material**	Vial / glass
MAH	**Package size(s)**	1, 2, 3, 4, and 5 vials per pack
MAH	**Local legal basis**	Directive 2001/83/EC, Article 10(4)
MAH	**Local biosimilar guidelines**	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid

		=WC0b01ac058002958c
MAH	**Date of authorisation/licensing of biosimilar**	10 September 2013
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Remicade
MAH	**Authorised indications for RBP**	Rheumatoid arthritis (RA; in combination with methotrexate), Adult Crohn's disease (CD), Paediatric Crohn's disease (in combination with conventional immunosuppressive therapy), Ulcerative colitis (UC), Paediatric ulcerative colitis, Ankylosing spondylitis (AS), Psoriatic arthritis (PsA), Psoriasis (Ps). For further details see EPAR: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&mid=WC0b01ac058001d124
MAH	**Pharmaceutical form**	Powder for concentrate for solution for intravenous infusion
MAH	**Quantitative composition**	100 mg per vial
MAH	**Route of administration**	Intravenous infusion
MAH	**Packaging/material**	Vial / glass
MAH	**Package size(s)**	Packs of 1, 2, 3, 4 and 5 vials
MAH	**MAA number (of RBP)**	EU/1/99/116/001-005
MAH	**Date of authorization (of RBP)**	13 August 1999
MAH	**MAH (of RBP)**	Janssen Biologics B.V.
MAH	**Source of RBP (or other comparator) for comparability exercise**	EU
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	EPAR- Public Assessment Report (English): http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&mid=WC0b01ac058001d124
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from: physicochemical, biological, *in vitro*, *in vivo*, PK, PD, efficacy, safety and immunogenicity studies.
Reviewer, NRA	**Availability of full assessment report** (language)/**link**	EPAR- Public Assessment Report (English): http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002576/human_med_0

		01682.jsp&mid=WC0b01ac058001d124
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorised for RBP (see section "Authorised indications" for further details).
Reviewer, NRA	**Authorised indications for biosimilar**	RA (in combination with methotrexate), CD disease, Paediatric CD (in combination with conventional immunosuppressive therapy), UC, Paediatric UC, AS, PsA, Ps. For further details see EPAR: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002576/human_med_001682.jsp&mid=WC0b01ac058001d124

MAH (Marketing Authorisation Holder)
NRA (National Regulatory Authority)

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Entered by	**Procedure: Initial Application**
MAH	**Quality data. Composition of the biosimilar product(s)**
	Infliximab, 100 mg Sucrose Polysorbate 80 Sodium dihydrogen phosphate monohydrate Disodium phosphate dihydrate
MAH	**Quality data. State-of-the-art methods**
	Physicochemical Test Methods. Amino acid analysis, peptide mapping (LC-MS) in combination with MS/MS, peptide mapping (HPLC), N-terminal sequencing, C-terminal sequencing, reduced mass, disulphide bonds, free thiol analysis, FTIR, CD, DSC, SEC-HPLC, CE-SDS (reduced/non-reduced), IEF, IEC-HPLC, Sialic acid analysis, Monosaccharide analysis, Oligosaccharide profiling, N-linked glycan analysis, Protein concentration (UV280) Product specific ELISA. Biological activity studies. Comparative binding to Fcγ receptors: FcγRI, FcγRIIa, FcγRIIb and FcRn using SPR; FcγRIIIa (V and F hemizygotes) and FcγRIIIb using SPR and *ex vivo* assay using NK cells and neutrophils, Comparative hTNF-α binding affinity (ELISA, SPR), Comparative transmembrane TNFα binding affinity (cell-based ELISA), Comparative human TNFβ binding specificities, Comparative human tissue cross-reactivity (immunohistochemistry), Comparative TNFα binding affinity from different species (SPR), Comparative hTNF-α neutralisation assay, Comparative apoptosis, Comparative reverse signalling, Effect of blocking soluble TNFα in in vitro IBD model, Comparative C1q binding affinity (ELISA), Comparative CDC, Comparative ADCC using tmhTNFα-Jurkat cells// transfected Jurkat cells/ LPS-stimulated monocytes from healthy donor or CD patient as target cells and human PBMC/NK from healthy donor/ PBMCs or NK cells from CD patients/whole blood from healthy donor or CD patients as effector cells, Evaluation of Regulatory Macrophage Function.
NRA	**Quality data assessment outcome**
	All major physicochemical characteristics and biological activities of Remsima were comparable to those of Remicade. The CHMP noted a small difference in the amount of afucosylated infliximab, translating into a lower binding affinity towards specific Fc receptors and a lower activity in the most sensitive ADCC assay using NK cells as effector cells and tmTNFα Jurkat target cells. This difference was, however, not considered clinically meaningful, as it did not affect the activities of Remsima in in-vitro models regarded as more relevant to the pathophysiological conditions in patients.
MAH	**Mechanism of action**
	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 lymphotoxin α (TNF_{β}).
MAH	**Nonclinical data. *In vitro* studies**
	Primary PD was performed. It consisted of 33 in vitro studies assessing the binding affinity of Remsima and Remicade to soluble (from different species) and transmembrane

