PANPOTIN

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Panpotin Prefilled Syringe 2000IU (Epoetin alfa) Panpotin Prefilled Syringe 4000IU (Epoetin alfa)
MAH	**MAH**	PanGen Biotech Inc. Woncheon-dong, 4F Innoplex 2-dong 306, Sinwon-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea
NRA	**Authorisation / Licence number**	PanGen Biotech Inc./ 3 and 4
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Confidential – Not Released
MAH	**Name of the active substance**	Epoetin alfa
MAH	**Pharmaco-therapeutic group**	ATC code: B03XA01
MAH	**Substance category**	Other hormones (Epoetin alfa)
MAH	**Pharmaceutical form**	Clear, colorless injection solution filled in glass material pre-filled syringe with single-use injection needle
MAH	**Quantitative composition**	2000 IU/0.5 mL, 4000 IU/0.4 mL
MAH	**Route of administration**	IV (Intravenous)
MAH	**Packaging/material**	Prefilled Syringe (Type I Glass)
MAH	**Package size(s)**	6 prefilled syringes / case
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 31 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	Guideline on Evaluation of Biosimilar Product (MFDS, 2014)

MAH	**Date of authorisation/licensing of biosimilar**	28 November 2019
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	EPREX
MAH	**Authorised indications for RBP**	Symptomatic Anemia or Anemia for Transfusion associated with Chronic renal failure
MAH	**Pharmaceutical form**	Solution for injection in pre-filled syringe. Clear, colourless solution.
MAH	**Quantitative composition**	2000 IU/0.5 mL, 4000 IU/0.4 mL, 10,000 IU/mL, 40,000 IU/mL
MAH	**Route of administration**	IV (Intravenous), SC (Subcutaneous)
MAH	**Packaging/material**	Prefilled Syringe (Type I Glass)
MAH	**Package size(s)**	Package contains 6 pre-filled syringes
MAH	**Authorisation (Licence) number (of RBP)**	[Malaysia] EPREX 2000IU/0.5ml: MAL19962530A EPREX 4000IU/0.4ml: MAL19962532A [Germany] ERYPO FS 2000 I.E./0,5 ml: 32077.02.00 ERYPO FS 10 000 I.E./ml: 32077.05.00 ERYPO FS 40 000 I.E./ml: 64493.00.00 [Switzerland] EPREX: 49078 [Turkey] EPREX 2000IU/0.5ml: 26.12.2003-115/19
MAH	**Date of authorisation (of RBP)**	[Malaysia] N/A [Germany] N/A [Switzerland] N/A [Turkey] N/A
MAH	**Authorisation (Licence) Holder (of RBP)**	[Malaysia] JOHNSON & JOHNSON SDN BHD (3718-D) [German] JANSSEN-CILAG GmbH [Switzerland] JANSSEN-CILAG AG, Zugo, ZG [Turkey] Gürel İlaç Ticaret A.Ş.
MAH	**Source of RBP (or other comparator) for comparability**	EPREX in Malaysia ERYPO FS in Germany

	exercise	EPREX in Switzerland EPREX in Turkey
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	Unknown
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Physicochemical and biological, in vitro and in vivo functional study Toxicological study PK/PD study Efficacy study (safety and efficacy)
NRA	**Availability of full assessment report** (language)/**link**	N/A
MAH	**Indications applied for** (if different to RBP)	N/A
NRA	**Authorised indications for biosimilar**	Symptomatic Anemia or Anemia for Transfusion associated with Chronic renal failure

