Chong Kun Dang Ranibizumab inj.

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Chong Kun Dang Ranibizumab inj.
MAH	**MAH**	Chong Kun Dang Pharm. 8, Chungjeong-ro, Seodaemun-gu, Seoul, Republic of Korea
NRA	**Authorisation / Licence number**	Chong Kun Dang pharmaceutical Corp./ 5353
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential – Not Released
MAH	**Name of the active substance**	Ranibizumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: S01LA04
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Clear to slightly opalescent, colorless to pale yellow solution
MAH	**Quantitative composition**	0.5 mg/vial (10 mg/mL)
MAH	**Route of administration**	Intravitreal (IVT)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 42 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS 2021)

MAH	**Date of authorisation/licensing of biosimilar**	20 October 2022
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Lucentis
MAH	**Authorised indications for RBP**	Neovascular (wet) age-related macular degeneration (AMD) Visual impairment due to diabetic macular oedema (DME) Proliferative diabetic retinopathy (PDR) Visual impairment due to macular oedema secondary to Retinal vein occlusion (branch RVO or central RVO) Visual impairment due to choroidal neovascularization (CNV) Retinopathy of prematurity (ROP) in preterm infants
MAH	**Pharmaceutical form**	Clear to slightly opalescent, colorless to pale yellow soltuion
MAH	**Quantitative composition**	0.5 mg/vial (10 mg/mL)
MAH	**Route of administration**	Intravitreal (IVT)
MAH	**Packaging/material**	Glass vial
MAH	**Package size(s)**	1 vial/pack
MAH	**Authorisation (Licence) number (of RBP)**	Novartis Korea Ltd.
MAH	**Date of authorisation (of RBP)**	27 July 2007
MAH	**Authorisation (Licence) Holder (of RBP)**	Ranibizumab (INN)
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=200708787aupdateTs2023-07-03%2017:55:00.0b
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data form: Physicochemical and biological charaterization, *In vitro* and *In vivo* non-clinical studies, toxicological study, PK, efficacy, safety and immunogenicity studies

NRA	**Availability of full assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBAC02/getItem?searchYn=true&title=%EB%A3%A8%EC%84%BC%EB%B9%84%EC%97%90%EC%8A%A4%EC%A3%BC&totalPages=2&limit=10&page=1&jdgmnResultInfoSeq=20220000203
MAH	**Indications applied for** (if different to RBP)	The indication applied for authorized for RBP not included retinopathy of premature
NRA	**Authorised indications for biosimilar**	Neovascular (wet) age-related macular degeneration (AMD) Visual impairment due to diabetic macular oedema (DME) Proliferative diabetic retinopathy (PDR) Visual impairment due to macular oedema secondary to Retinal vein occlusion (branch RVO or central RVO) Visual impairment due to choroidal neovascularization (CNV)

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>	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Ranibizumab L-Histidine L-Histidine hydrochloride hydrate α,α-Trehalose dihydrate Polysorbate 20 Water for injection
MAH	**Quality data. State-of-the-art methods**
	Physicochemical Properties N-terminal/C-terminal sequence, Amino acid sequence, Post-translational modification, Amino acid composition, Disulfide bond, Free thiol content, Molecular weight (LC-MS, NR/R SDS-PAGE), Extinction coefficient, Isoelectric point (IEF, cIEF), Secondary and tertiary structure (CD spectrum, FT-IR, Fluorescence spectrum), Thermal stability(DSC), Particles (MFI, DLS), Size variants (SE-HPLC, SEC-MALS, CE-SDS (NR/R)), Charge variants (WCX-HPLC), Hydrophobic variants (RP-UPLC), Protein content (UV), Polysorbate 20 content (FMA), Extractable volume (Volume measurement). **Biological properties** VEGF ($VEGF_{165}$, $VEGF_{121}$, $VEGF_{110}$) binding affinity (SPR, ELISA), VEGF ($VEGF_{165}$, $VEGF_{121}$, $VEGF_{110}$) neutralizing assay.

	Immunochemial properties Western blot analysis
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head comparability studies performed using state-of-the art analytical procedures demonstrated that all major quality attributes of Chong Kun Dang Ranibizumab inj. were comparable to those of Lucentis with respect to physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from KR Lucentis. Through various condition of forced degradation studies (temperature stress (40°C), photostability, oxidation and high pH stress), it was confirmed that degradation patterns between Chong Kun Dang Ranibizumab inj. and Lucentis were also similar. Overall, based on the totality of evidence with respect to all quality characteristics and clinical studies, the biosimilarity of Chong Kun Dang Ranibizumab inj. to Lucentis was concluded.
MAH	**Mechanism of action**
	Chong Kun Dang Ranibizumab inj. is a humanized recombinant monoclonal antibody fragment. It binds to the receptor binding site of human vascular endothelial growth factor A (VEGF-A).
MAH	**Nonclinical data. *In vitro* studies**
	VEGF neutralizing assay ($VEGF_{165}$, $VEGF_{121}$, $VEGF_{110}$)
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** **Pharmacokinetics** Pharmacokinetic study in NZW rabbits following single intravitrenous injection of Chong Kun Dang Ranibizumab inj. and Lucentis Comparative analysis of exposure in serum, aqueus humor and vitreous humor between Chong Kun Dang Ranibizumab inj. and Lucentis **Toxicity Study (including TK)** 4-week Intravitreal (IVT) Toxicity Study in the Monkey followed by a 4-week recovery period in comparison to Lucentis (ranibizumab).
NRA	**Nonclinical data assessment outcome**
	1. ***In vitro* studies** See Quality assessment outcome 2. ***In vivo* studies** A repeated-dose toxicity study, Chong Kun Dang Ranibizumab inj. and Lucentis were