	form of human TNFα, TNFβ, FcγRI, FcγRIIa, FcγRIIIa, FcRn and C1q; the TNFα neutralisation activity; the CDC, ADCC, apoptotic effects; and the cross-reactivity with various human tissues.
MAH	**Nonclinical data. *In vivo* studies**
	The PK data consisted in a single study in rats (Study N09067), supported by validation of methods to detect and quantify Remsima, Remicade and antibody formation performed for GLP studies (via ELISA). Serum samples were collected over 336 h after a single IV administration of Remsima or Remicade at a dose level of 10 or 50 mg/kg (5 rats/dose group). Two 2-weeks repeat dose toxicity studies in rats were performed to compare off-target toxicity profiles of Remsima and Remicade. Study 8214167: 2-Week IV injection dose finding study with Remicade in rats; 5 male and 5 female rats, aged 11 weeks old, who were dosed with a bolus IV injection of Remicade twice, on Day 1 and day 8 at doses of 0, 10 or 40 mg/kg. Study 8214158: 2-Week repeat-dose IV toxicity and toxicokinetics (TK) study with Remsima and Remicade in rats; 10 male and 10 female rats, aged 10-11 weeks old, were dosed by IV bolus injection with Remsima or Remicade on two occasions, one week apart at doses of doses 0, 10 or 40 mg/kg. Study G09197: 2-Week IV dose toxicity comparison study in rats (Remsima and Remicade); 10 male and 10 female rats, aged 6-7 weeks old, were dosed intravenously with Remsima or Remicade on two occasions, one week apart at doses of doses 0, 10 or 50 mg/kg.
NRA	**Nonclinical data assessment outcome**
	All comparative in vitro primary PD studies results were presented and discussed in the quality section of this report and the difference observed in FcγRIIIa binding was further discussed and analysed (see quality data assessment outcome section). In study N09067 the geometric mean AUC0-t ratio of Remsima compared to Remicade at 10 and 50 mg/kg were 96.66 (90% CI 79.69 to 117.23) and 112.70% (90% CI 87.30 to 145.49) respectively. The degree of variability shown may be attributed to the small sample used in each group. Overall, the PK of Remsima and Remicade are considered similar. Repeat dose toxicity evaluation in the non-responsive species rat revealed no significant test-article related off-target toxicity. The minimal treatment related findings were of similar magnitude and frequency with both Remsima and Remicade. In terms of off-target toxicity Remsima can be considered biosimilar to Remicade. However, as infliximab is not active in rats, these studies are not relevant for predicting human safety and are of little relevance for determining biosimilarity. Overall, there appears to be no difference between Remsima and Remicade in relation to general toxicity.
	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic, PK** • **Pharmacodynamic, PD** • **Efficacy,** • **Safety,** • **Immunogenicity.**
MAH	**Clinical data. PK studies**
	Study CT-P13 1.1: PK equivalence study (prospective Phase 1, randomised, double-blind, multicentre, multiple 5mg/kg repeat dose, i.v. infusion, parallel-group). Primary objective: to demonstrate comparable PK at steady state in terms of AUCτ, Cmax,ss between

