HERZUMA

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Herzuma
MAH	**MAH**	Celltrion Inc. 13-6 Songdo-dong, Yeonsu-gu, Incheon City, Republic of Korea
NRA	**Authorisation / Licence number**	Celltrion / 6 Celltrion / 7
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential – Not Released
MAH	**Name of the active substance**	Trastuzumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L01XC03
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	White to pale yellow lyophilized powder / Clear to slightly opalescent/ Colourless to pale yellow solution
MAH	**Quantitative composition**	150 mg/vial 440mg/vial
MAH	**Route of administration**	IV (Intravenous, Infusion)
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 Products (MFDS 2009)"
MAH	**Date of authorisation/licensing of biosimilar**	15 January 2014
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Herceptin
MAH	**Authorised indications for RBP**	· Metastatic Breast Cancer

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		· Early Breast Cancer · Metastatic Gastric Cancer
MAH	**Pharmaceutical form**	Powder for concentrate for solution for infusion. White to pale yellow lyophilised powder
MAH	**Quantitative composition**	150 mg/vial 440mg/vial
MAH	**Route of administration**	IV(Intravenous, Infusion)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	Metastatic Breast Cancer, Early Breast Cancer and Metastatic Gastric Cancer http://www.mfds.go.kr/index.do?searchkey=product_nm&mid=1176&searchword=허셉틴&cd=191&pageNo=1&seq=14215&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=허쥬마&cd=191&y=0&pageNo=1&seq=19725&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**	Metastatic Breast Cancer Early Breast Cancer Metastatic Gastric Cancer

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

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PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Trastuzumab 150 mg, Trastuzumab 440 mg
MAH	**Quality data. State-of-the-art methods**
	Physicochemical Test Methods 1. Primary structure : Amino Acid Analysis, Molar Absorptivity, Peptide Mapping(LC-MS, HPLC), N-terminal Sequencing, C-terminal Sequencing, Reduced Mass / Intact Mass 2. High order structure : Disulphide Bonds, Free Thiol Analysis, FTIR, CD, DSC 3. Micro-heterogeneity and Post-translational Forms : IEF, IEC-HPLC, Oligosaccharide Profiling(HPLC), N-linked Glycan Analysis, Monosaccharide Analysis, Sialic Acid Analysis **Biological Activity** 1. *In vitro* Bioactivity(Anti-proliferation assay) 2. HER2 Binding Affinity (ELISA) 3. Cell Based Binding Affinity 4. C1q Binding Affinity (ELISA) 5. FcγRI Binding Affinity (ELISA) 6. FcγRIIa Binding Affinity (SPR) 7. FcγRIIIa Binding Affinity (SPR) 8. FcRn Binding Affinity (SPR) 9. ADCC
NRA	**Quality data assessment outcome**

Attributes	Comparability	Remarks
Primary Structure		
Amino acid analysis	Comparable	
N/C-terminal sequence	Comparable	
Peptide mapping(LC-MS, HPLC)	Comparable	
Molecular weight(LC-MS); Intact, reduced	Comparable	
Molecular absorptivity		
Higher-order structure		
FTIR, CD, DSC	Comparable	
Disulfide bond	Comparable	
Free thiol residue	Comparable	
Physicochemical tests		
Aggregates, Fragments	Comparable	

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	CE-SDS (subunits)	Comparable	
	IEF(isomers)	Comparable	
	IE-HPLC(charge variants)	(Minor)Difference	No effect on biological activity
	Protein content	Comparable	
	Forced degradation		
	Glycosylation analysis		
	Monosaccharide	Comparable	
	Sialic acid content	Comparable	
	Oligosaccharide profile (HPLC)	Difference	No effect on biological activity
	N-linked Glycan Analysis	Comparable	
	Biological activity		
	In vitro Bioactivity(Anti-proliferation assay)	Comparable	
	HER2 Binding Affinity (ELISA)	Comparable	
	Cell Based Binding Affinity	Comparable	
	C1q Binding Affinity (ELISA)	Minor difference	Few outlier batches exist
	FcγRI Binding Affinity (ELISA)	Comparable	
	FcγRIIa Binding Affinity (SPR)	Minor difference	Few outlier batches exist
	FcγRIIIa Binding Affinity (SPR)	Difference	Comparable in ADCC
	FcRn Binding Affinity (SPR)	Comparable	
	ADCC(Effector cells: PBMC)	Comparable	