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)**
	Epoetin alfa 2000 IU/0.5 mL, Epoetin alfa 4000 IU/0.4 mL
MAH	**Quality data. State-of-the-art methods**
	(1) Physicochemical studies : Amino acid sequencing, N-terminal/C-terminal sequencing & peptide mapping (HPLC, LC-MS/MS), Molecular weight (LC-MS), Deamidation/Oxidation (LC-MS), Acetylation (HILIC-UPLC-FLD/MS), N/O-linked glycosylation site (LC-MS/MS), disulphide bonds confirmation, fluorescence spectroscopy, FT-IR, CD, NMR, DLS, DSC, SEC-MALS, R/NR SDS-PAGE, SE-HPLC, RP-HPLC, IEF, CZE, Monosaccharide composition, Sialic acid content, Oligosaccharide profiling (HILIC-UPLC-FLD/MS, WAX-UPLC-FLD/MS), N-glycan structure & site-specific glycan profiling (LC-MS/MS), Glycosylation site occupancy (LC-MS/MS), O-glycan profiling (LC-MS, LC-MS/MS), NGNA, Absorption coefficient, Protein concentration (UV280), fill volume, Particulate profiling(FlowCam) (2) Immunological studies R/NR SDS-PAGE/Western blotting (3) Biological activity studies EPO receptor binding (SPR), Cell-based potency assay, in vivo potency assay (Normocythaemic mice method) (4) Forced degradation studies : Temperature stresses, Photostability, Oxidation induction,

	Low/High pH, freeze-thaw, agitation
NRA	**Quality data assessment outcome**
	This product was developed as a biosimilar of 'EPREX' with two(2) of the four(4) presentation of reference product, which had been licensed and sold domestically in Korea (withdrawn in 2004). The dosage form, route of administration and formulation are same, and CHO cell line was used as host cells. PANPOTIN was demonstrated to be comparable to EPREX using extensive, orthogonal, and sensitive testing methods with multiple lots (14 lots) of reference products of Malaysia (4 lots), Germany (4 lots) and Switzerland (6 lots). The comparability acceptance criteria were set reasonably and generally used a statistical approaches (equivalence testing, mean +/- 3SD) with criticality assessment of quality attributes from analytic data of multiple lots (2~33 lots) of reference product (Malaysia, Germany, Switzerland). There were slight differences in N-glycan profile, size profile and charge profile between PANPOTIN and reference product from multiple countries. In relation to these differences, the effects on quality and safety/efficacy were evaluated using structure-activity studies and additional complementary analytical methods. Based on these data, differences were considered to have no clinically significant impact and adequately support the conclusion that PANPOTIN is highly similar to EPREX. .
MAH	**Mechanism of action**
	Epoetin 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** Comparative pharmacodynamics/pharmacokinetics of PANPOTIN compared to EPREX following daily intravenous administration over 5 days to Beagle dogs in a cross-over design. **Toxicity Study (including TK)** Comparative toxicity study following daily IV administration with 100 IU/kg or 500 IU/kg of

	PANPOTIN and EPREX for 4 weeks to Beagle dogs consisting of males and females. 2-weeks recovery period was allowed to some animals. Toxicokinetics of PANPOTIN and EPREX were obtained at Day 0 and Day 28.
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 PANPOTIN and EPREX treated group. Pharmacokinetic studies showed similar properties between two groups. TK studies in repeat dose toxicity in Beagle dogs, showed similar PK profile (C_{max}, T_{max} and AUC_{0-t}). In a repeated-dose toxicity study, PANPOTIN and EPREX were well tolerated with no physiology-related effects. There was no difference detected in toxicity profiles between PANPOTIN and EPREX 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: PG-EPO-Ph1 (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: 27 healthy male volunteers - PANPOTIN/EPREX (13 subjects completed) - EPREX/PANPOTIN (14 subjects completed) Objective and primary endpoint: Evaluation safety, tolerability and pharmacokinetics of PANPOTIN as a single dose IV injection. Exploration of the immunogenicity of PANPOTIN as a single dose IV injection. Comparision of the pharmacokinetic characteristics of PANPOTIN and EPREX, an active control, when administered as a single dose IV injection. Dose used: Single dose administration of 100 IU/kg of PANPOTIN or EPREX Length of the study : 12 weeks in total
NRA	**Clinical data. PK data assessment outcome**
	The primary PK results, the geometric mean ratio for the comparison of PANPOTIN and EPREX for PK parameters (AUC_{inf}, AUC_{last} and C_{max}) were comparable between the PANPOTIN and EPREX .

