Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dostiva, Denolia, Deskeltia, Dexeva

Active ingredient: Denosumab

Sponsor: Accord Healthcare Pty Ltd

March 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
AE(s)	Adverse event(s)
AIHW	Australian Institute of Health and Welfare
ANCOVA	Analysis of covariance
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AU	Australia(n)
$AUC_{0\text{-}CT}$	Area under serum concentration versus time curve from time zero to the cutoff time.
$AUC_{0\text{-}t}$	Area under concentration-time curve from time zero to the time of last measurable concentration as calculated by linear trapezoidal method
$AUC_{CT\text{-}t}$	Area under the serum concentration versus time curve from cutoff time to the last measurable concentration
$AUC_{0\text{-}\infty}$	Area under the concentration time curve from time zero to infinity
$AUEC_{0\text{-}t}$	Area under the concentration versus time curve from time zero to the last measurable concentration
BALP	Bone-specific alkaline phosphatase
BMD	Bone mineral density
BPD	Biosimilar product development
CFB	Change from baseline
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CTX	C-telopeptide of collagen type 1
DLP	Data lock point
DPD	Deoxypyridionoline
DXA	Dual-energy X-ray absorptiometry (scan)
EMA	European Medicines Agency
E_{max}	Maximum % reduction from baseline
EU	European Union
FDA	Food and Drug Administration (USA)

Abbreviation	Meaning
GCP	Good clinical practice
ITT	Intent-to-treat
LS	Lumbar spine
LSM	Least squares mean
P1NP	Procollagen-type 1 N-terminal-propeptide
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PP	Per Protocol Set
PPQ	Process Performance Qualification
PSUR	Periodic safety update report
PYD	Pyridinoline
RANK	Receptor activator of nuclear factor kappa-β
RANKL	Receptor activator of nuclear factor kappa-β ligand
RMP	Risk management plan
SE-HPLC	Size exclusion high-performance liquid chromatography
SERMs	Selective estrogen-receptor modulators
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
TNFR	Tumour necrosis factor receptor
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	New biosimilar entity
Product names:	Dostiva, Denolia, Deskeltia, Dexeva
Active ingredient:	Denosumab
Decision:	Approved
Date of decision:	19 September 2025
Date of entry onto ARTG:	31 October 2025
ARTG numbers:	450305, 450306, 450307, 450308.
▼*Black Triangle Scheme*	No
for the current submission:	
Sponsor's name and address:	Accord Healthcare Pty Ltd Level 24, 570 Bourke Street Melbourne VIC 3000 Australia
Dose forms:	**450305** – Dostiva (denosumab) 70 mg/ mL (120 mg/1.7 mL) solution for injection vial **450306** – Denolia (denosumab) 60 mg/1 mL solution for injection prefilled syringe with automatic needle guard **450307** – Deskeltia (denosumab) 60 mg/1 mL solution for injection prefilled syringe with automatic needle guard **450308** – Dexeva (denosumab) 70 mg/ mL (120 mg/1.7 mL) solution for injection vial
Containers:	• A single-use pre-filled syringe (PFS) • A single-use 2 mL Type 1 glass vial.
Pack sizes:	One pre-filled syringe, or one glass vial.
Approved therapeutic use for the current submission:	The approved indications for **Dostiva** and **Dexeva** are: *Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.* *Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.* *Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.*

	The approved indications for **Denolia** and **Deskeltia** are: *The treatment of osteoporosis in postmenopausal women. Denolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.* *Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer (see section 5.1 Pharmacodynamic properties, Clinical trials).* *Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.* *Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.*
Route of administration:	Subcutaneous (SC) injection
Dosage:	The recommended dose of **Denolia, Deskeltia** is a single subcutaneous (SC) injection of 60 mg, once every 6 months. If **Denolia, Deskeltia** treatment is discontinued, consider transitioning to an alternative antiresorptive therapy. The recommended dose of **Dexeva, Dostiva** for the prevention of skeletal related events is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. **Dexeva, Dostiva:** For the treatment of giant cell tumour of bone and hypercalcaemia of malignancy is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with a loading dose of 120 mg on days 8 and 15 of the initial 4-week treatment period. Administration should be performed by an individual who has been adequately trained in injection techniques. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	Pregnancy Category: D There are no adequate and well-controlled studies of denosumab in pregnant women. Denosumab is contraindicated for use during pregnancy and in women trying to get pregnant. Premenopausal women with reproductive potential should be advised of the potential effects of denosumab in pregnancy. Contraception should be discussed. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the

sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Accord Healthcare to register Dostiva and Dexeva (denosumab) 70 mg/mL (120 mg/1.7 mL) solution for injection vial, and Denolia and Deskeltia (denosumab) 60 mg/1 mL solution for injection prefilled syringe with automatic needle guard for the following proposed indication:[1]

Denolia and Deskeltia (denosumab)

The treatment of osteoporosis in postmenopausal women. Denolia/Deskeltia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer (see section 5.1 Pharmacodynamic properties, Clinical trials).

Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.

Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.

Dostiva and Dexeva (denosumab)

Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.

Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.

Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.

This is a Category 1 Type A application is for four new biosimilar products. The innovator products are Prolia (denosumab rch) 60 mg/1 mL solution for injection prefilled syringe with automatic needle guard[2] and Xgeva (denosumab rch) 70 mg/ mL (120 mg/1.7 mL) solution for injection vial.[3]

Subsequently, Denolia and Deskeltia have the same formulation and presentation as Prolia (60 mg/1 mL solution for injection prefilled syringe with automatic needle guard). While Dostiva (formally known as Denogeva) and DEXEVA have the same formulation as Xgeva (70 mg/ mL (120 mg/1.7 mL) solution for injection vial.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] PROLIA denosumab (rch) 60mg/1mL solution for injection prefilled syringe (159322) | Therapeutic Goods Administration (TGA)

[3] XGEVA denosumab (rch) 70mg/mL (120mg/1.7mL) solution for injection vial (175041) | Therapeutic Goods Administration (TGA)

Disease or condition

Osteoporosis is characterised by both low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to decreased bone strength, increased bone fragility and a consequent increase in fracture risk.[4] Bone morphogenesis and remodelling involve the combined activities of osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Bone remodelling can be divided into three stages based on the dynamic activities of osteoblasts and osteoclasts.[5] The initial stage is the differentiation of osteoclast precursor cells, activation of osteoclasts and bone resorption. Osteoclast apoptosis occurs in the intermediate stage, during which osteoblasts accumulate and differentiate to form new bone in the bone lacuna. In the final stage, bone resorption is completed through osteogenesis and mineralisation. The control and regulation of osteoclast activation and differentiation is achieved by a family of biologically related tumour necrosis factor (TNF) receptor (TNFR)/TNF-like proteins including osteoprotegerin, RANK and RANKL.[6]

Osteoclast is also affected by hormonal routes such as oestrogen. Oestrogen inhibits activity and survival of the osteoclasts, which is responsible for the high rate of osteoporosis in postmenopausal women.[7] There are other risk factors such as cancer, which can lead to bone loss due to direct effects of cancer cells on the skeleton, as well as detrimental effects of cancer-specific therapies on bone cells.[8] Of note, malignancies also commonly lead to hypercalcaemia through various mechanisms (including osteolytic process) which requires similar pharmacological therapies used for osteoporosis.[9]

Osteoporosis imposes a significant health burden in Australia and worldwide. The Australian Institute of Health and Welfare (AIHW) estimated that approximately 924,000 Australians (3.8% of the total population) were affected by osteoporosis or osteopenia, although there is likely to be a significant underestimation.[10] Furthermore, a study analysing the burden of osteoporosis in Australia between 2012-2022, concluded 66% of those over 50 years of age (approximately 4.74 million people) were thought to be affected by osteoporosis and osteopenia.[11] Over the 10-year period, it was estimated that approximately 1.6 million cases of fractures were attributable to osteoporosis and osteopenia. Osteoporotic fractures occur most frequently in the vertebrae, carpals, hips, pelvis and upper arms.[12] Many patients require long-term nursing home care, which would leave a significant burden on the patient's family and society.

Osteoporosis is a 'silent disease' as deterioration of skeletal tissue proceeds with no symptoms until a symptomatic fracture occurs. Thus, the condition is under-recognised with affected

[4] Black DM, Rosen CJ. Postmenopausal osteoporosis. New Engl J Med. 2016; 374: 254–262.
[5] Lemaire V, Tobin FL, Greller LD, Cho CR, Suva LJ. Modeling the interactions between osteoblast and osteoclast activities in bone remodeling. J Theor Biol. 2004; 229(3): 293-309.
[6] Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998; 93(2): 165-76.
[7] Kameda T, Mano H, Yuasa T, et al. Estrogen inhibits bone resorption by directly inducing apoptosis of the bone-resorbing osteoclasts. J Exp Med. 1997; 186(4): 489-95.
[8] Drake MT. Osteoporosis and cancer. Curr Osteoporos Rep. 201;11(3):163-70.
[9] Mirrakhimov AE. Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. N Am J Med Sci. 2015;7(11):483-93.
[10] Chronic musculoskeletal conditions : Osteoporosis and minimal trauma fractures - Australian Institute of Health and Welfare (aihw.gov.au)
[11] Watts JJ, Abimanyi-Ochom J, Sanders KM. Osteoporosis costing all Australians. A new burden of disease analysis – 2012 to 2022. Osteoporosis Australia. (https://healthybonesaustralia.org.au/wp-content/uploads/2022/09/burden-of-disease-analysis-2012-2022.pdf)
[12] Warriner A H, Patkar N M, Curtis J R, Delzell E, Gary L, Kilgore M, et al. Which fractures are most attributable to osteoporosis? J. Clin. Epidemiol. 2011; 64: 46–53.

