Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

DENOTAS

Denosumab 60 mg solution for injection in a prefilled syringe

Product legal distribution category: prescription-only medicine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

Excipient with known effect:

This medicine contains 47 mg sorbitol in each mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

1. Therapeutic indications

Denosumab is indicated for the:

(i) Treatment of postmenopausal women with osteoporosis at high risk of fracture
(ii) Treatment to increase bone mass in men with osteoporosis at high risk of fracture
(iii) Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer
(iv) Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

2. Posology and method of administration

During a phase III study in women with postmenopausal osteoporosis, Intas Denosumab was administered as single subcutaneous (SC) injection of 60 mg every 6 months in combination with daily calcium and vitamin D.

Information provided below is based on the innovator data.

Posology

The recommended dose of denosumab is 60 mg administered as a single SC injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium 1000 mg daily and at least 400 IU vitamin D daily (see section 4.4).

The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of

denosumab on an individual patient basis, particularly after 5 or more years of use (see section 4.4).

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (see section 4.4 for recommendations relating to monitoring calcium).

Patients with hepatic impairment

The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Elderly Patients (age ≥65)

No dose adjustment is required in elderly patients.

Paediatric population

Denosumab is not recommended in paediatric patients (age <18 years) as the safety and efficacy of denosumab in these patients have not been established. Inhibition of RANK/ RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption (see section 5.3).

Information essential to safe dosing or administration

Pregnancy must be ruled out prior to administration of denosumab. Perform pregnancy testing in all females of reproductive potential prior to administration of denosumab. Based on findings in animals, denosumab can cause fetal harm when administered to pregnant women (see section 4.6).

Method of administration

For subcutaneous use.

Administration should be performed by an individual who has been adequately trained in injection techniques.

The instructions for use, handling and disposal are given in section 6.6.

3. Contraindications

Information provided in this section is based on the innovator data.

Hypocalcaemia (see section 4.4).

Hypersensitivity to active substance or to any of the excipients listed in section 6.1.

Pregnancy.

4. Special warnings and precautions for use

Information provided in this section is based on the innovator data.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Calcium and Vitamin D supplementation

Adequate intake of calcium (1000 mg daily) and vitamin D (at least 400 IU daily) is important in all patients.

Precautions for use

Hypocalcaemia

It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8 for symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8), with most cases occurring in the first weeks of initiating therapy, but it can occur later.

Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.

Renal impairment

Patients with severe renal impairment (creatinine clearance <30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients.

Skin infections

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalization (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the jaw (ONJ)

ONJ has been reported rarely in patients receiving denosumab for osteoporosis (see section 4.8).

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur

Atypical femoral fractures have been reported in patients receiving denosumab (see section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Long-term antiresorptive treatment

Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling (see section 4.2).

Concomitant treatment with other denosumab-containing medicinal products

Patients being treated with denosumab should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Dry natural rubber

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Warnings for excipients

This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

5. Interactions with other medicinal products and other forms of interaction

Information provided in this section is based on the innovator data.

In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolized by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

6. Fertility, pregnancy and lactation

Information provided in this section is based on the innovator data.

Fertility

No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

Pregnancy

There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. Any effects of denosumab are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a “knockout mouse”), studies suggest absence of RANKL (the target of denosumab see section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.

7. Effects on ability to drive and use machines

Information provided in this section is based on the innovator data.

Denosumab has no or negligible influence on the ability to drive and use machines.

8. Undesirable effects

Information provided below is based on the study conducted with Intas Denosumab.

In a multicentric, randomized, assessor-blind, parallel-group, phase III study, 114 women with postmenopausal osteoporosis were randomized to receive 6 monthly SC injection of 60 mg denosumab (manufactured by Intas Pharmaceuticals Limited; n=58) or Prolia® (manufactured by Amgen, USA; n=56) for an year. Patients also received calcium 1000 mg daily and vitamin D 400 IU daily for 12 months. All 114 randomized patients were included in safety population.

Total 64 adverse events (AEs) were reported in 45 patients during the study; 34 AEs in 26 patients from Intas Denosumab group and 30 AEs in 19 patients from Prolia® group.

The most commonly reported AEs (incidence in ≥3% patients) during the study were pyrexia (7.02%), asthenia (6.14%), arthralgia (4.39%), hyperchlorhydria (4.39%) and urinary tract infection (3.51%).

