Eucept

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Eucept
MAH	**MAH**	LG Chem, Ltd. LG Twin Tower. 128, Yeoui-daero, Yeongdeungpo-gu, Seoul, Korea
NRA	**Authorisation / Licence number**	LG Chem. / 5150, 5151
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Osong Plant LG Chem, Ltd. 151, Osongsaengmyeong 1-ro, Osong-eup, Heungdeok–gu, Cheongju-si, Chungcheongbuk-do, Korea
MAH	**Name of the active substance**	Etanercept
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB01. Immuno-suppressants, tumor necrosis factor alpha(TNFα) inhibitors
MAH	**Substance category**	Fusion protein
MAH	**Pharmaceutical form**	Solution for injection
MAH	**Quantitative composition**	25mg/0.5mL, 50 mg/1.0mL solution/pre-filled syringe 50 mg/1.0mL solution/Auto-injector
MAH	**Route of administration**	Subcutaneous
MAH	**Packaging/material**	Primary container/glass syringe
MAH	**Package size(s)**	1 pre-filled syringe/box, 4 pre-filled syringe/box 1 auto-injector/box, 4 auto-injector/box
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 and Enforcement for the drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS, 2014)

MAH	**Date of authorisation/licensing of biosimilar**	16 March 2018
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Enbrel®
MAH	**Authorised indications for RBP**	Adult · Rheumatoid arthritis · Psoriatic arthritis · Ankylosing spondylitis · Non-radiographic axial spondyloarthritis · Plaque psoriasis Paediatric · Juvenile idiopathic arthritis
MAH	**Pharmaceutical form**	Solution for injection in a pre-filled syringe Solution for injection in a pen Powder and solvent for solution for injection
MAH	**Quantitative composition**	- 50 mg of etanercept in a total volume of 1 ml - 25 mg of etanercept in a total volume of 0.5 ml - 25 mg of etanercept in powder and solvent for solution for injection
MAH	**Route of administration**	Subcutaneous
MAH	**Packaging/material**	- Syringe / glass - Vial / glass (for powder)
MAH	**Package size(s)**	4 pre-filld pen/box 4 pre-filled syringe/box 4 vial/box
MAH	**Authorisation (Licence) number (of RBP)**	Pfizer Korea/144, 145, 146, 286
MAH	**Date of authorisation (of RBP)**	12 Dec 2007 12 Jan 2017 06 Oct 2003
MAH	**Authorisation (Licence) Holder (of RBP)**	Pfizer Korea
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea Japan

MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	Provide link to public assessment report in local language for reference biotherapeutic product http://www.nifds.go.kr/brd/m_88/list.do?page=2&srchFr=&srchTo=&srchWord=%EC%97%94%EB%B8%8C%EB%A0%90#none
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from physiochemical, biological, *in vitro* and *in vivo* non-clinical studies(PK/PD study) Comparative clinical studies(PK, efficacy, safety and immunogenicity)
NRA	**Availability of full assessment report** (language)/**link**	http://www.nifds.go.kr/brd/m_88/list.do?itm_seq_1=&srchTp=0&srchWord=%EC%9C%A0%EC%85%89%ED%8A%B8#none
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorised for RBP (see section "Authorised indications" for further details)
NRA	**Authorised indications for biosimilar**	Adult · Rheumatoid arthritis(2018.03) · Psoriatic arthritis(2018.03) · Ankylosing spondylitis(2018.03) · Non-radiographic axial spondyloarthritis(2018.03) · Plaque psoriasis(2018.03) Paediatric · Juvenile idiopathic arthritis(2018.08)

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)**
	Etanercept Sodium Chloride L-Methionine Sodium dihydrogen phosphate dihydrate Sodium phosphate dibasic anhydrous Water for injection
MAH	**Quality data. State-of-the-art methods**
	Include high level summary of physicochemical test methods and biological activity studies used for characterisation (Tables may be used for clarity).

Category	Analytical Methods used for Characterization
Structural Characterisation	Amino acid anlaysis, Peptide mapping, N-terminal sequencing, C-terminal sequencing, Amino acid sequencing, Disulfide bonds ID,

	Free sulfhydryl content. Molecular weight using mass spectrometry, Oligosaccharide profiling, Sialic acid analysis, N-glycan profiling, O-glycan profiling
Physicochemical	SDS-PAGE, IEF, SE-HPLC, HI-HPLC, CEX-HPLC, UV spectrometry, Fluorescence spectrometry, Circular Dichroism, FT-IR, Micro DSC, Western blotting
Biological activity	TNF-α neutralizing activity, TNF-α binding activity, TNF-β binding activity, Fcγ Receptor binding activity, FcRn binding activity, C1q binding activity, CDC, ADCC

NRA

Quality data assessment outcome

Comprehensive head-to-head comparability studies performed using a number of orthogonal analytical methods demonstrated that all major quality attributes of Eucept were comparable to those of Enbrel® with respect to the primary and higher order structures, post-translational modifications, physicochemical and biophysical properties, and biological activities. Comparability was assessed based on the overall originator product range defined using the sufficient batches of Enbrel®.
Due to the complex heterogeneity in the structure of Etanercept, slight differences were found in the glycosylation profile, charge variants, and Fc-related activity such as Fc receptor binding and antibody-dependent cell-mediated cytotoxicity (ADCC) compared to Enbrel®. However, those differences were not considered clinically meaningful since those had no impact on the biological activities related to the primary mechanism of action, as determined by Structure-activity relationship (SAR) studies. In addition, although a slightly lower trend of mannose and sialic acid was observed, this minor difference was 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 Eucept to the Enbrel® was concluded.

MAH

Mechanism of action

Etanercept interferes with the soluble TNF-α and down-regulate immune response.

