<RENFLEXIS>

<Ministry of Food and Drug Safety>

<APPROVED>

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Renflexis
MAH	**MAH**	Samsung Bioepis Co. Ltd., Yeonsu-gu Cheomdan-daero 107 Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis / 2
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Manufacturer of the biological active substance: **Biogen (Denmark) Manufacturing ApS** Biogen Allé 1 DK-3400 Hillerød Denmark Manufacturer responsible for batch release: **Biogen (Denmark) Manufacturing ApS** Biogen Allé 1 DK-3400 Hillerød Denmark
MAH	**Name of the active substance**	Infliximab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB02. Immuno-suppressants, tumour necrosis factor alpha (TNFα) inhibitors
MAH	**Substance category**	Monoclonal antibody
MAH	**Pharmaceutical form**	Powder for concentrate for solution for infusion
MAH	**Quantitative composition**	100 mg / vial
MAH	**Route of administration**	Intravenous infusion
MAH	**Packaging/material**	Vial / glass
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**	"Guideline on the Evaluation of Biosimilar Products, Revision 1 (MFDS, Dec 2014)"
MAH	**Date of authorisation/licensing of biosimilar**	04 Dec 2015

	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Remicade
MAH	**Authorised indications for RBP**	Adult Crohn's disease Paediatric Crohn's disease Ankylosing spondylitis Adult ulcerative colitis Paediatric ulcerative colitis Rheumatoid arthritis Psoriatic arthritis Plaque Psoriasis
MAH	**Pharmaceutical form**	Powder for concentrate for solution for infusion
MAH	**Quantitative composition**	100 mg / vial
MAH	**Route of administration**	Intravenous infusion
MAH	**Packaging/material**	Vial / glass
MAH	**Package size(s)**	1 vial / pack
MAH	**Authorisation (Licence) number (of RBP)**	81-5011
MAH	**Date of authorisation (of RBP)**	Aug 23, 2005
MAH	**Authorisation (Licence) Holder (of RBP)**	Janssen Korea Co. Ltd.,
MAH	**Source of RBP (or other comparator) for comparability exercise**	European Union United States Republic of Korea
MAH / NRA	**Availability of the RBP assessment report** (Korean)/**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=19

		1&y=0&pageNo=1&seq=9456&cmd=v
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Physicochemical and biological characterisation study Comparative *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** (Korean)/**link**	http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&searchword=렌플렉시스&cd=1911&y=0&pageNo=1&seq=24099&cmd=v
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 Crohn's disease Paediatric Crohn's disease Ankylosing spondylitis Adult ulcerative colitis Paediatric ulcerative colitis Rheumatoid arthritis Psoriatic arthritis Plaque Psoriasis

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)**
	Infliximab 100 mg Sucrose polysorbate 80 monobasic sodium phosphate monohydrate dibasic sodium phosphate heptahydrate
MAH	**Quality data. State-of-the-art methods**

Category	**Analytical Methods used for Characterisation**
Structural characteristics	Amino acid sequencing, N-terminal/C-terminal sequencing & peptide mapping (HPLC, LC-MS, LC-MS/MS), molecular weight (LC-MS), deamidation/oxidation (LC-MS), N-linked glycosylation site (LC-MS/MS), disulphide bonds, free thiol analysis, FTIR, intrinsic/extrinsic fluorescence spectroscopy, CD, HDX-MS, DSC, SEC-MALLS, SV-AUC, DLS, MFI
Physicochemical characteristics	SEC-HPLC, CE-SDS (reduced/non-reduced), icIEF, IEC-HPLC, N-glycan structure (LC-MS/MS), oligosaccharide profiling (HILIC-UPLC), protein concentration (UV280), absorption coefficient
Biological activity	1) Fab related evaluations hTNF-α binding, hTNF-α neutralisation assay, transmembrane TNFα binding, apoptosis assay, hTNFβ binding 2) Fc related evaluations FcγRIa binding, FcγRIIa/FcγRIIb/FcRn binding, FcγRIIIa binding, FcγRIIIb binding, C1q binding, CDC, ADCC using modified NK cell line/human PBMC, regulatory macrophage function by mixed lymphocytes reaction, cytokine release profiling in *in vitro* IBD model, inhibitory activity of apoptosis in *in vitro* IBD model
Degradation characteristics	Temperature stresses (25°C, 40°C), photostability, oxidation induction, freeze-thaw cycling

NRA	**Quality data assessment outcome**
	All major structural, physicochemical characteristics and biological activities of Renflexis were comparable to those of Remicade. However, there were observed quantitative and qualitative differences in the relative content of C-terminal Lys, charge profile, afucosylation and %charged glycan level, binding affinity to specific Fc receptors and ADCC activities using sensitive system of NK cells and tmTNFα Jurkat cells. Specifically, Renflexis has a slightly higher level of % afucosylation, a slightly higher binding affinity to specific Fc receptors and a slightly higher NK cell-mediated ADCC activ ity as compared to those of Remicade. The sponsor performed biological assays using additi onal batches of reference product and orthogonal studies such as ADCC assay using PBMC regarded as more relevant to the physiological conditions in patients. Based on the additional results of the physicochemical and *in vitro* biological analyses, the observed minor differences in NK-mediated ADCC activities did not affect clinical safety and efficacy.