	Remsima and Remicade determined between Weeks 22 and 30. Secondary objective: long-term efficacy, PK and overall safety up to Week 54. Study population: AS patients with active disease (Study population: 250 patients were randomised, 125 received Remsima and 125 received Remicade).
NRA	**Clinical data. PK data assessment outcome**
	The 90% CIs of the geometric means ratios for both AUCτ and Cmax,ss lied between 93% and 116%, well contained within the standard bioequivalence interval of 80%-125%; this demonstrates that the PK of infliximab is equivalent between Remsima and Remicade at the dose of 5 mg/kg. Furthermore, equivalent PK was also shown in the antibody-negative subset of the patient population. The main secondary PK endpoints such as Tmax, Cmin,ss, T½, CLss, Vss between Weeks 22 and 30, as well as Cmax and Cmin after the 9 treatment doses, were also comparable in the Remsima and Remicade treatment arms in the PK population and its antibody-negative subset, providing further evidence of a similar PK behaviour. Supportive PK data were generated in study CT-P13 3.1 providing estimates of Cmin, Cmax, and Tmax in RA patients. Generally, peak and trough levels measured after the 9 treatment doses of 3 mg/kg were similar between Remsima and Remicade arms.
NRA	**Clinical data. PD studies**
	In the absence of clinically relevant marker of therapeutic activity, several markers of inflammation or disease activity (RF, anti-CCP, ESR, and CRP) were measured as PD parameters during the efficacy trial CT-P13 3.1 (See section "Clinical data. Efficacy studies" for further details).
NRA	**Clinical data. PD data assessment outcome**
	Great variability was observed in individual changes, but overall, their evolution suggested a similar decrease in the disease activity under treatment with Remsima or Remicade.
MAH	**Clinical data. Efficacy studies**
	Study CT-P13 3.1: efficacy trial, which was designed to show therapeutic equivalence of Remsima and Remicade (prospective Phase 3, randomised, double-blind, multicentre, multiple 3 mg/kg repeat dose, i.v. infusion, parallel-group). Primary objective: to demonstrate that Remsima is equivalent to Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30. Secondary: long-term efficacy, PK, PD, and overall safety up to Week 54. RA patients with active disease while receiving MTX (Study population: 606 patients were randomised, 302 received Remsima and 304 received Remicade; Equivalence margin: ± 15%). A small pilot study (CT-P13 1.2) in RA patients was performed primarily to facilitate the conduct of the trial CT-P13 3.1. It was on-going (up to 2 years of treatment) at the time of the MAA procedure (Study population: 19 patients were randomised, 9 received Remsima and 10 received Remicade; Equivalence margin: ± 15%).
NRA	**Clinical data. Efficacy data assessment outcome**
	The efficacy and safety trial in RA patients achieved its primary endpoint since the 95% confidence interval for the difference in the ACR20 response rate at Week 30 was contained within the predefined equivalence margin (± 15%) in both the all-randomised (95% CI: -0.06, 0.10) and Per Protocol populations (95% CI: -0.04, 0.12). At week 30, the results of the secondary endpoints (in particular ACR50 and ACR70, decreases in DAS28, SDAI and CDAI, increases in SF-36) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 54. Additional supportive efficacy data were provided in another indication by the PK study

	CT-P13 1.1 conducted in AS patients. The efficacy results were comparable between treatment arms up to Week 54.
MAH	**Clinical data. Safety/ Immunogenicity studies**
	The safety data of Remsima were collected in the 3 clinical trials: the pilot trial CT-P13 1.2 in RA patients, the PK trial in AS patients CT-P13 1.1, and the efficacy trial CT-P13 3.1 in RA patients. The safety analysis was performed on the safety population defined as all patients who received at least one full or partial dose of either of the study treatments during any dosing period. The safety monitoring included monitoring of adverse events (AEs), serious adverse event (SAE), treatment-emergent adverse events (TEAEs), serious TEAEs, death, hypersensitivity via vital signs, electrocardiogram (ECG), physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis (TB), and pregnancy. Infections, infusion-related reactions and safety issues of special interest for infliximab were closely monitored. The areas of special interest were heart failure, serious infections (including TB, Hepatitis B virus reactivation, sepsis and opportunistic infections) as well as serious infusion reactions, delayed hypersensitivity reactions (serum sickness), systemic lupus erythematosus/lupus-like syndrome, hepatobiliary events, demyelinating disorders (i.e. multiple sclerosis, Guillain-Barré syndrome), haematologic reactions, lymphoma (including hepatosplenic T-cell lymphoma). The immunogenicity profile of Remsima has been well characterised in the two clinical studies CT-P13 1.1 and CT-P13 3.1.
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	Safety: ADRs were observed. The ADRs were equivalent to the ADRs observed with the RBP. A numerical imbalance in serious adverse events was observed in the RA trial CT-P13 3.1 with a higher incidence of serious infections, including active tuberculosis. However, the numbers involved are small and a thorough review of all available data suggests that the observed difference was most likely a chance finding. Serious infections, including tuberculosis will be closely monitored on a longer term and in larger patient cohorts as part of post authorisation measures through registries as described in the RBP. Rare adverse reactions known to Remicade, such as malignancies and lymphoproliferative disorders, will also be closely monitored as part of these registries. Immunogenicity: over the 54-week treatment period, a generally similar proportion of patients developed anti-infliximab antibodies (ADA) in the two treatment arms: 34.4% (CT-P13) vs. 32.0% (Remicade) in the AS study CT-P13 1.1 and 55.6% (CT-P13) vs. 54.3% (Remicade) in the RA study CT-P13 3.1. Essentially, all these antibodies were found to be neutralising (Nabs). Antibody titres of ADA and Nabs increased slightly over time up to 30 weeks and no marked differences were observed between the two treatment arms. As expected, these antibodies significantly reduced the systemic exposure to infliximab. Antibody formation in Remsima was considered to be comparable to that in the RBP, using appropriately validated methods.
MAH	**Interchangeability with the RBP**
	No additional data were provided
MAH	**Additional information about the comparability exercise** | N/A
MAH	**Post-authorization measures**
	Study CT-P13 1.2: randomized, double-blind, parallel-group, Phase 1 study to evaluate the