individuals undertreated. [13] The total direct and indirect cost towards osteoporosis, osteopenia and fractures was estimated to be around $33.6 billion in Australia between 2012 and 2022.[8] In the US, the total costs of treatment for osteoporotic fractures were estimated to be $17 billion in 2003 and is predicted to exceed $25 billion by the year 2025.[14]

Based on the WHO definition of osteoporosis and osteopenia (Table 1), approximately 3% of men and 13% of women in Australia aged 50–69 years are osteoporotic, rising to 13% and 43% for men and women aged >70 years. Fifty-five per cent of men and 49% of women between 50 and 69 years of age are osteogenic, with a similar prevalence in those aged >70 years. By 2022, approximately 72% of women and 62% of men aged >50 years will have osteoporosis or osteopenia based on WHO criteria. [5,15]

Table 1. WHO definitions of osteoporosis and osteopenia. [16]

World Health Organisation Definitions: osteoporosis and osteopenia		
Normal BMD	T-score: -1.0 or above	A value for BMD within 1 SD of the young adult reference mean.
Osteopenia	T-score: between -1.0 and -2.5	A value for BMD more than 1 SD below the young adult reference mean, but less than 2.5 SD below the value.
Osteoporosis	T-score: less than -2.5	A value for BMD 2.5 SD or more below young adult mean.

Current treatment options

Management of osteoporosis usually requires multifaceted approach involving pharmacological and non-pharmacological therapies. Non-pharmacological therapies include lifestyle changes including physical activity and weight bearing exercises, as well as cessation of smoking. Dietary supplements such as calcium and vitamin D are also commonly recommended.

Pharmacological approaches to prevention and treatment may be divided as follows: [17]

- antiresorptive therapy (inhibits osteoclast activity)
  - bisphosphonates (eg alendronate, risedronate, zoledronate/zoledronic acid)
  - denosumab
  - menopausal hormone therapy (eg oestrogen, tibolone)
  - selective oestrogen receptor modulators (SERMs; eg raloxifene)
- osteoanabolic therapy (predominant stimulatory effect on osteoblasts)
  - teriparatide

[13] RACGP - Osteoporosis management and fracture prevention in post-menopausal women and men > 50 years of age

[14] Cauley JA. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci. 2013; 68(10): 1243-51.

[15] Chen W, Simpson JM, March LM, et al. Comorbidities only account for a small proportion of excess mortality after fracture: A record linkage study of individual fracture types. J Bone Miner Res 2018;33(5):795–802. (https://doi.org/10.1002/jbmr.3374)

[16] World Health Organization (WHO). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO study group (content) [meeting held in Rome from 22 to 25 June 1992]. WHO, 1994.

[17] RACGP - Osteoporosis management and fracture prevention in post-menopausal women and men > 50 years of age

– romosozumab (also inhibits osteoclast activity)

For pharmacological therapies, bisphosphonate has been widely used as the first-line treatment of osteoporosis. Bisphosphonate is known to work by reducing osteoclast-mediated bone resorption.[18] Several randomised trials have shown the benefit of oral and intravenous bisphosphonates in reducing the risk of fractures.[19,20] Bisphosphonate is considered relatively safe, however known to be associated with rare but serious adverse events such as osteonecrosis of the jaw and atypical femoral fractures. Bisphosphonate is cleared by kidneys and should be avoided in those with poor renal function. Oral bisphosphonate is administered weekly or monthly (depending on the product), while intravenous bisphosphonate can be given yearly. Adherence to oral bisphosphonate can be low, with less than 40% of those who are prescribed still taking it after 1 year.[21]

Denosumab is the first biologic therapy approved to treat osteoporosis. Denosumab inhibits bone resorption by binding to the RANKL, thereby preventing the differentiation of osteoclast precursor cells to osteoclasts. Unlike bisphosphonates, denosumab can be used in women with compromised renal function. In a large trial (FREEDOM study), it was shown that the relative risks of fracture in those receiving denosumab vs placebo were 68%, 40%, 20%, and 16% for radiographic vertebral, hip, nonvertebral, and wrist fractures, respectively, along with increased BMD.[22,23] As with bisphosphonates, rare cases of atypical femoral fractures and osteonecrosis of the jaw have been observed with denosumab treatment.

Teriparatide is an anabolic agent that works primarily by increasing bone formation. Teriparatide is administered by daily self-injection. Teriparatide has been shown to increase the incidence of osteosarcoma in rats, and its use is restricted to up to 2 years as a precautionary measure.[24] Teriparatide is also contraindicated in individuals with severe renal failure.