MAH

Nonclinical data. *In vitro* studies

TNF-α neutralizing activity
TNF-α binding activity
TNF-β binding activity
Fcγ Receptor binding activity
FcRn binding activity
C1q binding activity
CDC
ADCC

MAH

Nonclinical data. *In vivo* studies

Type of Study	Species
Efficacy study (Collagen Induced Arthritis model)	Mouse, DBA/1

Pharmacokinetic study	Cynomolgus monkey
13-week repeat dose toxicity including toxicokinetics and anti-drug antibody assessment	Cynomolgus monkey

NRA

Nonclinical data assessment outcome

All comparative *in vitro* primary PD studies were presented and discussed in the quality section of this report. In *in vivo* efficacy study and PK study, overall, the PK, PD and general toxicity of LBEC0101 (=Eucept) and Enbrel® are considered similar.

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

Clinical evidence for demonstrating similarity in PK between LBEC0101 and Enbrel® consists of one clinical studies

Study No.	Objectives	Design	Study Population	Endpoints
LG-ECCL003	To compare the safety and pharmacokinetic properties of LBEC0101 and Enbrel® subcutaneously injected into healthy volunteers	Randomized, double-blind, single dosing, two-sequence, two-period, cross-over	Healthy male subjects N = 48 (24 per group)	1. Safety Endpoints : AEs, ECG, etc. 2. PK Endpoints: AUC_{last}, AUC_{inf}, C_{max}

NRA

Clinical data. PK data assessment outcome

The point estimates (90% CIs) of the geometric mean ratio (GMRs: LBEC0101/Enbrel®) of AUC_{last}, AUC_{inf} and C_{max} were 0.96(0.87-1.06), 0.96(0.87-1.05), and 1.02(0.92-1.13), respectively. The calculated CIs for the log-transformed ratios of the AUC_{last}, AUC_{inf}, and C_{max}, were within the bioequivalence criteria range of 0.8-1.25.

MAH

Clinical data. PD studies

The clinical development program for Eucept aimed to demonstrate the similarity between Eucept and the reference products Enbrel® and therefore further clinical studies on the pharmacodynamics of Eucept were not conducted.

NRA

Clinical data. PD data assessment outcome

Not applicable

MAH

Clinical data. Efficacy studies

The Applicant has assessed the efficacy parameters from the clinical Phase III study.

Study No.	Objectives	Design	Study Population	Primary Endpoint
LG-ECCL002	To evaluate the similarity in efficacy after 24 weeks of treatment between LBEC0101 and Enbrel®	Randomized, double- blind, multi-center, parallel group, active control	Patients with active RA who had an inadequate response to MTX N = 374 (187 per group)	Mean change from baseline in DAS28-ESR score at Week 24

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 estimated treatment difference in change from baseline to Week 24 in DAS28-ESR between the two treatment groups was contained within the pre-specified equivalence margin(-0.6 to 0.6) in the Per-protocol Set(95% CI: -0.3768, 0.0775).

Treatment	Least Square Means with 95% CI	Estimated treatment difference with 95% CI
LBEC0101(N=164)	-3.009 (-3.1981,-2.8198)	-0.150 (-0.3768, 0.0775)
Enbrel®(N=165)	-2.859 (-3.0513, -2.6673)	

The results of the secondary efficacy endpoints (the change from baseline in DAS28–ESR score at weeks 12 and 52, ACR20 response rates at weeks 12, 24 and 52) had consistent pattern with the results of primary efficacy endpoint. These data were further supported by comparable response rates at Week 52.

MAH

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

Safety and immunogenicity data was collected from all clinical studies; LG-ECCL003, LG-ECCL002.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

1. Safety: The overall safety profile was similar for between LBEC0101 and Enbrel® treatment group
2. Immunogenicity: There was a difference in overall ADA formation between LBEC0101 and Enbrel® during the 52-week study. The results of ADA assays demonstrate that LBEC0101 is not more immunogenic than Enbrel®. Antibody formation in LBEC0101 was considered to be favorable to that in the Enbrel®, using appropriately validated methods.

The ADA formation did not seem to cause a different efficacy and safety profile.

	LBEC0101(N=187) n(%)	Enbrel®(N=187) n(%)	Treatment difference (%) 95% CI
Enbrel®-based assay			

ADA	3(1.6)	18(9.6)	-8.0(-12.6, -3.4)
NAb	0	0	
LBEC0101-based assay			
ADA	7(3.7)	28(15.0)	-11.2(-17.0, -5.4)
NAb	2(1.1)	3(1.6)	-0.5(-2.9, -1.8)

MAH	**Interchangeability data**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	Not applicable
MAH	**Post-authorization measures**	
	Post-marketing surveillance study of Eucept in Korea - Period: Mar 16, 2018 to Mar 15, 2022 - Number of subjects (600)	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. Number of subjects of Eucept for re-examination study met the MFDS criteria (over 600)	
MAH	**Availability of additional relevant information in the local language/ link**	As required /appropriate

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 Eucept were comparable to those of the reference biotherapeutic product Enbrel®

Nonclinical

No major differences in nonclinical data were observed for Eucept compared to the reference biotherapeutic product Enbrel®.

Clinical Studies

The PK and efficacy studies to demonstrate biosimilarity conducted in healthy subjects and Rheumatoid Arthritis patients provided robust evidence there are no clinically meaningful differences versus the reference biotherapeutic product Enbrel®

Safety: The ADRs observed with Eucept were similar to the ADRs observed with the reference biotherapeutic product Enbrel®

Immunogenicity: In terms of ADA formation, it was observed lower ADA incidence in Eucept group, as compared to the reference biotherapeutic product Enbrel® group during the 52-week study. The ADA formation did not seem to cause a different efficacy and safety profile.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Eucept 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.

The biosimilar product Eucept was considerable approvable.