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Mechanism of action

Herzuma (Trastuzumab) is a humanized monoclonal antibody that binds with high affinity and specificity to the extracellular domain of HER2.

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Nonclinical data. *In vitro* studies

1. Inhibition of proliferation of HER2 over-expressing tumour cells
2. Evaluation of ADCC and CDC
3. Comparative analysis for cell cycle profile and cell cycle controlling proteins
4. HER2 binding affinity to immobilised target by ELISA
5. Cell based HER2 binding affinity
6. Inhibition of growth of HER2 positive cell line
7. FcγRI binding affinity
8. FcγRIIa binding affinity
9. FcγRIIIa binding affinity
10. FcRn binding affinity
11. ADCC bioactivity
12. C1q binding affinity
13. Tissue cross-reactivity

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Nonclinical data. *In vivo* studies

In vivo pharmacological study

Inhibition of tumour xenograft growth in nude mice

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	Pharmacokinetics The Pharmacokinetics of Herzuma and Herceptin® in the female cynomolgus monkey following single and 4-week repeat dose intravenous administration. **Toxicity Study (including TK)** • Repeat dose toxicity(Comparative design) 1. Two-week pilot study to compare two intravenous dosing regimens of CT-P6 in the Cynomolgus Monkey 2. Four-week Intravenous Repeat-Dose Toxicity Study in the Cynomolgus Monkey (GLP) 3. 13-Week Intravenous Repeat Dose Toxicity Study in the Cynomolgus Monkey (GLP)
NRA	**Nonclinical data assessment outcome**
	1. In vitro studies See Quality assessment data outcome. In tissue cross reactivity, Herzuma and Herceptin showed same results. 2. In vivo studies - In vivo pharmacological study (Inhibition of tumour xenograft growth in nude mice) showed similar result. - In repeat dose toxicity, both Herzuma and Herceptin showed similar responses. In 13-week repeat study, reduced heartbeats were observed in both groups at 6 and 13 weeks. No immunogenicity was observed in both groups. - In ADME studies, single and 4 week repeat dose IV studies in monkey showed similar PK profile.
	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-P6 1.1 Summary of design: Comparative PK study for Double-blind, randomized, Parallel group, phase I/IIb trial Population: Metastatic Breast Cancer patient with active disease (Randomized 170: Herceptin: 85 and Herzuma: 85) Objective and primary endpoint: Demonstration of equivalence PK in terms of area under the curve at steady state (AUC_{SS}) between Herzuma and Herceptin in patients with metastatic breast cancer. Dose used: Initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks, plus paclitaxel (175 mg/m^2) in 3 week cycles, over 1 year. Length of the Study: Until disease progression, death, or discontinuation **Study Number: CT-P6 1.2** Summary of design: Initial PK study for CT-P6 in combination with paclitaxel, phase I trial Population: 8 patients with active disease Metastatic Breast Cancer

