<TRUXIMA>

<Ministry of Food and Drug Safety>

<APPROVED>

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Truxima
MAH	**MAH**	Celltrion Inc. 23, Academy-ro, Yeonsu-gu, Incheon, 22014, Republic of Korea 20, Academy-ro 51beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea
NRA	**Authorisation / Licence number**	Celltrion / 8
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	N/A < Confidential – Not Released >
MAH	**Name of the active substance**	Rituximab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code : L01XC02
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	Concentrate for solution for infusion. Clear, colourless liquid.
MAH	**Quantitative composition**	500mg/vial 100mg/vial
MAH	**Route of administration**	IV (Intravenous)
MAH	**Packaging/material**	Vial/Glass
MAH	**Package size(s)**	500mg 1 vial/pack 100mg 2 vials/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	"Guideline on the Evaluation of Biosimilar Product (MFDS 2014)"
MAH	**Date of authorisation/licensing of biosimilar**	16 November 2016
	Reference Biotherapeutic Product (RBP) Information	

MAH	**Name of the RBP**	MabThera
MAH	**Authorised indications for RBP**	• Rheumatoid Arthritis • Non-Hodgkin's Lymphoma • Chronic Lymphocytic Leukaemia • Wegener's Glanulomatosis • Microscopic Polyangiitis
MAH	**Pharmaceutical form**	Concentrate for solution for infusion. Clear, colourless liquid.
MAH	**Quantitative composition**	500mg/vial 100mg/vial
MAH	**Route of administration**	IV(intravenous)
MAH	**Packaging/material**	Vial/Glass
MAH	**Package size(s)**	500mg 1 vial/pack 100mg 2 vials/pack
MAH	**Authorisation (Licence) number (of RBP)**	69
MAH	**Date of authorisation (of RBP)**	21 November 2003
MAH	**Authorisation (Licence) Holder (of RBP)**	Roche Korea
MAH	**Source of RBP (or other comparator) for comparability exercise**	EU, US, Korea.
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	Initial Authorisation http://www.mfds.go.kr/index.do?x=13&searchkey=product_nm&mid=1176&searchword=%B8%BF%C5%D7%B6%F3&cd=191&y=4&pageNo=1&seq=6150&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 Safety and Efficacy study
NRA	**Availability of full assessment report** (Korean)/**link**	http://www.mfds.go.kr/index.do?mid=1176&cd=191&pageNo=1&seq=30632&cmd=v
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorised for RBP (see section **Authorised indications for RBP**)
NRA	**Authorised indications for**	Rheumatoid Arthritis

	biosimilar	Non-Hodgkin's Lymphoma Chronic Lymphocytic Leukaemia Wegener's Glanulomatosis Microscopic Polyangiitis

MAH (Marketing Authorisation Holder) or Sponsor
NRA (National Regulatory Authority) i.e. CA (Competent Authority)

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Procedure: <Initial Application> <Variation / Supplement> **<Variation number and scope: [Quality / Safety / Efficacy / Risk Management] and description>**	
MAH	**Quality data. Composition of the biosimilar product(s)**
	<u>500mg</u> Active ingredient: Rituximab 500mg Excipients: Sodium Chloride, Trisodium Citrate Dihydrate, Polysorbate 80, Water for Injection <u>100mg</u> Active ingredient: Rituximab 100mg Excipients: Sodium Chloride, Trisodium Citrate Dihydrate, Polysorbate 80, Water for Injection
MAH	**Quality data. State-of-the-art methods**
	<u>Physicochemical Test Methods</u> Physicochemical comparability between CT-P10 and the comparator (MabThera) was examined. Amino acid analysis, Molar absorptivity, N-terminal sequencing, C-terminal sequencing, Peptide mapping were conducted to compare primary structure and Disulphide bond, free thiol residue analysis, FTIR, CD and DSC were examined for high-order structure analysis. Micro-heterogeneity and post-translational forms comparability were observed using monosaccharide analysis, N-linked glycan, sialic acid analysis and oligosaccharide profile analysis. <u>Biological activity</u> Comparability of CT-P10 and the comparator in terms of biological activity was investigated by comparing Cell-based CD20 binding affinity, C1q binding affinity, FcγRIIIa binding affinity, FcγRIIa binding affinity, FcγRI binding affinity, FcRn binding affinity, Apoptotic activity and ADCC.
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head characterisation studies performed using state-of-the-art analytical procedures demonstrated that all major quality attributes of Truxima with respect to the primary and higher order structures, post-translational modifications, physicochemical and biophysical properties, and biological activities were comparable to those of MabThera. The similarity range was defined using the sufficient batches of EU MabThera, and the bridging data demonstrated the equivalence of EU MabThera and Korea MabThera. Due to the complex heterogeneity in the structure of Rituximab, slight differences were found in the glycosylation profile and size and charge variants compared to MabThera; higher intact IgG, non-glycosylated heavy chain (NGHC), high-mannose glycan, and basic variants, and lower acid variants. However, those differences were not considered clinically meaningful since those had no impact on the biological activities related to the primary mechanism of action including CD20, C1q, FcγRIIIa, and FcγRn binding affinity, apoptosis, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP), as determined by Structure-activity relationship (SAR) studies. In addition, although a slightly lower trend of protein contents in terms of concentrations were observed, these minor differences in the protein and mannose contents were not considered to be significant to possess a