Table 1: Adverse Events Reported in Postmenopausal Women with Osteoporosis Treated with Intas Denosumab or Prolia® (Safety Population)

System organ class; Preferred term	Number of AEs (% of patients)	
	Intas Denosumab (n=58)	Prolia® (n=56)
Gastrointestinal disorders		
Aphthous ulcer	1 (1.72%)	0 (0%)
Diarrhoea	0 (0%)	1 (1.79%)
Dyspepsia	1 (1.72%)	0 (0%)
Hyperchlorhydria	3 (5.17%)	2 (3.57%)
General disorders and administration site conditions		
Asthenia	1 (1.72%)	6 (10.71%)
Pain	1 (1.72%)	0 (0%)
Pyrexia	3 (5.17%)	6 (8.93%)
Infections and infestations		
Chikungunya virus infection	1 (1.72%)	0 (0%)
Nasopharyngitis	1 (1.72%)	1 (1.79%)
Pharyngitis	1 (1.72%)	0 (0%)
Upper respiratory tract infection	0 (0%)	2 (1.79%)
Urinary tract infection	3 (5.17%)	1 (1.79%)
Injury, poisoning and procedural complications		
Injury	1 (1.72%)	0 (0%)
Limb injury	1 (1.72%)	0 (0%)
Muscle injury	0 (0%)	1 (1.79%)
Investigations		
Aspartate aminotransferase increased	0 (0%)	1 (1.79%)
White blood cells urine	1 (1.72%)	0 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (6.90%)	1 (1.79%)
Back pain	2 (3.45%)	1 (1.79%)
Musculoskeletal pain	1 (1.72%)	0 (0%)
Musculoskeletal stiffness	1 (1.72%)	0 (0%)
Neck pain	1 (1.72%)	0 (0%)
Pain in extremity	0 (0%)	1 (1.79%)
Polyarthritis	1 (1.72%)	0 (0%)

System organ class; Preferred term	Number of AEs (% of patients)	
	Intas Denosumab (n=58)	Prolia® (n=56)
Nervous system disorders		
Dizziness	0 (0%)	1 (1.79%)
Headache	1 (1.72%)	1 (1.79%)
Lethargy	0 (0%)	1 (1.79%)
Renal and urinary disorders		
Haematuria	1 (1.72%)	0 (0%)
Ketonuria	1 (1.72%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (1.72%)	2 (3.57%)
Sneezing	0 (0%)	1 (1.79%)
Surgical and medical procedures		
Skin graft	1 (1.72%)	0 (0%)

Immunogenicity

In a multicentric, randomized, assessor-blind, parallel-group, phase III study in 114 female patients with postmenopausal osteoporosis, incidence of anti-drug antibody against Intas Denosumab and Prolia® was evaluated. Blood samples were collected at baseline, day 84, day 85, day 168 and day 364 (end of study). All samples were negative for anti-drug antibodies.

Information provided below is based on the innovator data.

Summary of the safety profile

The overall safety profile of denosumab was similar in patients with osteoporosis and in breast or prostate cancer patients receiving hormone ablation in five Phase III placebo-controlled clinical trials.

The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures (see sections 4.4 and 4.8 – description of selected adverse reactions) have been observed in patients taking denosumab.

Tabulated list of adverse reactions

The data in Table 2 below describe adverse reactions reported from Phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting.

The following convention has been used for the classification of the adverse reactions (Table 2): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse Reactions Reported in Patients with Osteoporosis and Breast or Prostate Cancer Patients Receiving Hormone Ablation

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common	Urinary tract infection
	Common	Upper respiratory tract infection
	Uncommon	Diverticulitis[1]
	Uncommon	Cellulitis[1]
	Uncommon	Ear infection
Immune system disorders	Rare	Drug hypersensitivity[1]
	Rare	Anaphylactic reaction[1]
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]
Nervous system disorders	Common	Sciatica
Eye disorders	Common	Cataracts[1]
Gastrointestinal disorders	Common	Constipation
	Common	Abdominal discomfort
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Eczema
	Common	Alopecia
	Uncommon	Lichenoid drug eruptions[1]
	Very rare	Hypersensitivity vasculitis
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity
	Very common	Musculoskeletal pain[1]
	Rare	Osteonecrosis of the jaw[1]
	Rare	Atypical femoral fractures[1]
	Not known	Osteonecrosis of the external auditory canal[2]

[1] See section Description of selected adverse reactions
[2] See section 4.4 Special warnings and precautions for use

In a pooled analysis of data from all phase II and phase III placebo controlled studies, Influenza-like illness was reported with a crude incidence rate of 1.2% for denosumab and 0.7% for placebo. Although this imbalance was identified via a pooled analysis, it was not identified via a stratified analysis.

