Xbryk® 120 mg Solution for Injection

Ministry of Food and Drug Safety

APPROVED

PART A - ADMINISTRATIVE INFORMATION

Entered by:	Biosimilar Product Information	
MAH	**Name of the biosimilar medicinal product**	Xbryk® 120 mg solution for injection
MAH	**MAH**	Samsung Bioepis Co. Ltd., 76, Songdogyoyuk-ro, Yeonsu-gu Incheon, Republic of Korea
NRA	**Authorisation / Licence number**	Samsung Bioepis Co. Ltd., / 13
MAH / NRA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Not disclosable
MAH	**Name of the active substance**	Denosumab (INN)
MAH	**Pharmaco-therapeutic group**	ATC code: M05BX04
MAH	**Substance category**	Monoclonal antibodies
MAH	**Pharmaceutical form**	Clear, colorless to slightly yellow, sterile and preservative-free solution for injection
MAH	**Quantitative composition**	120 mg / 1.7 ml
MAH	**Route of administration**	Subcutaneous (SC)
MAH	**Packaging/material**	Vial / glass
MAH	**Package size(s)**	1 vial/box (vial (1.7 mL))
MAH	**Local legal basis**	Pharmaceutical Affairs Act article 42 and Enforcement for drug safety article 4
MAH	**Local biosimilar guidelines**	Guidelines on the Evaluation of Biosimilar Products (MFDS 2021)

MAH	**Date of authorisation/licensing of biosimilar**	May 30, 2025
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Xgeva Injection
MAH	**Authorised indications for RBP**	Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors Skeletal events include pathologic fractures, radiation to bone, spinal cord compression, and bone surgery. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
MAH	**Pharmaceutical form**	Colorless to slightly yellow, transparent or opalescent, containing almost no particles, in a colorless transparent vial for injection
MAH	**Quantitative composition**	120 mg/1.7 mL (70 mg/mL)
MAH	**Route of administration**	Subcutaneous (SC) injection
MAH	**Packaging/material**	Vial
MAH	**Package size(s)**	1 vial/box (vial (1.7 mL))
MAH	**Authorisation (Licence) number (of RBP)**	Amgen Inc / 4
MAH	**Date of authorisation (of RBP)**	Sep 29, 2014
MAH	**Authorisation (Licence) Holder (of RBP)**	Amgen Inc.
MAH	**Source of RBP (or other comparator) for comparability exercise**	Republic of Korea European Union United States
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=201404453aupdateTs2025-11-10%2012:18:14.0b
	Summary of outcomes	

MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from: physicochemical, biological characterization, *in vitro* non-clinical studies, PK, PD, efficacy, safety and immunogenicity studies
NRA	**Availability of full assessment report** (language)/**link**	
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorized for RBP (see section Authorized indications for RBP).
NRA	**Authorised indications for biosimilar**	1. Reduce the risk of developing skeletal-related events in patients with multiple myeloma and in patients with solid tumor bone metastases. Skeletal events include pathologic fractures, radiation to bone, spinal cord compression, and bone surgery. 2. Treatment of giant cell tumors of bone in adults and adolescents with skeletal maturity that are unresectable or for whom surgical resection is likely to cause severe morbidity

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)**
	Denusomab Histidine Histidine hydrochloride monohydrate Polysorbate 20 Sorbitol Water for injections
MAH	**Quality data. State-of-the-art methods**
	Structural Chracteristics - Primary structure: molecular weights, sequence, peptide mapping, N-terminal sequence, C-terminal sequence, extinction coefficient, PTMs - High order structure: disulfide bond, free thiol, CD, ITF, FTIR, DSC, H/DX-MS, DLS **Physicochemical Test** - Glycan profiles, Size variants, Charge heterogeneity, Hydrophobicity, protein concentration **Biological properties**

	- RANKL binding assay, Anti-differentiation assay, RANKL neutralization assay, FcRn binding assay **Immunochemial properties** - Fc gamma Receptor (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa) binding assay, C1q binding assay, mRANKL binding assay, ADCC assay, CDC assay
NRA	**Quality data assessment outcome**
	Comprehensive head-to-head comparability studies performed using state-of-the art analytical procedures demonstrated that all major quality attributes of Xbryk were comparable to those of Xgeva with respect to physiochemical, biological and immunochemical properties. The similarity range was determined using the sufficient characterization data from EU Xgeva, and the bridging data demonstrated the equivalence of EU Xgeva and KR Xgeva. There were slight differences in peptide mapping, PTMs, glycan profile, charge variants, free-thiol, SEC-HPLC, CE-SDS. The differences were appropriately justified with comparability on the biological activity of Xgeva. Comparative forced degradation studies including heat stress, exposure to akaline/acidic condition, oxidation and photostress demonstrated similar degradation profiles for Xbryk and Xgeva. Overall, based on the totality of evidence with respect to all quality characteristics and global clinical studies, the biosimilarity of Xbryk and Xgeva was concluded.
MAH	**Mechanism of action**
	Denosumab is a human immunoglobulin G2 (IgG2) monoclonal antibody with affinity and specificity to human receptor activator of nuclear factor kappa-B ligand (RANKL). Thus, by preventing the RANKL from activating human receptor activator of nuclear factor kappa-B (RANK), its receptor on the osteoclast precursors and osteoclasts, denosumab inhibits osteoclast formation, function and survival. Increased osteoclast activity, stimulated by RANKL, is also a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab prevents the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction. Giant cell tumours of bone are characterized by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.
MAH	**Nonclinical data. *In vitro* studies**
	Non-clinical *in vitro* studies were performed between SB-16 and Xgeva and the results were similar (refer to Quality data section)
MAH	**Nonclinical data. *In vivo* studies**