	initial PK/ E/ S of Remsima compared with Remicade when co-administered with methotrexate in patients with active RA (Philippines); Study CT-P13 1.3: open-label, single-arm, extension study to demonstrate long-term E/ S of Remsima in patients with AS who were treated with Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 (Global); Study CT-P13 3.2: an open-label, single-arm, extension study to demonstrate long-term E/S of Remsima when co-administered with methotrexate in patients with RA who were treated with infliximab (Remicade or CT-P13) in Study CT-P13 3.1 (Global); Study CT-P13 3.3: Phase 3 study to demonstrate equivalence in E/S of Remsima compared with Remicade when co-administered with methotrexate in patients with active RA (Russia); Study B1P13101: double-blind, parallel-group, comparative study of Remsima and Remicade in treatment of patients with RA (Japan); Study B2P13111: extension study of the Phase I/II clinical study of Remsima in treatment of patients with RA (Japan); Registry CT-P13* 4.2: observational, prospective cohort study to evaluate S/E of Remsima in patients with RA (EU and Korea); Post Marketing Surveillance of REMSIMA 100 mg (Infliximab): to evaluate S/ E in Korea; BSRBR-RA**: longitudinal observational study of patients with RA treated with biologic and other new advanced targeted therapies (UK); Registry CT-P13 4.3: observational, prospective cohort study to evaluate the S/E of Remsima in patients with CD and UC (EU and Korea); Study CT-P13 3.4: a randomized, double-blind, parallel-group, Phase 1/3 study to demonstrate comparable E/PK/S of Remsima to Remicade in patients with active CD (Global); RABBIT*** Long-term Observation of Treatment with Biologics in RA (Germany). * Remsima ** British Society for Rheumatology Biologics Register – Rheumatoid Arthritis *** Rheumatoid Arthritis Observation of Biologic Therapy	
NRA	**Post-authorization measures assessment outcome.**	
	The risk management plan was considered to be acceptable. An educational program will also be developed by the Marketing Authorisation Holder.	
MAH	**Availability of additional relevant information in the local language/ link**	N/A

PART C - REVIEWER CONCLUSIONS	
NRA	**Conclusions on biosimilarity, approval**

The data provided by the Applicant were in line with the local legislation, guidelines and international guidelines.

Quality
All major physicochemical characteristics and biological activities of Remsima were comparable to those of the reference biotherapeutic Remicade.

Non-clinical
Overall, the PK/PD data for Remsima and Remicade are considered similar and no differences between Remsima and the reference biotherapeutic Remicade were apparent in relation to general toxicity.

Clinical Studies
Pharmacology: The pivotal PK trial demonstrated that Remsima and Remicade exhibit a similar PK profile in AS patients, and additional supportive PK data were obtained in RA patients. PD data were supportive.

Efficacy: The pivotal efficacy study to demonstrate biosimilarity was conducted in RA patients and provided robust evidence of therapeutic equivalence between Remsima and the reference product Remicade. PD data were supportive.
Safety: The ADRs observed with Remsima were in the same range as the ADRs observed with the reference biotherapeutic Remicade.

Immunogenicity: The proportion of patients who developed anti-infliximab antibodies (ADA) over the 54-week treatment period was generally similar between the biosimilar Remsima and Remicade arms.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Remsima (see Section A, summary of outcomes) were considered to be approvable.

Risk Management
The risk management plan was considered to be acceptable.

Overall Conclusion
Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise.

Concerns raised during the review relating to afucosylation and ADCC in relation to the claimed inflammatory bowel disease indications were resolved during the procedure.

The biosimilar product Remsima was considered approvable.