Nesbell

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Nesbell
MAH	**MAH**	Chong Kun Dang Pharm. 8, Chungjeong-ro, Seodaemun-gu, Seoul, Republic of Korea
NRA	**Authorisation / Licence number**	Chong Kun Dang pharmaceutical Corp./ 5248, 5249, 5250, 5251, 5252
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential – Not Released
MAH	**Name of the active substance**	Darbepoetin alfa (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: B03XA02
MAH	**Substance category**	Erythropoietin type blood factors
MAH	**Pharmaceutical form**	Clear, colourless solution for injection
MAH	**Quantitative composition**	20 mcg/0.5 mL PFS 30 mcg/0.5 mL PFS 40 mcg/0.5 mL PFS 60 mcg/0.5 mL PFS 120 mcg/0.5 mL PFS
MAH	**Route of administration**	Intravenous or Subcutaneous
MAH	**Packaging/material**	Glass prefilled syringe (PFS)
MAH	**Package size(s)**	1 PFS/pack 10 PFS/pack
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 and Enforcement for drug safety article 4

MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS 2014) Guidelines on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (MFDS 2011)
MAH	**Date of authorisation/licensing of biosimilar**	29 November 2018
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Nesp
MAH	**Authorised indications for RBP**	Anemia associated with chronic renal failure (CRF) Anemia in solid cancer patients receiving chemotherapy
MAH	**Pharmaceutical form**	Clear, colourless solution for injection
MAH	**Quantitative composition**	20 mcg/0.5 mL PFS 30 mcg/0.5 mL PFS 40 mcg/0.5 mL PFS 60 mcg/0.5 mL PFS 120 mcg/0.5 mL PFS
MAH	**Route of administration**	Intravenous or Subcutaneous
MAH	**Packaging/material**	Plastic prefilled syringe (PFS)
MAH	**Package size(s)**	1 PFS/pack
MAH	**Authorisation (Licence) number (of RBP)**	13, 14, 15, 119, 120
MAH	**Date of authorisation (of RBP)**	NESP 20: 20 October 2009 NESP 30: 20 October 2009 NESP 40: 4 September 2014 NESP 60: 20 October 2009 NESP 120: 4 September 2014
MAH	**Authorisation (Licence) Holder (of RBP)**	Kyowa Kirin Korea Co., Ltd.
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?itm_seq_1=&srchTp=0&srchWord=%EB%84%A4%EC%8A%A4

		%ED%94%84
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data form : physicochemical, biological, *in vitro*, *in vivo*, PK/PD, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report** (language)/**link**	Not yet published
MAH	**Indications applied for** (if different to RBP)	The indication applied for were all authorized of RBP
NRA	**Authorised indications for biosimilar**	Anemia associated with Chronic renal failure Chemotherapy-induced anemia in cancer patients

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)**
	Dabepoetin alfa Sodium dihydrogen phosphage monohydrate Disodium phosphate dihydrate Sodium chloride Polysorbate 80 Water for injection
MAH	**Quality data. State-of-the-art methods**
	(1) Physicochemical studies : Amino acid composition, Amino acid sequencing, N-terminal/C-terminal sequencing & peptide mapping (HPLC, LC-MS/MS), Molecular weight (ESI-MS), Deamidation/Oxidation (LC-MS/MS), N-linked glycosylation site (LC-MS/MS), Disulphide bonds confirmation, UV spectroscopy, fluorescence spectroscopy, CD, DSC, SEC-MALLS, DLS, MFI, Native PAGE, R/NR SDS-PAGE, SE-HPLC, RP-HPLC, CE-SDS (intact/deglycosylated), IEF, CZE, Monosaccharide composition, Sialic acid content, Carbohydrate structure (NP-UPLC with FLD, LC-MS, WAX-UPLC), N-glycan structure & site-specific glycan profiling (LC-MS/MS), Glycosylation site occupancy (LC-MS/MS), Absorption coefficient, Protein concentration (UV280), fill volume (2) Biological activity studies : EPO receptor binding (ELISA, SPR), Cell-based potency assay, *in vivo* potency assay (Normocythaemic mice method) (3) Forced degradation studies : Temperature stress (40℃), Photostability, Oxidation induction, High pH

