Brenzys

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Brenzys
MAH	**MAH**	Samsung Bioepis Co. Ltd., Yeonsu-gu Cheomdan-daero 107 Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis / 1
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 (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**	Etanercept (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: L04AB01. Immuno-suppressants, tumour necrosis factor alpha (TNFα) inhibitors
MAH	**Substance category**	Fusion protein
MAH	**Pharmaceutical form**	Solution for injection
MAH	**Quantitative composition**	50 mg of etanercept in a total volume of 1 ml
MAH	**Route of administration**	Subcutaneous
MAH	**Packaging/material**	Syringe / glass
MAH	**Package size(s)**	4 pre-filled syringes
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**	Sep 07, 2015

	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**	- Powder and solvent for solution for injection - Solution for injection in a pre-filled syringe
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**	- Vial / glass (for powder) - Syringe / glass
MAH	**Package size(s)**	- 4 vials per pack - 4 pre-filled syringes
MAH	**Authorisation (Licence) number (of RBP)**	87-144/145/146
MAH	**Date of authorisation (of RBP)**	Oct 06, 2003 Dec 12, 2007
MAH	**Authorisation (Licence) Holder (of RBP)**	Pfizer Pharmaceuticals Korea
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** (language)/**link**	http://www.mfds.go.kr/index.do?x=0&searchkey=product_nm&mid=1176&cd=191&searchword=엔브렐&y=0&pageNo=2&seq=6227&cmd=v http://www.mfds.go.kr/index.do?searchkey=product_nm&mid=1176&cd=191&searchword=엔브렐&pageNo=2&seq=6306&cmd=v http://www.mfds.go.kr/index.do?searchkey=product_nm&mid=1176&cd=191&searchword=엔브렐&pageNo=2&seq=6372&cmd=v http://www.mfds.go.kr/index.do?searchkey=product_nm&mid=1176&searchword=엔브렐&cd=191&pageN

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	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from: physicochemical, biological, *in vitro*, *in vivo*, PK, PD, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report** (language)/**link**	http://www.mfds.go.kr/index.do?cd=191&searchkey=product_nm&y=0&searchword=브렌시스&x=0&mid=1176&pageNo=1&seq=24094&cmd=v
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorised for RBP except paediatric use (see section “Authorised indications” for further details)

NRA	**Authorised indications for biosimilar**	Adult · Rheumatoid arthritis · Psoriatic arthritis · Ankylosing spondylitis · Non-radiographic axial spondyloarthritis · 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)**
	Etanercept 50 mg Sucrose Sodium chloride Sodium phosphate monobasic monohydrate Sodium phosphate dibasic heptahydrate Water for injection
MAH	**Quality data. State-of-the-art methods**

Category	**Analytical Methods used for Characterisation**
Structural Characterisation	Amino acid sequencing, N-terminal/C-terminal sequencing & peptide mapping (HPLC, LC-MS, LC-MS/MS), molecular weight (LC-MS), deamidation (LC-MS), N-linked glycosylation site (LC-MS/MS), Disulphide bond analysis, Peptide mapping, Met oxidation, Free sulfhydryl group quantification, H/D exchange, DSC, CD, FT-IR, N-linked glycosylation site, N-glycan identification, N-glycan profile, O-glycan Site, O-glycan identification, O-glycan profile, Total sialic acid
Physicochemical	Absorption coefficient, protein concentration, Intrinsic & Extrinsic fluoresence, MFI, DLS, SV-AUC, SEC, HP-SEC-MALLS, CE-SDS, HIC, CEX, icIEF, AEX
Biological activity	TNF-α, Binding Assay to TNF-α/ LTα3 (TNF-β) from different species(by ELISA), TNF-α neutralisation assay, FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, FcRn, C1q, ADCC, CDC, Apoptosis
Degradation characteristics	Temperature stresses, Photostability, Oxidation induction, Freeze-thaw cycling

NRA	**Quality data assessment outcome**
	All major characteristics of Brenzys including the primary and higher order structures, physicochemical characteristics, sialic acid content and biological activities related to the mechanism of action were comparable to those of Enbrel. Although, due to the complex heterogeneity in the structure of Etanercept, some differences were found in the glycosylation profile (O-glycan, afucosylation) and charge variants, those differences were not considered clinically meaningful since those had no impact on the biological activity. Based on the totality of evidence, the biosimilarity of Brenzys to the RBP was concluded.
MAH	**Mechanism of action**
	Etanercept interferes with the soluble TNF-α and down-regulate immune responses.
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

Type of Study	Species/Organism
Efficacy study (collagen antibody induced arthritis)	Mouse, BALB/c
Pharmacokinetic study	Rat, Sprague Dawley
4-Week repeat dose toxicity including toxicokinetics and anti-drug antibody assessments	Cynomolgus monkey