	The heterogeneity of C-terminal Lys residues is known that it has no clinical impact. Therefore these uncertainties were not considered clinically meaningful and demonstrated to be comparable to Remicade.
MAH	**Mechanism of action**
	Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα. Infliximab prevents TNFα receptor activation by binding to TNFα, thereby neutralising the biological activity of TNFα.
MAH	**Nonclinical data. *In vitro* studies** Comparison of biological activity including binding/specificity to TNF-α (refer to biological assays performed for quality analyses)
MAH	**Nonclinical data. *In vivo* studies**
	• *In vivo* efficacy study to demonstrate pharmacodynamic (PD) similarity using Tg197 transgenic mouse model of arthritis • Single and repeated dose PK studies in Sprague Dawley (SD) rats and the Tg197 mouse model of arthritis, and the evaluation of potential anti-drug antibody (ADA) formation performed to demonstrate PK and immunogenic similarities between Renflexis and Remicade
NRA	**Nonclinical data assessment outcome**
	All comparative *in vitro* primary PD studies results were presented and discussed in the quality section of this report and the difference observed in binding affinity to specific Fc receptor and ADCC activities were further discussed and analysed (see quality data assessment outcome section). In *in vivo* efficacy study and PK study, Overall, the PK and PD of Renflexis and Remicade 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**

Study	Study Objectives	Design	Study Population	Primary Endpoints

	SB2-G11-NHV (Phase I study)	Comparative PK, safety, tolerability, immunogenicity To investigate and compare the PK profiles of Renflexis (SB2) and EU Remicade® in healthy subjects.	Randomised, single-blind, three-arm, parallel group, single-dose study; Total duration: 10 weeks Single dose *i.v.* infusion of 5 mg/kg either SB2, EU or US Remicade®	159 healthy subjects (53/arm)	AUC_{inf}

NRA	**Clinical data. PK data assessment outcome**
	The 90% CIs of the geometric LSmean ratio for AUC_{inf} lied between **89.7% and 108.3%**, well contained within the standard bioequivalence interval of 80-125%; this demonstrates that the PK of infliximab is equivalent between Renflexis and Remicade at the dose of 5 mg/kg. Furthermore, equivalent PK was also shown in the antibody-negative and antibody-positive subset of the healthy subject population.
MAH	**Clinical data. PD studies**
	The clinical development programme for Renflexis aimed to demonstrate the similarity between Renflexis and the reference product Remicade and therefore further clinical studies on the pharmacodynamics of Renflexis were not conducted.
NRA	**Clinical data. PD data assessment outcome**
	Not applicable
MAH	**Clinical data. Efficacy studies**

Study	**Study Objectives**	**Design**	**Study Population**	**Primary Endpoints**
SB2-G31-RA (Phase III studies)	Safety, efficacy, immunogenicity, and PK To demonstrate the equivalence of Renflexis (SB2) to EU Remicade® at Week 30, in terms of the ACR20 response rate in subjects with moderate to severe RA despite methotrexate (MTX) therapy	Randomised, double-blind, parallel group, multicentre study; Total duration: 78 weeks Randomised, Double- Blind period: 54 weeks Transition-Extension period: 24 weeks	584 RA subjects (291 for SB2, 293 for EU-Remicade)	Efficacy: ACR20 at Week 30

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 ACR20 response rate at Week 30 was contained within the **predefined equivalence margin (± 15%)** in the Per Protocol populations **(95% CI: -10.13, 6.78)**. At week 30, the results of the secondary endpoints (in particular ACR50 and ACR70, DAS28, EULAR response) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 54.

Treatment	n/N	(%)	Adjusted Difference Rate(%)	95% CI
Renflexis	148/229	(64.6%)	-1.67	(-10.13, 6.78)
Remicade (EU)	159/241	(66.0%)		

* N: number of patients in the per-protocol set, n: number of responder
* The adjusted difference and its 95% confidence intervals were analysed by non-parametric method with baseline C-reactive protein as covariate and stratified by region.

MAH

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

Safety and immunogenicity data was collected from two studies: the Phase III study in RA patients, and the Phase I study in healthy volunteers.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

Safety. ADRs were observed. The ADRs were equivalent to the ADRs observed with the RBP.

Treatment	Renflexis N=290			Remicade N=293		
Number of subject experiencing	n	(%)	E	n	(%)	E
TEAE	167	(57.6)	499	170	(58.0)	529

* E: frequency of treatment-emergent adverse events

Immunogenicity. Antibody formation in Renflexis was considered to be comparable to that in the RBP, using appropriately validated methods.

Time point	ADA result	Renflexis N=290			Remicade N=293			p-value
		N	n	(%)	N	n	(%)	
Week 30	Positive	287	158	(55.1)	292	145	(49.7)	0.212
Week 54	Positive	287	169	(58.9)	292	161	(55.1)	0.401

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 Renflexis in Korea
- Period: Dec 04, 2015 to Dec 03, 2019
- 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 Renflexis 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 Renflexis were comparable to those of the reference biotherapeutic product Remicade.

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

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 Remicade.

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

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with Renflexis was generally similar for the reference biotherapeutic product Remicade.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Renflexis (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 Renflexis was considered approvable.