	well tolerated with no physiology related effects. There was comparable TK profiles (Cmax, Tmax and AUC0-t) without any difference in immunogenicity profiles between Chong Kun Dang Ranibizumab inj. and Lucentis treated group. Pharmacokinetic studies showed similar properties between two groups.
	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**
	No specific PK study was conducted.
NRA	**Clinical data. PK data assessment outcome**
	Not applicable
MAH	**Clinical data. PD studies**
	No specific PD study was conducted.
NRA	**Clinical data. PD data assessment outcome**
	Not applicable
MAH	**Clinical data. Efficacy studies**
	Study Number: 177AMD17019 Summary of design : A Multicenter, Randomized, Double-blind, Active-controlled, Parallel group, Phase III Clinical Trial Population: patients with neovascular (wet) age-related macular degeneration (AMD) 312 subjects (Chong Kun Dang Ranibizumab inj. group: 156 subjects, Lucentis group: 156 subjects) Objective and endpoint: Evaluation the Efficacy, Safety, Pharmacokinetics and Immunogenicity of Chong Kun Dang Ranibizumab inj. and Lucentis in Patients with Neovascular(wet) Age related Macular Degeneration Dose used: ranibizumab 3 mg/0.3 mL as a single dose Length of the study : 12 months
NRA	**Clinical data. Efficacy data assessment outcome**
	This study(177AMD17019) met its primary end points, demonstrating equivalence in efficacy between the proposed biosimilar product intravitreous Chong Kun Dang

Ranibizumab inj. and Lucentis.

- When the proportion of subjects who lost <15 letters in BCVA score from baseline at 3 months was compared between the treatment groups of the PPS, which was the primary analysis set, the 95% confidence interval [-3.63, 2.32] for the difference between the Chong Kun Dang Ranibizumab inj. group and Lucentis group was contained within the predefined equivalence margin of ±11.5%.

	Chong Kun Dang Ranibizumab inj. (n=146)	Lucentis (n=145)	Difference	95% CI
Proportion of subjects who lost <15 letters in BCVA score from baseline at 3 months (%)	97.95	98.62	-0.66	-3.63, 2.32

*n : number of patients in the per-protocol set

In addition, as a result of additional analysis of the change in BCVA after 8 weeks, similar results were confirmed between administration groups.

	Chong Kun Dang Ranibizumab inj. (n=146)	Lucentis (n=145)	LS-Mean (SE) Difference	95% CI	P-Value[1]
	Least Squares-Mean (SE)	Least Squares-Mean (SE)			
The change in BCVA after 8 weeks	5.87	5.32	0.55	-1.32, 2.43	0.5614

[1] ANCOVA results for LS-Mean comparison between treatment groups (Covariate: presence or absence of PCV)

MAH

Clinical data. Safety/ Immunogenicity studies

Safety data was collected from clinical study 177AMD17019. Analysed patients who received at least 1 administration of study drug during the period after randomization. Immunogenicity profile was collected from 177AMD17019 study.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

Safety. Overall incidence of AEs including TEAEs, ADRs, SAEs, SADRs, AESIs, ocular AEs in the study eye and fellow eye, and non-ocular AEs were similar between Chong Kun Dang Ranibizumab inj. and Lucentis.

Immunogenicity. Overall immunogenicity profiles were similar between the Chong Kun Dang Ranibizumab inj. and Lucentis.

MAH

Interchangeability data

No additional data were provided

MAH

Additional information about the comparability exercise	Not applicable

MAH	**Post-authorization measures**	
	Re-examination study in Korea. - Period: 2022. 10. 20. ~ 2026. 10. 19	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. Number of subjects of Chong Kun Dang Ranibizumab inj. for re-examination 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
All major physicochemical characteristics and biological activities of Chong Kun Dang Ranibizumab inj. were comparable to those of the reference biotherapeutic product Lucentis.

Nonclinical
No major differences in nonclinical data were observed for Chong Kun Dang Ranibizumab inj. compared to the reference biotherapeutic product Lucentis.

Clinical Studies
The PK / efficacy studies to demonstrate biosimilarity conducted in (w)AMD patients provided robust evidence of therapeutic equivalence between Chong Kun Dang Ranibizumab inj. and the reference bioterapeutic product Lucentis.

Safety: The ADRs observed with Chong Kun Dang Ranibizumab inj. were in the same range as the ADRs observed with the reference biotherapeutic product Lucentis.

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with Chong Kun Dang Ranibizumab inj. was generally similar for the reference biotherapeutic product Lucentis.

Extrapolation of indications: Based on the totality of evidence, all indication requested for Chong Kun Dang Ranibizumab inj. 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 demonstarated using an appropriate comparability exercies.

The biosimilar product Chong Kun Dang Ranibizumab inj. was considered approvable.