REMSIMA

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Remsima
MAH	**MAH**	Celltrion Inc. 13-6 Songdo-dong, Yeonsu-gu, Incheon City, Republic of Korea
NRA	**Authorisation / Licence number**	Celltrion / 3
MAH/ NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential – Not Released
MAH	**Name of the active substance**	Infliximab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB02
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	White lyophilized powder in vial. After reconstitution, clear to yellowish solution
MAH	**Quantitative composition**	100 mg/vial
MAH	**Route of administration**	IV (Intravenous)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	"Guideline on Evaluation of Biosimilar Product (KFDA 2009)"
MAH	**Date of authorisation/licensing of biosimilar**	20 July 2012

	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Remicade
MAH	**Authorised indications for RBP**	· Rheumatoid Arthritis · Ankylosing Spondylitis · Psoriasis · Psoriatic Arthritis · Adult Crohn's disease · Pediatric Crohn's disease · Adult Ulcerative Colitis · Paediatric Ulcerative Colitis
MAH	**Pharmaceutical form**	White lyophilized powder in vial
MAH	**Quantitative composition**	100 mg/vial
MAH	**Route of administration**	IV(Intravenous)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH/ NRA	**Availability of the RBP assessment report** (language)/**link**	Adult Crohn's disease, Ankylosing Spondylitis: http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=레미케이드&cd=191&y=0&pageNo=1&seq=6319&cmd=v Adult Ulcerative Colitis, Rheumatoid Arthritis: http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=레미케이드&cd=191&y=0&pageNo=1&seq=6367&cmd=v Psoriatic Arthritis ; http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=레미케이드&cd=191&y=0&pageNo=1&seq=6435&cmd=v Pediatric Crohn's disease: http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=레미케이드&cd=191&y=0&pageNo=1&seq=9456&cmd=v
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Physicochemical and biological, in vitro and in vivo functional study Toxicological study PK/PD study Efficacy study (safety and efficacy)
NRA	**Availability of full assessment report** (language)/**link**	http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=램시마&cd=191&y

		=0&pageNo=1&seq=14295&cmd=v
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorized for RBP (see section **Authorised indications for RBP)**
NRA	**Authorised indications for biosimilar**	· Rheumatoid Arthritis(2012.7) · Ankylosing Spondylitis(2012.7) · Psoriatic Arthritis(2012.7) · Psoriasis(2012.7) · Adult Crohn's disease(2012.7) · Adult Ulcerative Colitis(2012.7) · Pediatric Ulcerative Colitis(2015.2) · Pediatric Crohn's disease (2015.2)

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

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Infliximab 100 mg
MAH	**Quality data. State-of-the-art methods**
	Physicochemical Test Methods 1. Primary structure : Amino acid Analysis(Whole, C-terminal, N-terminal), Peptide map ping (LC-MS, HPLC), 2. High-order structure : Disulfide bonds, Free-thiol residue , FTIR, CD, DSC 3. Micro-heterogeneity and Post-translational Forms : IEF, IEC-HPLC, Monosaccharide, Sialic acid content, Oligosaccharide profile (LC-MS, Bio-LC), N-linked glycan analy sis Biological activity 1. TNF alpha binding activities: SPR, ELISA 2. TNF alpha neutralization activity 3. Fcγ Binding activities: FcγRI(SPR), FcγRIIa(SPR), FcγRIIIa(SPR), FcRn(SPR), 4. C1q binding activity(ELISA) 5. CDC 6. ADCC 7. Apoptosis
NRA	**Quality data assessment outcome**

Attributes	**Comparability**	**Remarks**
Structure		
Peptide mapping(amino acid sequence)	Comparable	
N/C-terminal sequence	Comparable	
Disulfide bond	Comparable	
Free thiol residue	Comparable	
Physicochemical analyses		
High-order structure(FTIR, CD, DSC)	Comparable	
Molecular weight(LC-MS)	Comparable	
SE-HPLC	Comparable	
CE-SDS	Minor difference	No effect on biological activity
SDS-PAGE	Comparable	