Oestrogen and selective estrogen-receptor modulators (SERMs) are also used particularly for postmenopausal osteoporosis. However, evidence for these treatments in terms of preventing nonvertebral and hip fractures are rather limited. In addition, these treatments are known to be associated with several adverse events including thrombosis (including deep vein thrombosis and pulmonary embolism) and therefore are not recommended as a first-line therapy for osteoporosis.[25]

Clinical rationale

Denosumab is a human monoclonal Immunoglobulin G2 (IgG2) antibody.

Denosumab is an inhibitor of receptor activator of nuclear factor kappa-β ligand (RANKL). RANKL is a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab binds to RANKL with high

[18] Alendronate - StatPearls - NCBI Bookshelf (nih.gov)

[19] Crandall, CJ, Newberry, SJ, Diamant, A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med 2014;161:711-723.

[20] Khosla, S, Bilezikian, JP, Dempster, DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab 2012;97:2272-2282.

[21] Modi, A, Siris, ES, Tang, J, Sen, S. Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy. Curr Med Res Opin 2015;31:757-765

[22] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–765.

[23] Simon JA, Recknor C, Moffett AH, et al. Impact of denosumab on the peripheral skeleton of postmenopausal women with osteoporosis: bone density, mass, and strength of the radius, and wrist fracture. Menopause. 2013;20:130–137.

[24] AU PI for TERROSA (teriparatide). Attachment: Product Information for Teriparatide

[25] Compston, J, Bowring, C, Cooper, A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013;75:392-396

affinity and specificity, thereby preventing the activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Bone metastasis from solid tumours

RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption.

Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in bone disease in metastatic tumours and multiple myeloma. Denosumab binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of RANKL-RANK interaction results in reduced osteoclast numbers and function and thereby decreases bone resorption and cancer-induced bone destruction.

RANKL inhibition resulted in reduced bone lesions and delayed formation of de novo bone metastases in some nonclinical models. RANKL inhibition reduced skeletal tumour growth, and this effect was additive when combined with other anticancer therapies.

Giant cell tumour of bone

Giant cell tumours of bone are characterised by stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma can be replaced with non-proliferative, differentiated, woven new bone which may show an increase in density.

Hypercalcaemia of malignancy refractory to intravenous bisphosphonates

The primary aetiology of both skeletal and humoral hypercalcaemia of malignancy is increased bone resorption, which leads to elevated calcium concentrations in the extracellular fluid. The increase in bone resorption is initiated by the release of signalling molecules such as PTHrP, prostaglandins, and cytokine by malignant and stromal cells. These molecules stimulate osteoblasts and other stromal cells to express RANKL, which upon binding its receptor RANK upregulates osteoclast recruitment and differentiation and thus bone resorption, with a resultant increase in calcium concentrations of the extracellular fluid and serum. Denosumab binds to RANKL preventing RANK/RANKL mediated osteoclast formation, function, and survival thereby lowering serum calcium levels.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

The reference denosumab products Prolia and Xgeva were first approved in Australia on 22 June 2010 and 8 September 2011, respectively. There are several other denosumab products registered on the ARTG.[26]

[26] Australian Register of Therapeutic Goods (ARTG) | Therapeutic Goods Administration (TGA)

International regulatory status

At the time the TGA considered this submission, similar submissions had been approved in the European Union (EU) on 26 May 2025, and the United Kingdom (UK) on 30 June 2025 (Osvyrti), and 4 July 2025 (Jubereq). A similar submission was under consideration in the United States (US) (submitted on 11 March 2024), under the trade names Osvyrti and Jubereq.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1. Timeline for Submission PM-2024-02065-1-5.

Description	Date
Submission dossier accepted and first round evaluation commenced	1 July 2024
Evaluation completed (End of round 2)	6 June 2025
Registration decision (Outcome)	19 September 2025
Registration in the ARTG completed	31 October 2025
Number of working days from submission dossier acceptance to registration decision*	236

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Denosumab (INTP23.1) is a full-length human monoclonal antibody that belongs to the IgG2 class, produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology. Each vial contains a deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/ mL). Each 1 mL single-use pre-filled syringe contains 60 mg denosumab.

Denosumab (INTP23.1) is supplied as a sterile, preservative-free, clear, colourless to pale yellow solution for injection at pH 5.2. The solution may contain trace amounts of translucent to white proteinaceous particles.

In terms of stability conclusions, all parameters for the drug substance remained within stability specifications at -20 ±5 °C over 24 months for developmental and phase-III clinical batches, as well as 6 months for Process Performance Qualification (PPQ) batches. No discernible trends indicating quality changes were noted during this period. For the accelerated condition (5 ± 3 °C), similar results were observed after 6 months, with all stability results staying within specifications.