Description of selected adverse reactions

Hypocalcaemia

In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following denosumab administration. Declines of serum calcium levels (less than 1.88 mmol/l) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported predominantly in patients at increased risk of hypocalcaemia receiving denosumab, with most cases occurring in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status. Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.

Skin infections

In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus denosumab [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus denosumab [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus denosumab [1.4%, 12 out of 860]). Skin infections leading to hospitalization were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving denosumab. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the denosumab (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw

ONJ has been reported rarely, in 16 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients. Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with denosumab for up to 10 years. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of denosumab treatment. The risk of ONJ increased with duration of exposure to denosumab.

Atypical fractures of the femur

In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab (see section 4.4).

Diverticulitis

In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for non-metastatic breast cancer.

Drug-related hypersensitivity reactions

In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab.

Musculoskeletal pain

Musculoskeletal pain, including severe cases, has been reported in patients receiving denosumab in the post-marketing setting. In clinical trials, musculoskeletal pain was very common in both denosumab and placebo groups. Musculoskeletal pain leading to discontinuation of study treatment was uncommon.

Lichenoid drug eruptions

Lichenoid drug eruptions (e.g. lichen planus-like reactions) have been reported in patients in the postmarketing setting.

<u>Other special populations</u>

Renal impairment

In clinical studies, patients with severe renal impairment (creatinine clearance <30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product

9. Overdose

Information provided in this section is based on the innovator data.

There is no experience with overdose in clinical studies. Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1,080 mg over 6 months), and no additional adverse reactions were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1.Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases – Other drugs affecting bone structure and mineralization, ATC code: M05BX04

Mechanism of action

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing 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 in cortical and trabecular bone.

Pharmacodynamic effects

Denosumab treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-telopeptides (CTX) (85% reduction) by 3 days, with reductions maintained over the dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥87% to approximately ≥45% (range 45-80%), reflecting the reversibility of denosumab's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Immunogenicity

In clinical studies, neutralizing antibodies have not been observed for denosumab. Using a sensitive immunoassay <1% of patients treated with denosumab for up to 5 years tested positive for non-neutralizing binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

Clinical efficacy

Information provided below is based on the study conducted with Intas Denosumab.

Treatment of osteoporosis in postmenopausal women

Efficacy and safety profile of denosumab (manufactured by Intas Pharmaceuticals Limited) and Prolia® (manufactured by Amgen, USA) was evaluated in a multicentric, randomized,

assessor-blind, parallel-group, phase III study in postmenopausal women with osteoporosis. Total 114 female patients who had completed one year since last menstruation and having bone mineral density (BMD) absolute value consistent with T-score between -2.5 and -4 at either lumbar spine or total hip were randomized to receive single SC injection of 60 mg Intas Denosumab (n=58) or Prolia® (n=56) 6 monthly for an year. Patients also received calcium 1000 mg daily and vitamin D 400 IU daily. Primary efficacy endpoint was to assess mean percent change in BMD at the lumbar spine from baseline to month 12. Secondary efficacy endpoint included mean percent change in bone formation marker (bone-specific alkaline phosphatase) from baseline to months 3, 6, 9 and 12.

Out of 114 patients randomized, 110 patients were included in per-protocol (PP) population (56 from Intas Denosumab group and 54 from Prolia® group). All 114 patients qualified for intent-to-treat (ITT) population analysis. Results of the primary and secondary efficacy endpoint analysis from PP population are summarized in Table 3. There was no statistically significant difference between two groups. Similar conclusions were reported for the ITT population analysis.