	physiological effect based on the PK equivalence demonstrated in the global clinical study. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Truxima to the MabThera was concluded.
MAH	**Mechanism of action**
	Rituximab binds highly specifically to CD20 positive B-cell and induces B-cell depletion
MAH	**Nonclinical data. *In vitro* studies**
	Non-clinical studies conducted during development of CT-P10 include examination of Cell-based CD20 binding affinity, C1q binding affinity, FcγRIIIa binding affinity, FcγRIIa binding affinity, FcγRI binding affinity, FcRn binding affinity, Apoptotic activity, ADCC and Tissue cross-reactivity.
MAH	**Nonclinical data. *In vivo* studies**
	Toxicity studies were conducted using cynomolgus monkeys (IV) with comparative manner
NRA	**Nonclinical data assessment outcome**
	1. In vitro studies See Quality assessment data outcome. 2. In vivo studies TK studies in repeat dose toxicity in cynomolgus monkey, showed similar $C_{max,}$ T_{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-P10 1.1 • Summary of Design: Pharmacokinetics study with randomized, double-blind, parallel group, phase 1 trial • Population: Rheumatoid Arthritis (CT-P10 103, MabThera 51) • Objective and Primary endpoint: Demonstration of steady sate in terms of $AUC_{0\text{-}last}$ and C_{max} between CT-P10 and MabThera up to Week 24 • Secondary endpoints: Assessment in additional PK variables of CT-P10 compared with MabThera up to Week 24 and Evaluation of long-term efficacy, pharmacodynamics, overall safety and biomarkers of CT-P10 compared with MabThera up to Week 72 • Dose used: 1000mg of CT-P10 or MabThera • Length of the study: 72 weeks
NRA	**Clinical data. PK data assessment outcome**
	The primary PK endpoint, the geometric mean of $AUC_{0\text{-}last}$, C_{max} were also comparable in the Truxima and MabThera. The 90% CI of geometric mean of $AUC_{0\text{-}last}$ was 97.72% ~