The stress condition analysis showed compliance with acceptance criteria for physical appearance, pH, protein concentration, SE-HPLC, and relative potency for up to 28 days, with only minor changes observed in impurities and no significant alterations in protein oxidation or

purity. Furthermore, testing for photostability revealed that exposure to high light intensity did not significantly affect the drug substance's quality. Although Denosumab is photosensitive, it is not subjected to conditions likely to cause degradation during its production process.

The sponsor initially proposed a 24-month shelf life for the product when stored between 2°C and 8°C. However, a complete dataset to support this claim was not submitted. Furthermore, only 6 months of initial long-term stability data from full-scale commercial batches were provided.

This data covered a period of up to 12 months under long-term storage conditions of 5 ± 3°C. The submitted data indicate that all tested batches met the established specification acceptance criteria at all provided time points, and no significant trends were observed. Based on the currently available data, a 24-month shelf life for the drug product can be supported. Therefore, it is recommended to:

- store pre-filled syringes in a refrigerator at 2°C to 8°C in the original carton,
- do not freeze,
- protect from direct light,
- do not excessively shake the pre-filled syringe, and
- do not expose to temperatures above 25 °C.

If removed from the refrigerator, denosumab (INTP23.1) should be kept at room temperature (up to 25 °C) in the original container and must be used within 30 days.

Regarding biosimilarity, similarity studies were conducted in accordance with CHMP/437/04, ICH Q5E, TGA guidance document Biosimilar medicines regulation (Version 2.2, April 2018) and EMA/CHMP/BWP/247713/2012. The results of all tests demonstrated that INTP23.1 denosumab is highly similar to US-Prolia/Xgeva, EU- Prolia/Xgeva and AU-Prolia/Xgeva in all (physicochemical and biological) attributes studied.

There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects. Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Deskeltia, Denolia, Dostiva and Dexeva have been controlled to an acceptable level.

Nonclinical evaluation summary

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.[27,28]

Clinical evaluation summary

Summary of clinical studies

Two clinical studies were submitted to support the proposed denosumab products.

[27] AusPAR for Prolia (denosumab) AusPAR: Denosumab | Therapeutic Goods Administration (TGA)
[28] AusPAR for Xgeva (denosumab) AusPAR: Denosumab | Therapeutic Goods Administration (TGA)

Study 0568-19

Study 0568-19 was a randomized, double-blind, three-arm, balanced, single-dose, parallel-group study comparing pharmacokinetics (PK) and pharmacodynamics (PD) of Intas Denosumab (120 mg/1.7 mL) of Intas Pharmaceuticals Limited, India with Xgeva of Amgen Inc., USA and Xgeva of Amgen Europe B.V., The Netherlands in normal, healthy, adult human male subjects.

Regarding pharmacokinetic biosimilarity, the 90% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed C_{max}, AUC_{0-t}, partial AUC's AUC_{0-CT} and AUC_{CT-t} and $AUC_{0-\infty}$ of Intas denosumab relative to Xgeva (US) and Xgeva (EU) were within the acceptance range of 80.00% to 125.00% in Study 0568-19.

Study 0774-19

Study 0774-19 was a randomised, double-blind, active-controlled, parallel-arm, multicentre study designed to compare the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and clinical efficacy of denosumab of Intas (60 mg/mL) with Prolia in postmenopausal women with osteoporosis.

Pharmacokinetics

The 90% confidence interval for pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were found to be within the prespecified bioequivalence limits of (80.00, 125.00) in Study 0774-19 (Table 3).

Table 3. Study 0774-19 - Summary statistics of pharmacokinetic parameters for Denosumab after first dose (N=261).

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Patients CV (%)	Power (%)
	Denosumab (T)	Prolia (R)	Ratio (T/R)%			
lnC_{max}	6856.356	6251.419	109.7	101.85 - 118.11	37.1	99.9
$lnAUC_{0-t}$	6052572.354	5378094.961	112.5	103.12 - 122.82	44.2	99.5
$lnAUC_{0-\infty}$	6156141.837	5501141.954	111.9	102.39 - 122.31	45.0	99.3

Efficacy

The clinical efficacy objective of the study was to compare the efficacy of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis.

The primary efficacy endpoint for Study No. 0774-19 is percent change from baseline in BMD for lumbar spine (LS-BMD) measured by DXA at month 12, which was agreed by the FDA during the BPD Type 2 meeting held on 03 February 2020 and in scientific advice by EMA on 12 December 2019 (EMA/CHMP/SAWP/653442/2019).

Lumbar spine was chosen for assessment of BMD according to the guideline and study results of Prolia. It was recommended that measurements of BMD are mandatory at those sites where osteoporotic fractures most commonly occur, i.e., the spine (L1 to L2 or L2 to L4) and the hip.