	IEF	Comparable	
	IEC-HPLC	Difference	No effect on biological activity
	Protein content	Comparable	
	Glycosylation analysis		
	Monosaccharide	Comparable	
	Sialic acid content	Comparable	
	Oligosaccharide profile (LC-MS, Bio-LC)	Difference	No effect on biological activity (ADCC)
	Biological activity		
	CDC	Minor difference	Few outlier batches exist
	C1q Binding activity(ELISA)	Comparable	
	FcγRI Binding activity (SPR)	Comparable	Few outlier batches exist
	FcγRIIa Binding activity (SPR)	Comparable	
	FcγRIIIa Binding activity (SPR)	Difference	Lower Binding activity Comparable in ADCC
	FcRn Binding activity (SPR)	Comparable	
	TNFα Binding activity (SPR)	Comparable	
	TNFα Binding activity (ELISA)	Comparable	
	CELISA	Comparable	Few outlier batches
	TNFα Neutralization activity	Comparable	
	ADCC	Comparable	Effecter cells: PBMC
	Apoptosis	Comparable	

MAH	**Mechanism of action**
	Infliximab binds highly specifically to both soluble and transmembrane forms of TNF alpha
MAH	**Nonclinical data. *In vitro* studies**
	1. TNF alpha binding activities: SPR, ELISA 2. TNF beta binding activity(ELISA) 3. TNF alpha neutralization activity 4. Fcγ Binding activities: FcγRI(SPR), FcγRIIa(SPR), FcγRIIIa(SPR), FcRn(SPR), 5. C1q binding activity(ELISA) 6. CDC 7. ADCC 8. Apoptosis 9. Tissue cross-reactivity

MAH	**Nonclinical data. *In vivo* studies**
	One week (2 doses : day1, 8) toxicity studies in rats (IV) with comparative manner Toxicokinetics studies in rat (single and repeat dose) with comparative manner
NRA	**Nonclinical data assessment outcome**
	1. In vitro studies See Quality assessment data outcome In tissue cross reactivity, 40 kinds of human tissues were tested with Remsima and Remicade. Both showed same results. 2. In vivo studies In repeat dose toxicity, rat was not a relevant species for infliximab so purpose of comparative toxicity studies was to see off-target activity. In both Remsima and Remicade, all injected doses were tolerable and showed similar responses. In ADME studies, single IV studies in rat showed similar PK profile. Also in TK studies in repeat dose toxicity, showed similar C_{max} and $AUC_{0\text{-}168h}$.
	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 Number: CT-P13 1.1 (PLANET AS) Summary of design : Pharmacokinetics study with randomized, double-blind, parallel group, phase 1 trial Population: Active disease Ankylosing Spondylitis (CT-P13 125, Remicade 125 patients) Objective and primary endpoint: Demonstration of comparable PK at steady state in terms of AUC_{τ} and C_{maxSS} between CT-P13 and Remicade up to weeks 30. Secondary endpoint is to see long term efficacy, PK and safety up to weeks 54. Dose used : 5 mg/kg of CT-P13 or Remicade (Induction: at the weeks of 0,2,6(3 times), Maintenance : at the weeks of 14,22,30,38,46,54 (6 times) Length of the study : 54 weeks
NRA	**Clinical data. PK data assessment outcome**
	The primary PK endpoint, the geometric mean of AUC_{τ}, C_{maxSS} were also comparable in the CT-P13 and Remicade. The 90% CI of geometric mean of AUC_{τ} was 93% ~ 116%, C_{maxSS} was 95%~109%, which are within the limit of the acceptance margin (80%~125%). The 90% CI of geometric mean in antibody-negative subset patient was also within the limit of margin.
MAH	**Clinical data. PD studies**
	No specific PD study was conducted due to no relevant biomarker of therapeutic activity. However, in the efficacy study, several biomarkers were compared between Remsima and Remicade.

NRA	**Clinical data. PD data assessment outcome**
	There were no significant differences in the level of CRP, ESR, IgA RF, IgM RA between CT-P13 and Remicade although variability exists. Statistically significant differences were observed in anti-CCP level at the weeks of 30, IgG RF level at week 14. However, these biomarkers more represent overall pathological profile rather than detecting anti-TNF alpha effect.
MAH	**Clinical data. Efficacy studies**
	Study Number: CT-P13 3.1 (PLANET RA) Summary of design : Efficacy and safety study with randomized, double-blind, parallel group, phase 3 trial Population: Active disease Rheumatoid Arthritis with methotrexate concomitant treatment (CT-P13 302, Remicade 304 patients) Objective and primary endpoint: Demonstration of equivalence between CT-P13 and Remicade of response rate ACR20 at week 30. Secondary endpoint was other long-term efficacy parameter safety parameters, PK and PD up to week 54. Dose used : 3 mg/kg of CT-P13 or Remicade Length of the study : 54 weeks
NRA	**Clinical data. Efficacy data assessment outcome**
	The results of the primary endpoints met the equivalence margin either in the all randomized and per protocol population.