Table 3: Efficacy Results Comparing Intas Denosumab with Prolia® in Postmenopausal Women with Osteoporosis (Per-protocol Population)

Endpoint	Mean (SD) percent change from baseline		p-value
	Intas Denosumab (n=56)	Prolia® (n=54)	
BMD at lumbar spine			
Month 12	7.22 (12.722)	7.62 (16.332)	0.8861
Bone-specific alkaline phosphatase			
Month 3	-44.10 (24.079)	-45.92 (27.227)	0.7118
Month 6	-42.28 (31.428)	-45.44 (26.729)	0.5716
Month 9	-52.61 (30.349)	-56.24 (22.951)	0.4796
Month 12	-31.38 (30.431)	-35.13 (35.173)	0.5505

5.2.Pharmacokinetic properties

Information provided below is based on the study conducted with Intas Denosumab.

Pharmacokinetic (PK) profile of Intas Denosumab and Prolia® were evaluated in a subset of women with postmenopausal osteoporosis as a part of the multicentric, randomized, assessor-blind, parallel-group, phase III study. Patients were administered single SC injection of 60 mg Intas Denosumab or Prolia®. Serum samples were collected from 10 patients each from Intas Denosumab and Prolia® groups after administration of Intas Denosumab and Prolia® for up to 168 days. Descriptive statistics of PK parameters of Intas Denosumab and Prolia® is provided in Table 4.

Table 4: Pharmacokinetic Parameters of Intas Denosumab and Prolia® After Single Subcutaneous Injection in Women with Postmenopausal Osteoporosis

Parameters (Units)	Mean ± SD	
	Intas Denosumab (n=10)	Prolia® (n=10)

AUC_{0-t} (ng*h/mL)	5924825.476 ± 2261364.6291	6647544.580 ± 3122017.8998
AUC_{0-inf} (ng*h/mL)	6400008.236 ± 2602066.8847	6875238.211 ± 3139808.6644
C_{max} (ng/mL)	6683.330 ± 2133.6809	7715.027 ± 2785.1342
$T_{1/2}$ (h)	560.043 ± 158.7987	497.604 ± 61.5602

Information provided in this section is based on the innovator data.

Absorption

Following SC administration of a 1.0 mg/kg dose, which approximates the approved 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose level. For a 60 mg SC dose, maximum serum denosumab concentrations (C_{max}) of 6 µg/mL (range 1-17 µg/mL) occurred in 10 days (range 2-28 days).

Biotransformation

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

After C_{max}, serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent (53%) of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics with time was observed upon SC multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics was not affected by the formation of binding antibodies to denosumab and was similar in men and women. Age (28-87 years), race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of denosumab.

A trend was observed between higher body weight and lower exposure based on AUC and C_{max}. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and bone mineral density (BMD) increases were consistent across a wide range of body weight.

Linearity/non-linearity

In dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.

Renal impairment

In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

Hepatic impairment

No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

Paediatric population

The pharmacokinetic profile in paediatric populations has not been assessed.

5.3.Preclinical safety data

Information provided below is based on studies conducted with Intas Denosumab.

In a 28-day repeat-dose toxicity study, Wistar rats were administered Intas Denosumab at the dose levels of 12.4, 24.8 and 62 mg/kg/week and innovator product at the dose level of 12.4 mg/kg/week, by SC route. There was no adverse effect observed on the parameters such as mortality, clinical signs, body weight, food consumption, serum chemistry, organ weight, gross pathology and histopathology. The no observed adverse effect level of Intas Denosumab was 62 mg/kg/week.

Information provided below is based on the innovator data.

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

In preclinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus. An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK RANKL.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralization in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

In preclinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology. Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomized monkeys treated with denosumab.

In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

Knockout mice lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially

reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

6. PHARMACEUTICAL PARTICULARS

6.1.List of excipients

Sorbitol

Polysorbate 20

Glacial acetic acid

Sodium hydroxide*

Water for injection

*If required, adjust the pH of excipient solution (5.2±0.2) with NaOH (10% solution)

6.2.Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3.Shelf life

36 months when stored at 2°C to 8°C.

6.4.Special precautions for storage

Store Denosumab in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton.

Do not freeze.

Protect from direct light and heat.

Do not use Denosumab after the expiry printed on the label. Prior to administration, denosumab may be allowed to reach room temperature (up to 25°C/77°F) in the original container.