Summary statistics of change from baseline to 12 months for BMD of lumbar spine for Main phase PP set are presented in Table 4.

Table 4. Study 0774-19 - Summary statistics for %CFB in BMD of lumbar spine (Main phase, PP set, N=465).

Visit (Months)	Statistics	Denosumab (T) (N=235)	Prolia (R) (N=230)	Mean Difference	95% CI	Acceptance Criteria (T vs R)	Conclusion (For EMA)
6 months	n	235	229	-0.92	-2.47 to 0.64	Not Applicable	Not Applicable
	Mean	5.11	5.86				
	SD	10.209	6.383				
12 months	n	235	230	-0.20	-1.42 to 1.03	-1.45 to 1.45	Therapeutic equivalent
	Mean	6.25	6.36				
	SD	6.819	6.609				

Note 1: N=Number of Patient in respective analysis set, n= Available observation in respective group.

Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) X 100

Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.

The 95% confidence interval for the percentage change in BMD from baseline to 12 month was found to be within acceptance range (-1.45 to 1.45) for PP set.

Summary statistics of change from baseline to 12 months for BMD of lumbar spine for Main phase ITT set are presented in Table 5.

Table 5. Study 0774-19 - Summary statistics for %CFB in BMD of lumbar spine (Main phase, ITT set, N=552).

Visit (Months)	Statistics	Denosumab (T) (N=276)	Prolia (R) (N=276)	Mean Difference	95% CI	Acceptance Criteria (T vs R)	Conclusion (For USFDA)
6 months	n	252	243	-0.77	-2.31 to 0.76	Not Applicable	Not Applicable
	Mean	5.47	6.05				
	SD	10.380	6.566				
12 months	n	235	230	-0.20	-1.42 to 1.03	-1.45 to 1.45	Therapeutic equivalent
	Mean	6.25	6.36				
	SD	6.819	6.609				

Note 1: N=Number of Patient in respective analysis set, n= Available observation in respective group.

Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) X 100

Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.

The 95% confidence interval for the percentage change in BMD from baseline to 12 month is found to be within the acceptance range (-1.45 to 1.45) for ITT set.

Evaluator's overall conclusions on pharmacokinetics

In the current submission, the PK data was obtained from two clinical studies: 0568-19 and 0774-19.

Study 0568-19 was a phase 1 study performed in healthy male volunteers. The main purpose of the study was to compare the PK of the Intas Denosumab (120 mg/1.7 mL) with the PK of the reference product, Xgeva (US and EU products). In the 234 participants (78 in each group), the 90% CIs of the geometric LSM ratios derived from the analysis on the ln-transformed denosumab PK parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Intas denosumab relative to Xgeva (US product), and Xgeva (EU product) were within the acceptance range of 80.00% to 125.00%.

Study 0774 was a phase 3 study performed in 552 postmenopausal women with confirmed osteoporosis as diagnosed by DXA of the lumbar vertebrae. The subjects were randomly assigned 1:1 to receive either Denosumab or Prolia. The PK parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were found comparable between Denosumab and Prolia, with the 90% confidence intervals within the prespecified bioequivalence limits of (80.00%, 125.00%).

Overall, these two studies supported the bioequivalence of Intas denosumab with their reference counterparts in terms of pharmacokinetics.

Evaluator's overall conclusions on pharmacodynamics

Pharmacodynamic (PD) assessments were made in both Study 0568-19 and Study 0774-19. In these studies, the PD markers included serum CTX and P1NP following the first dose of denosumab. Based on these assessments, the serum concentrations of these PD markers were comparable between the sponsor's products and their counterparts (i.e. reference products), with the 90% CIs of the ln-transformed Emax, $AUEC_{0-t}$ within the acceptance criteria of 80.00% - 125.00%.

In Studies 0568-19 and 0774-19, only CTX and P1NP were assessed as PD biomarkers, whereas there are other biomarkers of bone turnover such as bone-specific alkaline phosphatase (BALP), deoxypyridionoline (DPD), or pyridinoline (PYD). It is presumed that CTX and P1NP were chosen to be consistent with the FREEDOM trial that took place as a part of the initial denosumab development.

Overall, the PD assessment is supportive of the bioequivalence of the sponsor's and reference products.

Evaluator's conclusions on clinical efficacy

The clinical efficacy was assessed in the pivotal study 0774-19. In this study, the clinical efficacy was assessed in postmenopausal women with osteoporosis (based on the DXA assessment in the lumbar vertebrae). The study compared the efficacy of the sponsor's product (Denosumab) with that of the reference product (Prolia).

