Unit: Technical Assessment Unit

Public assessment report for biological products

Jubbonti

Administrative information:

Trade name of the medicinal product:	Jubbonti 60 mg
INN (or common name) of the active substance(s):	Denosumab 60mg/1ml
Manufacturer of the finished product	Novartis Pharmaceutical Manufacturing GmbH, Biochemiestraße 10 6336 Langkampfen Austria - AUSTRIA
Marketing Authorization holder	Sandoz GmbH Biochemiestrasse 10 6250 Kundl - AUSTRIA
Applied Indication(s):	-Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures. -Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures. -Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Pharmaceutical form(s) and strength(s):	Solution for SC injection 60 mg/1ml
Route of administration	Subcutaneous injection
Registration track	EMA approved

List of abbreviations

EMA	European Medicines Agency
EU	European Union
Fab	Fragment antigen-binding
Fc	Fraction crystallizable
FcγR	Fc gamma receptors
FDA	U.S. Food and Drug Administration
GP2411	Denosumab
IgG2	Immunoglobulin G
PD	Pharmacodynamics
PK	Pharmacokinetics
RANK(L)	Receptor activator of nuclear factor kappa-B (ligand)
SC	subcutaneous
TNF	Tumor necrosis factor
US	United States of America

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1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. <u>Quality aspects:</u>

- **Manufacturer(s):**

- **Drug Substance**

- The Active substance is manufactured at Novartis Pharmaceutical Manufacturing LLC - Kolodvorska cesta 27, Mengeš, 1234 – Slovenia

- **Drug product**

- The Finished product is manufactured at Novartis Pharmaceutical Manufacturing GmbH, Biochemiestraße 10 6336 Langkampfen Austria - AUSTRIA

- **Stability**

Drug substance:

- Approved shelf life for the active substance: 48 months

- Approved Storage Conditions of the active substance: ≤ -60ºC

Drug product:

- Approved shelf life for the finished product: 36 months

- Approved Storage Conditions of the finished product:

- Store in a refrigerator (2 °C – 8 °C).
- Do not freeze.
- Do not shake.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- Once removed from the refrigerator, Jubbonti may be stored at room temperature (up to 25 °C) for up to 30 days in the outer carton in order to protect from light. It must be used within this 30-day period.

3. Non –clinical aspect:

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures.

Age and menopause are the two main determinants of osteoporosis. Other risk factors for osteoporotic fractures include race, being underweight, hormone ablation therapy, dietary calcium deficiency, sedentary lifestyle, alcohol use, family history, and cigarette smoking. Intake of adequate amounts of calcium and vitamin D and continuing exercise are basic preventive measures for persons of all ages.

Denosumab is a full-length human monoclonal antibody of the IgG2 subclass, consisting of 2 heavy chains, and 2 light chains of the kappa subclass. Denosumab is capable of inhibiting the receptor activator of nuclear factor-κB (RANK) Ligand on bone cells. This antibody binds with high affinity and specificity to RANKL, thereby neutralizing the ligand and inhibiting the differentiation of immature cells into osteoclasts. RANKL is a member of the tumor necrosis (TNF) group of proteins and is an essential factor for the formation, activation and survival of osteoclasts, thereby decreasing bone resorption and cancer induced bone destruction.

- **Pharmacology:** Several in-vitro assays were conducted within the comparability assessment exercise, evaluating the molecular and cellular mechanisms known for denosumab. Results of these assays, evaluating both the Fab-based and the Fc-based biological activity of denosumab in binding as well as functional assays, showed that the range of binding affinities and potency values for GP2411 were similar to those for US- and EU Prolia/Xgeva. The in-vitro assays showed similarity between GP2411 and Prolia/Xgeva regarding binding and neutralization of RANKL, the biological activity associated with the Fab-mediated function of denosumab. Binding to FcγRs, which is considered to be very low for antibodies of the IgG2 type, has been shown to be similar between GP2411 and Prolia/Xgeva.
  No in vivo pharmacodynamics animal studies investigating similarity between GP2411 and its referenced medicinal product Xgeva/Polia were conducted in addition to the analytical biosimilarity assessment.
  This is accepted and in agreement with the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1).
  Secondary pharmacodynamics, Safety pharmacology and Pharmacodynamic drug interactions studies are not required according to "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1".