	PANPOTIN and EPREX for IV showed comparability between the two products as the geometric mean ratios for C_{max} and AUC_{last} were 100.45 and 96.45, respectively, and their 90% CI for C_{max} and AUC_{last} were [96.38, 104.69] and [92.68, 100.37], respectively. The 90% CI of the geometric mean ratio for C_{max} and AUC_{last} fell within the acceptance range of 80-125%. Therefore, PANPOTIN and EPREX were concluded to be similar.
MAH	**Clinical data. PD studies**
	Study Number: PG-EPO-Ph1 (IV) Summary of design: PD study was implemented simultaneously with PK study mentioned above. The absolute reticulocyte count as the most relevant PD marker was determined up to 28 days following single-dose IV administration of EPREX or PANPOTIN to 27 healthy male volunteers. Population: - PANPOTIN/EPREX (13 subjects completed) - EPREX/PANPOTIN (14 subjects completed) Objective and endpoint: Comparision of pharmacodynamic characteristics of PANPOTIN and EPREX, an active control, when administered as a single dose IV injection. Dose used: Single dose administration of 100 IU/kg of PANPOTIN or EPREX Length of the study : 12 weeks in total
NRA	**Clinical data. PD data assessment outcome**
	The PD results, the geometric mean ratio for the comparison of PANPOTIN and EPREX for PD parameters (E_{max} and $AUEC_{last}$) were comparable between the PANPOTIN and EPREX . PANPOTIN and EPREX for IV showed comparability in PD parameters for reticulocyte count between the two products as the geometric mean ratios for E_{max} and $AUEC_{last}$ were 97.17 and 103.32, respectively, and their 90% CI for E_{max} and $AUEC_{last}$ were [89.71, 105.25] and [98.45, 108.44], respectively. The 90% CI of the geometric mean ratio for E_{max} and $AUEC_{last}$ fell within 80-125%. Therefore, PANPOTIN and EPREX were concluded to be similar
MAH	**Clinical data. Efficacy studies**
	Study Number: PG-EPO-Ph3 (IV) (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 receiving hemodialysis (PANPOTIN 136, EPREX 120 subjects; total 256 subjects) Objective and endpoint: Evaluation the efficacy and safety of PANPOTIN and EPREX administered intravenously for treatment of anemia in patients with chronic renal failure receiving hemodialysis. Dose used: The IV dose has to be adjusted individually to maintain hemoglobin between 10 ~ 12 g/dL Length of the study : 64 weeks

NRA

Clinical data. Efficacy data assessment outcome

Maintenance phase
The efficacy and safety trial in chronic renal failure patients treated by dialysis achieved its primary endpoint since the 95% confidence interval for the LS mean difference in the increasing hemoglobin level and LS mean dose difference from baseline period at Week 24-28 was contained within the predefined equivalence margin (±0.5g/dl, ±45IU/kg/week) in the Per Protocol population respectively.

Variable	PANPOTIN N=136	EPREX N=120	Difference	95% CI
Increasing of Hb (g/dl)	-0.259	-0.194	-0.066	-0.249, 0.117
Mean dose (IU/kg/week)	9.55	-8.71	18.26	8.31, 28.21

*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; PG-EPO-Ph1 (IV) (healthy male volunteers), PG-EPO-Ph3 (IV) (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 PG-EPO-Ph3 study.

NRA

Clinical data. Safety/ Immunogenicity data assessment outcome

Safety. Overall incidence of TEAEs and SAE were comparable in all treatment groups. And safety profile was similar between PANPOTIN and EPREX.

Immunogenicity. Overall immunogenicity profiles were similar between PANPOTIN and EPREX treatment groups.

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: 2019. 11. 28. ~ 2023. 11. 27

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 subjects)

MAH

Availability of additional | Not applicable

	relevant information in the local language/ link	

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 PANPOTIN were comparable to those of the reference biotherapeutic product EPREX.

Nonclinical

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

Clinical Studies

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

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

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with PANPOTIN was generally similar to that of the reference biotherapeutic product EPREX.

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