NRA	**Quality data assessment outcome**
	This product was developed as a biosimilar of 'NESP', which is licensed and sold domestically in Korea (developed 5 of the 6 presentations of reference product). The dosage form, route of administration are same, and CHO cell line was used as host cells, but there is a difference in formulation and container material. NESBELL was demonstrated to be comparable to NESP using extensive, orthogonal, and sensitive testing methods with multiple lots (6~30 lots) of reference product of Korea (NESP) and Japan (NESP). The comparability acceptance criteria were set reasonably and generally used a statistical approaches (equivalence testing, mean +/- 3SD) with criticality assessment of quality attributes. There were slight differences in oxidation, deamidation, N/O-glycan profile, size profile and charge profile, and hydrophobic profile. In particular, a difference in the change rate of oxidation was observed under the forced oxidation condition, which was expected to some extent due to compositional differences. In relation to these differences, the effects on quality and safety/efficacy were evaluated using structure-activity studies, additional batch analyses and the additional complementary analytical methods. Based on additional data, these differences were considered to have no clinically significant impact and adequately support the conclusion that NESBELL is highly similar to KOREA NESP. In addition, a risk mitigation strategy has been applied, such as applying enhanced specifications of drug substance and drug product with respect to higher change levels of oxidation and some purity profiles under stressed condition due to formulation difference.
MAH	**Mechanism of action**
	Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream.
MAH	**Nonclinical data. *In vitro* studies**
	Biological potency test (Cell based assay)
MAH	**Nonclinical data. *In vivo* studies**
	***In vivo* pharmacological study** Biological potency test (Normocythaemic mice) **Pharmacokinetics** Pharmacokinetic and pharmacodynamic study in Sprague Dawley rat following single intravenous administration of Nesbell and Nesp Comparative analysis of absorption between Nesbell and Nesp

	Toxicity Study (including TK) Comparative 90 day toxicity Study in the rat by intravenous administration with a recovery period Comparative local tolerance study in the rat by SC administration between Nesbell and Nesp
NRA	**Nonclinical data assessment outcome**
	1. *In vitro* studies See Quality assessment data out come 2. *In vivo* studies *In vivo* pharmacological study showed similar phamacodynamic properties between Nesbell and Nesp treated group. Pharmacokinetic studies showed similar properties between two groups. TK studies in repeat dose toxicity in rat, showed similar PK profile (C_{max}, T_{max} and AUC_{0-t}). A repeated-dose toxicity study, Nesbell and Nesp were well tolerated with no physiology-related effects. There was no difference detected in immunogenicity profiles between Nesbell and Nesp treated group.

	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: 136HPS12C (SC) Summary of design : Pharmacokinetics study with randomized, double-blind, active control, two-treatment, two-period, two-sequence, single dosing, crossover, phase 1 trial Population: healthy male volunteers (17 subjects in each group, total 34 subjects) - Group A : Period 1 Nesbell / Period 2 Nesp - Group B : Period 1 Nesp / Period 2 Nesbell Objective and primary endpoint: Evaluation safety, tolerability and pharmacokinetics of Nesbell as a single dose SC injection. Exploration the immunogenicity of Nesbell as a single dose SC injection. Comparision the pharmacokinetic and pharmacodynamic characteristics of Nesbell and Nesp, an active control, when administered as a single dose SC injection. Dose used: 60 mcg of Nesbell or Nesp Length of the study : 18 weeks Study Number: 136HPS12D (IV) Summary of design : Pharmacokinetics study with randomized, double-blind, active control,