	***In vivo* pharmacological study** No *in vivo* non-clinical studies were performed. **Pharmacokinetics** No *in vivo* non-clinical studies were performed. **Toxicity Study (including TK)** No *in vivo* non-clinical studies were performed.
NRA	**Nonclinical data assessment outcome**
	All in vitro PD studies demonstrated the similarity between SB-16 and Prolia (refer to Quality data section).
	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: SB16-1001 • Summary of design: A randomised, three-arm, double-blind, parallel group, single-dose study to compare the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of denosumab (SB16, European Union (EU) sourced Prolia, and United States of America (US) sourced Prolia) in healthy male subjects • Randomized subject: 168(56 subjects in each group) • Primary objective: Demonstration of the pharmacokinetic (PK) similarity between SB16 and EU sourced Prolia, between SB16 and US sourced Prolia, and between EU sourced Prolia and US sourced Prolia in healthy male subjects.
NRA	**Clinical data. PK data assessment outcome**
	Study Number: SB16-1001 The 90% Confidence Interval(CI) of the geometric least squares means(LSMeans) ratios of SB-1 Prolia for the PK parameters ($AUC_{0\text{-}inf}$, C_{max}) were contained within the predefined bioequivalen 80-125%.

MAH **Clinical data. PD studies**

PD data were collected from all clinical studies: SB16-1001 and SB16-3001.

NRA **Clinical data. PD data assessment outcome**

In Study SB16-1001, the mean $AUEC_0$-D197 of CTX percent inhibition was comparable among SB16, EU-sourced Prolia, and US-sourced Prolia.

In Study SB16-3001, the mean percent change from baseline in serum CTX and P1NP concentrations were comparable between SB16 and Prolia treatment groups up to Month 12, and also between SB16+SB16, Prolia+SB16 andProlia+Prolia treatment groups after transition, up to Month 18.

MAH **Clinical data. Efficacy studies**

Study Number: SB16-3001

- Summary of design: A Phase III, randomised, double-blind, multicentre clinical study to compare the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity between SB16 (proposed denosumab biosimilar) and Prolia in postmenopausal women with osteoporosis.
- Randomized subject (N=457): 225 for SB-16, 232 for Prolia
- Primary objective: Demonstration of the equivalence of SB16 to Prolia, in terms of percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12 in patients with postmenopausal osteoporosis (PMO).

NRA **Clinical data. Efficacy data assessment outcome**

Study Number: SB16-1001

The primary efficacy analysis was the equivalence analysis of the percent change from baseline inlumbar spine BMD at Month 12 for the FAS and PPS. The LSmean difference in percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia treatment groups for the FAS was 0.33 (SE: 0.354), and the 90% CI of the treatment difference was [–0.25, 0.91], which was completely contained within the equivalence margin of [–1.45,1.45]. Also, ANCOVA was conducted on the PPS and similar results were seen (-0.39 [95% CI: -0.36, 1.13]). The sensitivity analysis result using the tipping point analysis supported the robustness of the primary analysis result.

Table 11-6 Equivalence Analysis of Percent Change from Baseline in Lumbar Spine BMD at Month 12 (Full Analysis Set)

				Difference (SB16 – Prolia)		
Timepoint	**Treatment**	**n**	**LSmean (SE)**	**LSmean (SE)**	**90% CI**	**95% CI**
Month 12	SB16 (N = 225)	225	5.63 (0.250)	0.33 (0.354)	[–0.25, 0.91]	[–0.36, 1.03]
	Prolia (N = 231)	231	5.30 (0.254)			

Table 11-5 Equivalence Analysis of Percent Change from Baseline in Lumbar Spine BMD at Month 12 (Per-Protocol Set)

				Difference (SB16 – Prolia)		
Timepoint	**Treatment**	**n**	**LSmean (SE)**	**LSmean (SE)**	**90% CI**	**95% CI**
Month 12	SB16 (N = 191)	191	5.71 (0.268)	0.39 (0.378)	[–0.24, 1.01]	[–0.36, 1.13]
	Prolia (N = 192)	192	5.32 (0.267)			

MAH **Clinical data. Safety/ Immunogenicity studies**

Safety and immunogenicity data were collected from all clinical studies: SB16-1001 and SB16-3001.

NRA **Clinical data. Safety/ Immunogenicity data assessment outcome**

Safety

The overall safety profiles were similar between SB-16 and Prolia treatment groups.

Immunogenicity

The overall immunogenicity profiles were similar between SB-16 and Prolia treatment groups.

MAH **Interchangeability data**

No additional data were provided

MAH	**Additional information about the comparability exercise**	Not applicable

MAH	**Post-authorization measures**	
	Post-marketing surveillance in Korea. - Period: 2025.05.30. ~ 2029.05.29.	
NRA	**Post-authorization risk measures: assessment outcome.**	
	Post-marketing surveillance study (re-examination study) plan was considered to be acceptable.	
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 the product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to GMP requirements.

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

Nonclinical

No major differences in nonclinical data were observed for SB-16 compared to the reference biotherapeutic product Prolia.

Clinical Studies

The Phase III studies to demonstrate biosimilarity conducted in Patients with Postmenopausal Women with Osteoporosis provided robust evidence that there are no clinically meaningful differences between SB-16 and the reference biotherapeutic product Prolia.

Safety: The Adeverse drug reactions (ADRs) observed with SB-16 were in the similar range as the ADRs observed with the reference biotherapeutic product Prolia.

Immunogenicity: The proportion of patients who developed ADA with SB-16 was generally similar to the reference biotherapeutic product Prolia.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Xgeva(see Section A, summary of outcomes) were considered to be extrapolated to Xbryk .

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 Xbryk was considered approvable.