The primary endpoint was the %CFB in the BMD score at 12 months, which showed that 95% CI of the %CFB was -1.42 to 1.03; this narrowly met the prespecified equivalence margin of (-1.45%, +1.45%). Descriptive statistics for mean %CFB in BMD score for the lumbar spine, femoral neck and total hip were generally comparable at the 12 months (Main phase) and 18 months (Extension phase) were generally comparable between the two groups.

In the Main phase of the study, there was only one episode of fracture (upper limb fracture) in the Denosumab group, and none in the Prolia group. The number is considered to be too low for an objective comparison.

Overall, the study met the primary objective by meeting the pre-specified criteria in the form of the %CFB in the BMD score. The study could not conclusively assess whether this leads to a comparable reduction in the risk of clinical fracture, as the study was not designed to address this issue.

It should also be noted that the study may have a questionable applicability in the Australian context. Most (94.6%) patients were Indian and only a small subset (5.4%) of patients were Georgian.

The pathogenesis of osteoporosis and its complications (e.g. fractures) are affected by genetics, environment, lifestyle (e.g. diet, supplements, exercise) monitoring and support (e.g. family, services). There are reports that suggest that Caucasian women are more likely to have osteoporosis and osteoporotic fractures. As such, the clinical evaluator considers that a more

comprehensive clinical assessment of fractures over a longer period in a wider set of jurisdictions would have been helpful in validating the clinical efficacy.

Evaluator's overall conclusions on clinical safety

Clinical safety was assessed in the two clinical studies 0568-19 and 0774-19.

In Study 0568-19, a total of 234 healthy male volunteers were dosed with either Intas-Denosumab, US-Xgeva, and EU-Xgeva. The incidence and severity of adverse events (AEs) were generally consistent in all three groups. The most common AE was hypercalcaemia. There were 10 significant AEs (including two from the Test Product group), nine of which were considered to be unlikely in terms of causality, and one that was considered to be possibly related (Platelet count decreased, Reference Product R1 group).

In Study 0774-19, a total of 552 postmenopausal women with osteoporosis were included in Treatment Period of the study and 123 patients were re-randomised in Transition-extension Period of the study. 65.9% of the participants reported at least one AE during the Treatment Period, and the proportion was balanced between the Test and Reference Arms (65.2% and 66.7%, respectively). Most of the AEs (808 out of 830 AEs) were mild, and 4 were severe in nature. Most (776 AEs) recovered without sequelae. The incidence of AEs was much less in the Transition-extension period, and most (98 out of 99 AEs) were mild in nature. The types of AEs (by preferred term) were generally balanced between the two groups with hypocalcaemia being the most common AE, which is likely to have been exacerbated by denosumab. There was one death in the Reference Group during the Treatment period and an additional death in the Test group, neither of which was considered to related to the study treatments.

Overall, the safety profiles of the sponsor's Denosumab and Prolia appear to be comparable. It should be noted that the follow-up periods were relatively short, and the number of subjects were too low for detection and rare events.

Risk management plan

The Denolia/Deskeltia EU-Risk Management Plan (RMP) version 1.0 (dated 22 February 2024, data lock point 01 February 2024), with Australia-Specific Annex (ASA) version 1.2 (dated 03 March 2025), and Dostiva/Dexeva EU-Risk Management Plan (RMP) version 2.0 (dated 23 August 2024, data lock point 06 August 2024), with Australia-Specific Annex (ASA) version 1.2 (dated 03 March 2025) have been reviewed.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies for Denolia/ Deskeltia are summarised below:

Table 6. Summary of safety concerns for Denolia/ Deskeltia.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypocalcaemia	✓*	–	✓	–
	Skin infection leading to hospitalisation	✓*	–	✓	–
	Osteonecrosis of the jaw	✓*	–	✓	–
	Hypersensitivity reactions	✓*	–	✓	–
	Atypical femoral fracture	✓*	–	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	✓	–	✓	–
Important potential risks	Fracture healing complications	✓*	–	–	–
	Infection	✓*	–	✓	–
	Cardiovascular events	✓	–	–	
	Malignancy	✓*	–	✓	–
Missing information	None				

*Targeted follow up forms

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies for Dostiva / Dexeva are summarised below:

Table 7. Summary of safety concerns for Dostiva/ Dexeva.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Osteonecrosis of the jaw	✓*	–	✓	–
	Atypical femoral fracture	✓*	–	✓	–
	Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	✓	–	✓	–
Important potential risks	Cardiovascular events	✓	–	–	–
	Malignancy	✓	–	–	–
	Delay in diagnosis of primary malignancy in giant cell tumour of bone	✓	–	–	–
	Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	✓	–	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Missing information	Patients with prior intravenous bisphosphonate treatment	✓	–	✓	–
	Safety with long-term treatment and with long-term follow up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	✓	–	–	–
	Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	✓	–	–	–

*Targeted follow up forms

The RMP evaluation was reviewed. The summary of safety concerns for Denolia/Deskeltia and Dostiva/Dexeva was considered acceptable from an RMP perspective. The pharmacovigilance plan for Denolia/Deskeltia and Dostiva/Dexeva was considered acceptable from an RMP perspective. Only routine pharmacovigilance activities have been proposed for safety concerns of Denolia/Deskeltia and Dostiva/Dexeva including specific adverse reaction follow-up questionnaires for certain safety concerns. This aligns with the associated EU RMPs and was considered acceptable from an RMP perspective.