	two-treatment, two-period, two-sequence, single dosing, crossover, phase 1 trial Population: healthy male volunteers (15 subjects in each group, total 30 subjects) - Group A : Period 1 Nesbell / Period 2 Nesp - Group B : Period 1 Nesp / Period 2 Nesbell Objective and primary endpoint: Evaluation safety, tolerability and pharmacokinetics of Nesbell as a single dose IV injection. Exploration the immunogenicity of Nesbell as a single dose IV injection. Comparision the pharmacokinetic and pharmacodynamic characteristics of Nesbell and Nesp, an active control, when administered as a single dose IV injection. Dose used: 60 mcg of Nesbell or Nesp Length of the study : 15 weeks
NRA	**Clinical data. PK data assessment outcome**
	The primary PK results, the geometric LSMean ratio for the comparison of Nesbell and Nesp for PK parameters (AUC_{inf}, AUC_{last} and C_{max}) were comparable between the Nesbell and Nesp. Nesbell and Nesp for SC showed comparability between the two products as the 90% CIs of the geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 1.03, 1.09 and 1.06 respectively, and these were all within the acceptance range of 80-125%. Nesbell and Nesp for IV showed comparability between the two products as the 90% CIs of geometric mean ratios for AUC_{inf}, AUC_{last} and C_{max} were 1.03, 1.07, 1.05, respectively, and these were all within the acceptance range of 80-125%. Therefore, Nesbell and Nesp were concluded to be similar.
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: 136Ane14005 (SC, Correction phase) Summary of design : Efficacy and safety study with randomized, double-blind, multi-center, phase 3 trial Population: Patients with chronic renal failure not receiving dialysis (Nesbell 118, Nesp 130 patients; total 248 subjects) Objective and endpoint: Evaluation the efficacy and safety of Nesbell or Nesp administered subcutaneously for treatment of anemia in patients with chronic renal failure not receiving dialysis. Dose used: 20mcg~120mcg as a single dose Length of the study : 120 weeks Study Number: 136Ane14004 (IV, Maintenance phase) Summary of design : Efficacy and safety study with randomized, double-blind, multi-center, phase 3 trial

Population: Patients with chronic renal failure not receiving dialysis (Nesbell 203, Nesp 200 patients; total 403 subjects)
Objective and endpoint: Evaluation the efficacy and safety of Nesbell or Nesp administered intravenously for treatment of anemia in patients with chronic renal failure receiving hemodialysis.
Dose used: 20mcg~180mcg as a single dose
Length of the study : 107 weeks

NRA

Clinical data. Efficacy data assessment outcome

Correction phase
The efficacy and safety trial in chronic renal failure patients achieved its primary endpoint since the 95% confidence interval for the difference in the increasing hemoglobin level and mean dose at Week 20-24 was contained within the predefined equivalence margin(±0.5g/dl, ±36mcg) in the Per Protocol population (95% CI: - 0.21, 0.24 and -6.86, 4.06) respectively

Variable	Nesbell N=81	Nesp N=102	Difference	95% CI
Increasing of Hb (g/dl)	2.13	2.12	0.01	-0.21, 0.24
Mean dose (mcg)	29.63	31.03	-1.40	-6.86, 4.06

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

Maintenance phase
The efficacy and safety trial in dialysis chronic renal failure patients achieved its primary endpoint since the 95% confidence interval for the difference in the increasing hemoglobin level and mean dose at Week 20-24 was contained within the predefined equivalence margin(±0.5g/dl, ±27mcg) in the Per Protocol population (95% CI: - 0.19, 0.12 and - 2.92, 16.07) respectively.

Variable	Nesbell N=144	Nesp N=148	Difference	95% CI
Increasing of Hb (g/dl)	-0.01	0.03	-0.04	-0.19, 0.12
Mean dose (mcg)	74.90	61.96	6.58	-2.92, 16.07

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

MAH

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

Safety data were collected from all clinical study; 136HPS12C & 136HPS12D (healthy male volunteers), 136Ane14005 & 136Ane14004 (Patients with chronic renal failure). Analysed patients who administered at least one or partial dose of either of the study treatments during any dosing period.
Immunogenicity profile was collected from 136Ane14005 study.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

Safety. Overall incidence of TEAEs and SAE were comparable across all treatment group. And safety profile was similar between Nesbell and Nesp.

Immunogenicity. Overall immunogenicity profiles were similar between the Nesbell and Nesp treatment group.

MAH	**Interchangeability data**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	Not applicable
MAH	**Post-authorization measures**	
	Re-exzmination study in Korea. - Period: 2018. 11. 29. ~ 2022. 11. 28	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable. Number of subjects of Nesbell 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

The biosimilar manufacturer has developed and validated a process capable of consistently manufacturing a product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to cGMP requirements.

The quality attributes of high relevance for clinical safety and efficacy, e.g. physicochemical characteristics and biological activities of Nesbell were comparable to those of the reference biotherapeutic product Nesp.

Nonclinical

No major differences in nonclinical data were observed for Nesbell compared to the reference biotherapeutic product Nesp.

Clinical Studies

The Phase I and Phase III studies to demonstrate biosimilarity conducted in healthy volunteers and chronic renal failure patients provided robust evidence there are no clinically meaningful differences versus the reference biotherapeutic product Nesp .

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

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with Nesbell

was generally similar for the reference biotherapeutic product Nesp.

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