	107.00%, C_{max} was 97.57%~103.53%, which are within the limit of the acceptance margin (80%~125%).
MAH	**Clinical data. PD studies**
	No specific PD study was conducted due to no relevant biomarker of therapeutic activity. However, in the pharmacokinetics and efficacy study, several biomarkers were compared between Truxima and MabThera
NRA	**Clinical data. PD data assessment outcome**
	Not applicable
MAH	**Clinical data. Efficacy studies**
	Study Number: CT-P10 1.3 • Summary of Design: Efficacy study with single-arm, open-label maintenance study, phase 1 trial • Population: Rheumatoid Arthritis (CT-P10 58, MabThera 29) • Objective and Primary endpoint: Demonstration to confirm long-term efficacy(ACR criteria, DAS28) and safety of CT-P10 compared with MabThera • Length of the study: 104 weeks Study Number: CT-P10 3.2 • Summary of Design: Pharmacokinetics, Efficacy and Safety study with randomized, double-blind, parallel group, phase 3 trial • Population: Rheumatoid Arthritis (CT-P10 161, MabThera 60, Rituxan 151) • Objective and Primary endpoint: Demonstration of similar pharmacokinetics and efficacy of CT-P10 compared to reference products(Rituxan and MabThera) • Secondary endpoints: Evaluation of the additional pharmacokinetics and efficacy, pharmacodynamics, overall safety and biomarkers of CT-P10 compared with reference products • Dose used: 1000mg of CT-P10 or Rituxan or MabThera • Length of the study: 48 Weeks(Main Study Period) and 24 Weeks(Extension Study Period) Study Number: CT-P10 3.3 • Summary of Design: Pharmacokinetics and Efficacy study with randomized, double-blind, phase 3 trial • Population: Follicular Lymphoma (CT-P10 70, Rituxan 70) • Objective and Primary endpoint: Demonstration of similar pharmacokinetics and noninferior efficacy of CT-P10 compared to Rituxan • Secondary endpoints: Evaluation of the additional pharmacokinetics and efficacy, pharmacodynamics, overall safety and biomarkers of CT-P10 compared with Rituxan • Dose used: 375mg/m^2 of CT-P10 or Rituxan • Length of the study: 24 Weeks(Main Study Period) and up to 2 years(Extension Study Period)
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 DAS28(CRP) response rate at week 24 was contained within the predefined equivalence margin(±0.6) in the efficacy population(95% CI : -0.29, 0.20). At week 24, the results of the secondary endpoints(in particular DAS28(ESR), ACR20/50,70, EULAR response) were all consistent with the results of the

primary endpoint.

Treatment	N	Adjusted Mean	Estimate of Treatment Difference	95% CI
Truxima	139	-2.14(0.177)	-0.05	(-0.29, 0.20)
Reference Product	196	-2.09(0.176)		

MAH **Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)

Safety data were collected from all clinical study; CT-P10 1.1, 1.3, 3.2 & 3.3. 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, 1.3, 3.2 & 3.3 studies

NRA **Clinical data. Safety/ Immunogenicity data assessment outcome**

1. Safety:
The overall adverse event profile was similar for both the Truxima and Reference product groups.

	Truxima (N=161)	Rituxan (N=151)	MabThera (N=60)	Reference Products (N=211)	Total (N=372)
Total number of TEAEs	203	161	53	214	417
Number(%) of patients with at least 1 TEAE	95(59.0)	76(50.3)	33(55.0)	109(51.7)	204(54.8)

2. Immunogenicity: Immunogenicity of Truxima and Reference product from CT-P10 3.2 was similar.

	Truxima (N=161)	Rituxan (N=151)	MabThera (N=60)	Reference Products (N=211)	Total (N=372)
Week 0					
Positive	19(11.8%)	13(8.6%)	7(11.7%)	20(9/5%)	39(10.5%)
Negative	142(88.2%)	137(90.7%)	53(88.3%)	190(90.0%)	332(89.2%)
Week 24					
Positive	24(14.9%)	33(21.9%)	16(26.7%)	49(23.2%)	73(19.6%)
Negative	121(75.2%)	108(71.5%)	42(70.0%)	150(71.1%)	271(72.8%)

MAH **Interchangeability data**

< 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 Truxima - Period: 2016. 11.16 ~ 2020. 11.15 - Number of subjects: 600	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study plan was considered to be acceptable. Number of subjects of Truxima for PMS study met the MFDS criteria (over 600)	
MAH	**Availability of additional relevant information in the local language/ link**	Not Applicable

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

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

Quality
The biosimilar manufacturer has developed and validated a process capable of consistently manufacturing a product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to cGMP requirements.

The quality attributes of high relevance for clinical safety and efficacy, e.g. physicochemical characteristics and biological activities of Truxima were comparable to those of the reference biotherapeutic product MabThera.

Nonclinical
No major differences in nonclinical data were observed for Truxima compared to the reference biotherapeutic products, MabThera and Rituxan. .

Clinical Studies
The PK, efficacy studies to demonstrate biosimilarity conducted in Rhematoid Arthritis patients provided robust evidence there are no clinically meaningful differences versus the reference biotherapeutic products, MabThera and Rituxan.

Safety: The ADRs observed with Truxima were in the same range as the ADRs observed with the reference biotherapeutic products, MabThera and Rituxan.

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with Truxima was generally similar for the reference biotherapeutic products, MabThera and Rituxan.

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

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

Overall Conclusion
Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise. The biosimilar product Truxima was considered approvable.