The Sponsor has proposed routine risk minimisation in the form of PI and CMI for some of the safety concerns of Denolia/Deskeltia and Dostiva/Dexeva. At round 2, the patient reminder card has been removed from the ASAs for Denolia/Deskeltia and Dostiva/Dexeva to address the important identified risk of 'osteonecrosis of the jaw' as the patient reminder card is EU specific and is not a regulatory requirement imposed by TGA. The risk minimisation plan is considered acceptable for Denolia/Deskeltia and Dostiva/Dexeva. The Sponsor has been requested to provide the updated ASAs addressing the new and outstanding recommendations as an RMP update prior to the launch of the product.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

Intas denosumab has been developed as a proposed biosimilar to Prolia and Xgeva, with comparable proposed indication, dose and route of administration.

Comprehensive comparisons of physicochemical and biological quality attributes were undertaken to demonstrate biosimilarity of Intas denosumab to EU-sourced and US-sourced Prolia and Xgeva. A bridging study demonstrated high similarity of Australian-sourced Prolia and Xgeva to EU-sourced Prolia and Xgeva supporting biosimilarity of Intas denosumab to the Australian reference product.

The clinical development program consisted of two clinical studies, one single dose PK study in healthy male volunteers comparing the three formulations of denosumab (Intas denosumab, EU-sourced Xgeva and US-sourced Xgeva). Study 0774-19 was the pivotal study which assessed clinical efficacy of Intas denosumab compared to EU-sourced Prolia in postmenopausal women with osteoporosis. The primary efficacy endpoint was the mean percent change from baseline in BMD based on the DXA assessment in the lumbar vertebrae. The primary efficacy endpoint was met with satisfactory supportive analyses, and the two studies support the pharmacokinetic bioequivalence of Intas denosumab with the reference products studied.

For Study 0774-19, a relatively large number of patients did not complete the main phase of the trial due to the sponsor's decision to terminate 4 sites due to non-compliance with the eligibility criteria and falsification of DXA scans. These sites had recruited a total of 30 patients (15 in each arm). The Delegate notes that in light of this, the EMA's CHMP requested a re-analysis of the primary efficacy analysis which was considered satisfactory. The CHMP also triggered a Good Clinical Practice (GCP) inspection to verify the corrective and preventive measures taken and the conduct of the trial in other sites. The inspectors found some departures from GCP, but concluded that the trial was ethically conducted, and that the data were of sufficient quality to be evaluated in a Marketing Authorisation Application Therefore, CHMP considered the issue resolved. It is noted that this was not clearly communicated to the TGA by the Sponsor.

The extrapolation from one indication to other Prolia and Xgeva indications for Intas denosumab was based on the Sponsor's analytical and functional assessments as well as clinical data and is considered acceptable.

Conclusions

Biosimilarity of Intas denosumab to Prolia and Xgeva has satisfactorily been demonstrated, and therefore a benefit/risk balance comparable to the reference product can be concluded. While a decision is yet to be made, at this stage I am inclined to approve the registration of the product.

Approval will also depend on satisfactory negotiation of the PI, CMI and the fulfillment of conditions of registration.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register:

Dostiva and Dexeva (denosumab) 70mg/mL (120mg/1.7mL) solution for injection, indicated for:

Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.

Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.

Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.

Denolia and Deskeltia (denosumab) 60mg/1mL solution for injection prefilled syringe with automatic needle guard, indicated for:

The treatment of osteoporosis in postmenopausal women. Denolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer (see section 5.1 Pharmacodynamic properties, Clinical trials).

Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.

Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.

Specific conditions of registration

- The Denolia/Deskeltia EU-Risk Management Plan (RMP) version 1.0 (dated 22 February 2024, data lock point 01 February 2024), with Australia-Specific Annex (ASA) version 1.2 (dated 03 March 2025), and Dostiva/Dexeva EU-Risk Management Plan (RMP) version 2.0, (dated 23 August 2024, data lock point 06 August 2024), with Australia-Specific Annex (ASA) version 1.2 (dated 03 March 2025) included with submission PM-2024-02065-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- All batches of Deskeltia, Denolia, Dostiva and Dexeva denosumab 60 mg/1mL and 70mg/mL (120 mg/1.7mL) solution for injection supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au