NRA

Nonclinical data assessment outcome

All comparative *in vitro* primary PD studies results 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 Brenzys 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 SB4 and Enbrel consists of two clinical studies:

Study	Study Objectives	Design	Study Population	Primary Endpoint(s)
SB4-G11-NHV	Comparative PK, safety, tolerability, imunogenicity To investigate and compare the PK profiles of Brenzys (SB4), US Enbrel®, and EU Enbrel® in healthy subjects	Controlled, randomized, single-blind, three-part, cross-over; Single dose	Healthy male subjects; N=138 (N=46 per part, N=23 per sequence)	AUC_{inf}, C_{max}

: The clinical Phase I study SB4-G11-NHV in healthy subjects is considered the primary PK study for demonstrating similarity in PK between SB4 and Enbrel.

Study	Study Objectives	Design	Study Population	Primary Endpoint(s)
SB4-G31-RA	PK, safety, tolerability, efficacy, immunogenicity To demonstrate the equivalence of Brenzys (SB4) to EU Enbrel® at Week 24, in terms of the ACR20 response rate in subjects with moderate to severe RA despite methotrexate (MTX) therapy	Controlled, randomized, double-blind, parallel-group, multicenter; 24 weeks / 52 weeks (+4-week safety follow-up)	RA patients on MTX; N=596 (Randomised set: SB4: 299, Enbrel®: 297)	ACR20 response rate at Week 24

	: The steady-state PK subset in the clinical Phase III study SB4-G31-RA provides supporting evidence for PK similarity in a patient population.
NRA	**Clinical data. PK data assessment outcome**
	The 90% CIs of the geometric LSmean ratio for AUC_{inf} lied between **95.8% and 104.7%** well contained within the standard bioequivalence interval of 80-125%. Also the 90% CIs of the geometric LSmean ratio for C_{max} lied between **99.4% and 109.7%**; this demonstrates that the PK of etanercept is equivalent between Brenzys and Enbrel at the dose of 50 mg.
MAH	**Clinical data. PD studies**
	The clinical development programme for Brenzys aimed to demonstrate the similarity between Brenzys and the reference product Enbrel and therefore further clinical studies on the pharmacodynamics of Brenzys 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 SB4-G31-RA (See section "Clinical data. PK studies" for further details) to demonstrate therapeutic equivalence of SB4 with the reference EU Enbrel® in an appropriate study population (RA patients).
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 24 was contained within the **predefined equivalence margin (± 15%)** in the Per Protocol populations **(95% CI: -9.41, 4.98)**. At week 24, the results of the secondary endpoints (in particular ACR50 and ACR70, DAS28) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 52.

Treatment	n/N	(%)	Adjusted Difference Rate(%)	95% CI
Brenzys(SB4)	193/247	(78.1%)	-2.22	(-9.41, 4.98)
Enbrel	188/234	(80.3%)		

* N: number of patients in the per-protocol set, n: number of responder
* The adjusted difference and its95% 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: **Clinical Phase I PK Study SB4-G11-NHV** In the clinical Phase I PK single-dose study SB4-G11-NHV, a total of 138 healthy subjects were randomized to receive single etanercept doses (50 mg via SC injection), with 91 subjects exposed to SB4. **Clinical Phase III Efficacy and Safety Study SB4-G31-RAA** A total of 596 patients were enrolled and randomized to be exposed to etanercept (50 mg once weekly; SC injection [self-administration via pre-filled syringe]) as either SB4 or EU Enbrel® in the clinical Phase III 52-week study SB4-G31-RA.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

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

Treatment	Brenzys N=299			Enbrel N=297		
Number of subject experiencing	n	(%)	E	n	(%)	E
TEAE	165	(55.2)	475	173	(58.2)	600

* E: frequency of treatment-emergent adverse events

Immunogenicity. There was a significant (p-value < 0.001) difference in overall ADA formation at week 24. The results of ADA assays demonstrate that Brenzys is not more immunogenic than Enbrel.
Antibody formation in Brenzys was considered to be favourable to that in the RBP, using appropriately validated methods.
The ADA formation did not seem to cause a different efficacy profile, neither in ADA positive nor negative patients and therefore does not have a bearing in establishing biosimilarity between Brenzys and Enbrel.

Timepoint	ADA result	Brenzys N=299			Enbrel N=297			p-value
		N	n	(%)	N	n	(%)	
Week 24	Positive	299	2	(0.7)	297	39	(13.1)	< 0.001
Week 52	Positive	299	2	(0.7)	297	39	(13.1)	

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 Brenzys in Korea
- Period: Dec 02, 2015 to Sep 06, 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 Brenzys 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 Brenzys were comparable to those of the reference biotherapeutic product Enbrel.

Nonclinical
No major differences in nonclinical data were observed for Brenzys 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 Brenzys were in the same range as the ADRs observed with the reference biotherapeutic product Enbrel.

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

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