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	Objective and primary endpoint: collection of PK information of CT-P6 in patients with metastatic breast cancer. Dose used: CT-P6 at an initial dose of 8 mg/kg, then at a dose of 6 mg/kg every 3 weeks. All patients also received paclitaxel (175 mg/m^2) in 3-week cycles. Length of the study: until disease progression, death, or discontinuation **Study Number: CT-P6 1.3** Summary of design: Initial comparative PK study for CT-P6 and Herceptin with double-blind, randomized, parallel group, phase 1 trial Population: Active disease Metastatic Breast Cancer (CT-P6 4, Herceptin 3 patients) Objective: Demonstration of comparable pharmacokinetics (PK), in terms of trough concentration (C_{trough}) prior to the second dose, between CT-P6 and the comparator, Herceptin, in patients with metastatic breast cancer (MBC). Dose used: an initial dose (8 mg/kg) of CT-P6 or Herceptin and then a dose of 6 mg/kg of CT-P6 or Herceptin every 3 weeks. All the treated patients also received Paclitaxel (175 mg/m^2) in 3-week cycles. Length of the study: until disease progression, death, or discontinuation.
NRA	**Clinical data. PK data assessment outcome**
	The primary PK endpoint, the geometric mean of AUC at steady state (AUC_{SS}) at cycle 8 was comparable in the CT-P6 and Herceptin. The 90% CI of geometric mean of AUC_{SS} was 93.6% ~ 116.8%, 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.
NRA	**Clinical data. PD data assessment outcome** No specific PD study was conducted due to no relevant biomarker of therapeutic activity.
MAH	**Clinical data. Efficacy studies**
	Study Number: CT-P6 3.1 Summary of design: Efficacy and safety study of CT-P6 and Herceptin with double-blind, randomized, parallel group, phase 3 trial. Population: Metastatic Breast Cancer patient with active disease (Randomized 366: Herzuma: 244, Herceptin 231 patients) Objective: Demonstration of equivalence of Herzuma and Herceptin, both given in combination with paclitaxel, in terms of efficacy determined by overall response rate (ORR). Equivalence margin was ± 15% Dose used: CT-P6 or Herceptin at an initial dose of 8 mg/kg, then at a dose of 6 mg/kg every three weeks. All patients also received paclitaxel (175 mg/m^2) in 3-week cycles. Length of the study: 6 months
NRA	**Clinical data. Efficacy data assessment outcome**
	The results of the primary endpoints met the equivalence margin both in the full analysis population and per protocol population. The primary endpoint which is overall response rate at 6 month confirmed by ITRC(Independent Tumour Review Committee) was met the equivalence criteria(±15%)

	FAS set		PP set	
	CT-P6(244)	Herceptin(231)	CT-P6(236)	Herceptin(228)
ORR(CR+PR)(%)	138(56.6%)	143(61.9%)	135(57.2%)	142(62.3%)

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	95% CI	[-0.143:0.036]		[-0.141:0.041]	

Secondary endpoints which were time to progression, time to response at one year, disease progression or death due to disease at one year, best changes in total target lesion size were similar between Herzuma and Herceptin. Other secondary endpoints which are progression free survival and overall survival were not reported at the time of authorization.

MAH	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)
	Safety and immunogenicity data were collected from all clinical study; CT-P6 1.1, 1.2, 1.3 and 3.1.
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**
	1. Safety: The overall adverse event profile collected from all clinical studies was similar for both Herzuma and Herceptin groups. The percentage of TEAE in Herzuma and Herceptin were 89.3% and 90.9% respectively. 2. Immunogenicity Immunogenicities of Herzuman and Herceptin from all clinical studies were very low (<1%).
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 - Period: 2014. 1.15~2018. 1.14	
NRA	**Post-authorization measures assessment outcome.**	
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MAH	**Availability of additional relevant information in the local language/ link**	As required / appropriate

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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 Herzuma were comparable to those of the reference biotherapeutic product Herceptin.

Nonclinical
No major differences in nonclinical data were observed for Herzuma compared to the reference biotherapeutic product Herceptin .

Clinical Studies
The PK / PD / efficacy studies to demonstrate biosimilarity conducted in metastatic breast cancer patients provided robust evidence of therapeutic equivalence between Herzuma and the reference biotherapeutic product Herceptin

Safety: The ADRs observed with Herzuma were in the same range as the ADRs observed with the reference biotherapeutic product Herceptin.

Immunogenicity: The proportions of patients who developed anti-drug antibodies (ADA) with Herzuma and the reference biotherapeutic product Herceptin were very low (less than 1%).

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 Herzuma was considered approvable.

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