Treatment Group	n/N' (%)	Estimate of Treatment Difference[1]	95% CI of Treatment Difference[2]
All-Randomized Population			
CT-P13	184/302 (60.9)	0.02	(-0.06, 0.10)
Remicade	178/304 (58.6)		
Per-Protocol Population			
CT-P13	182/248 (73.4)	0.04	(-0.04, 0.12)
Remicade	175/251 (69.7)		

ACR20, American College of Rheumatology definition of a 20% improvement; CI, confidence interval.
Note: N'=the number of patients with an assessment, n=the number of patients with the event, (%)=n/N'×100.

1. Estimate of the difference in proportions between the 2 treatment groups (CT-P13 – Remicade) using the exact binomial test.
2. Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

	Secondary endpoint was ACR50, ACR 70, DAS28, SDAI and CDAI, increase in SF-36 including fatigue, ACR hybrid score, VAS by patient and global assessment, Good responder ratio by EULAR criteria, and others by the weeks of 30 (and 54). All are comparable with Remicade group except the onset time of ACR20 response.
MAH	**Clinical data. Safety/ Immunogenicity studies**
	Safety data were collected from all clinical study; CT-P13 1.1 (AS patients), 1.2 & 3.1 (RA patients). Analysed patients who administered at least one or partial dose of either of the study treatments during any dosing period. Immunogenicity profile was collected from CT-P13 1.1 and 3.1 studies.
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	1. Safety: The overall adverse event profile was similar for both the Remsima and Remicade groups.

	CT-P13 (ug/ml)	Remicade(ug/ml)
TEAE	181(60.1%) Latent Tuberculosis, Pharyngitis, Hypertension	183(60.8%) Latent Tuberculosis ALT increase headache

2. Immunogenicity: Immunogenicity of Remsima and Remicade from CT-P13 3.1 was similar.

표 2.7.2- 22: CT-P13 3 상 임상시험(CT-P13 3.1)의 면역원성 검사 요약: 안전성 분석군

Heading	CT-P13 3mg/kg (n=301)	Remicade® 3m/kg (n=301)	Total (n=602)
Screening			
ADA Positive	9 (3.0%)	6 (2.0%)	15 (2.5%)
NAb (as % of ADA positive)	4 (44.4%)	2 (33.3%)	6 (40.0%)
ADA Negative	284 (94.4%)	291 (96.7%)	575 (95.5%)
Week 14			
ADA Positive	68 (22.6%)	70 (23.3%)	138 (22.9%)
NAb (as % of ADA positive)	68 (100.0%)	67 (95.7%)	135 (97.8%)
ADA Negative	204 (67.8%)	201 (66.8%)	405 (67.3%)
Week 30			
ADA Positive	121 (40.2%)	120 (39.9%)	241 (40.0%)
NAb (as % of ADA positive)	118 (97.5%)	116 (96.7%)	234 (97.1%)
ADA Negative	129 (42.9%)	133 (44.2%)	262 (43.5%)

MAH	**Interchangeability with the RBP**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	As appropriate, if not previously included.
MAH	**Post-authorization measures**	
	Re-examination study in Korea; Observational, prospective cohort study to evaluate safety and efficacy of Remsima - Period: 2012. 7.20~2016. 7.19 Number of subjects (1600): Adult and pediatric crohn's disease and ulcerative colitis (600), Ankylosing spondylitis (600), Rheumatoid arthritis and plaque psoriasis and psoriatic arthritis (400)	
NRA	**Post-authorization measures assessment outcome.**	
	Number of subjects of Remsima for re-examination study met the MFDS criteria (over 400).	
MAH	**Availability of additional relevant information in the local language/ link**	As required /appropriate

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

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 product Remicade .

Nonclinical

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 studies to demonstrate biosimilarity were conducted in rhematoid arthritis patients and provided robust evidence of therapeutic equivalence between Remsima and the reference biotherapeutic Remicade

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-drug antibodies (ADA) with Remsima was generally similar for the reference biotherapeutic product Remicade

Risk Management

The risk management plan (or equivalent) was considered to be acceptable.

Overall Conclusion

Based on the robust comparisons of the physicochemical and in vitro and ex vivo biological analyses, Remsima was considered biosimilar to the reference product Remicade. These data, in combination with clinical data demonstrating pharmacokinetic and therapeutic equivalence in rheumatology conditions, allow for extrapolation to all other indications of Remicade.

Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise

The biosimilar product Remsima was considered approvable.