- **Pharmacokinetics:** Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with GP2411 and Xgeva, as the comparability exercise in the in vitro studies is considered satisfactory and no factors of concern are identified, or these factors of concern do not block direct entrance into humans, an in vivo animal study

may not be considered necessary. PK similarity was examined in a clinical PK and PD study (CGP24112101).

- **Toxicology:** As there are no concerns arising from the analytical biosimilarity exercise triggering the need fo in vivo studies, the absence of non-clinical toxicology studies conducted with Wyost and Xgeva/Polia is accepted and highly recommended regarding the principles of the 3Rs (EMA/CHMP/CVMP/3Rs/677407/2015).
  Studies regarding developmental and reproductive toxicity are not required for non-clinical testing of biosimilars according to the EMEA/CHMP/BMWP /42832/2005 Rev1 guideline. Neither are studies regarding genotoxicity, carcinogenicity and local tolerance.

- **Overall conclusion:**
  The non-clinical data provided by the applicant is considered sufficient to support the biosimilarity of Jubbonti to EU-US Xgeva/Prolia. Thus, **Jubbonti** *is acceptable from the non-clinical point of view.*

4. Clinical aspect:

- **Clinical Overview**

The clinical development program for GP2411 was designed in accordance with established biosimilar principles and relevant regulatory guidelines. All studies were conducted in compliance with International Council for Harmonization Good Clinical Practice (GCP), as stated by the applicant. The program follows a stepwise approach, integrating pharmacokinetic (PK), pharmacodynamic (PD), efficacy, safety, and immunogenicity data to support biosimilarity to the reference product denosumab Prolia.

Overview of Clinical Development Program

The clinical program comprised two pivotal studies:

- **Study CGP24112101 (Phase I)**:
  A randomized, double-blind, three-arm study in healthy male subjects comparing GP2411 with EU- and US-authorized Xgeva to demonstrate PK and PD similarity following a single subcutaneous dose.
- **Study CGP24112301 (Integrated Phase I/III)**:
  A randomized, double-blind study in postmenopausal women with osteoporosis comparing GP2411 with EU-authorized Prolia to evaluate PK, PD, efficacy, safety, and immunogenicity.

These studies collectively provide comparative data across relevant populations and endpoints.

Clinical Pharmacology (PK/PD)

PK similarity between GP2411 and the reference products was demonstrated in both studies, with all primary PK parameters (AUC and Cmax) within predefined equivalence margins.

PD comparability was confirmed using sensitive biomarkers of bone turnover (CTX and PINP), with equivalent responses observed across treatment groups.
Overall, the PK/PD data consistently demonstrate comparable pharmacological profiles between GP2411 and the reference products (**Prolia**).

- **Clinical Efficacy**

Efficacy was evaluated in Study CGP24112301 using percent change from baseline in lumbar spine bone mineral density (LS-BMD) at Week 52 as the primary endpoint.
Equivalence between GP2411 and Prolia was demonstrated, with the confidence interval for treatment differences fully contained within predefined margins. Secondary endpoints supported these findings, with no clinically meaningful differences observed.
Given the shared mechanism of action of denosumab across indications, the results are considered supportive of efficacy comparability for other approved uses.

- **Clinical Safety**

The safety profile of GP2411 was **comparable** to that of the reference products across studies.

- No new or unexpected safety signals were identified
- Adverse events were similar in frequency, severity, and type
- No clinically meaningful differences were observed in laboratory parameters, vital signs, or ECG findings

**Switching from reference product to GP2411 did not impact safety outcomes.

Clinical Immunogenicity

The incidence of anti-drug antibodies (ADAs) was comparable between GP2411 and reference products.
Although higher ADA rates were observed compared to historical data, this was attributed to the use of highly sensitive assays and did not impact PK, PD, efficacy, or safety.
No treatment-related hypersensitivity or immunogenicity-related adverse events were identified.

Overall Conclusion

The totality of clinical evidence demonstrates comparability between GP2411 and the reference products in terms of PK, PD, efficacy, safety, and immunogenicity.
These findings support the conclusion that GP2411 is biosimilar to denosumab reference products.

Benefit-Risk Analysis

The benefit-risk balance of **Jubbonti** is favorable for the use:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

The benefit-risk balance of ***Jubbonti*** has been evaluated based on the totality of evidence from the submitted clinical development program

Overall, the benefit–risk balance is favorable, and ***Jubbonti*** can be considered biosimilar to **Prolia** with no clinically meaningful differences in efficacy, safety, pharmacokinetics, or immunogenicity.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/jubbonti-epar-public-assessment-report_en.pdf