Denosumab may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, Denosumab must be used within this 30 day period.

6.5.Nature and contents of container

Denosumab is supplied as 1 mL solution in a single-use prefilled syringe made from type I glass with stainless steel 27 gauge needle.

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

6.6.Special precautions for administration, disposal and other handling

60 mg/1 mL prefilled syringe

Before administration, the solution should be inspected*.*

Do not inject the solution if it is cloudy or discoloured or has particulate matter.

Do not shake excessively.

Allow the prefilled syringe to reach room temperature (up to 25°C) before injecting. Inject the entire contents of the prefilled syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For the preparation and administration of subcutaneous injection, following are required:

- A new Denosumab prefilled syringe
- Alcohol wipes

Instructions for preparation for subcutaneous administration

1. Remove prefilled syringe from the refrigerator.

   Do not pick up the prefilled syringe by the plunger or needle cover. This could damage the device.

2. Allow prefilled syringe to reach room temperature.

   Do not warm it in any other way.

   Do not leave the syringe exposed to direct sunlight.

3. Do not shake the prefilled syringe excessively.
4. Do not remove the needle cover from the prefilled syringe until you are ready to inject.
5. Check the expiry date on the prefilled syringe label.

   Do not use it if the date has passed the last day of the month shown.

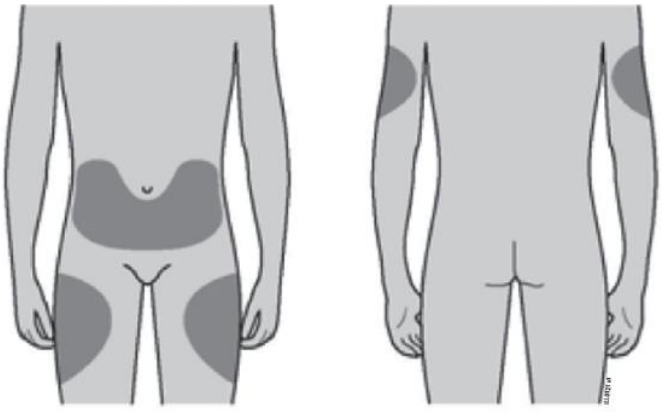
6. Check the appearance of denosumab solution.

   Do not use if solution is cloudy or discoloured or has particulate matter.

7. There may be a small air bubble in the prefilled syringe. This is normal. Removing air bubble from prefilled syringe before injection is not required.
8. Find a comfortable, well-lit, clean surface and put all the equipment within reach.
9. Wash your hands thoroughly.

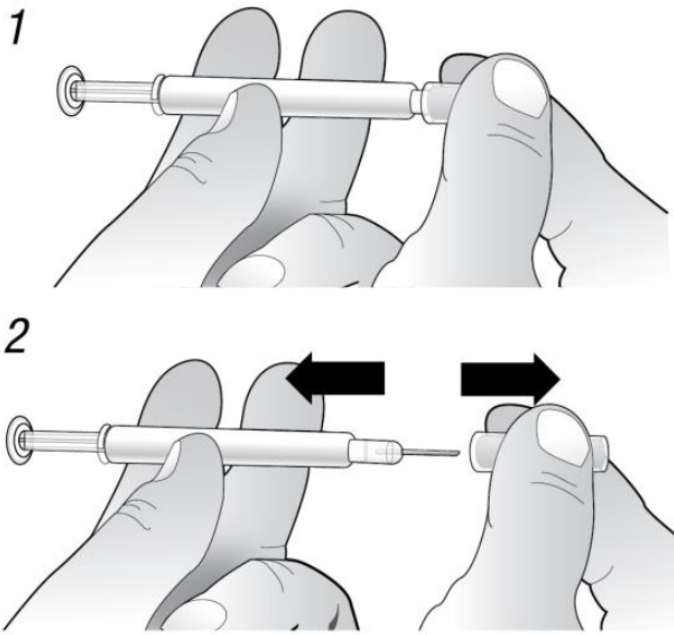
Instructions for subcutaneous administration

1. Choose an injection site. The recommended injections sites for denosumab include: upper arm or upper thigh or abdomen (see below picture).



2. Disinfect injection site skin by using an alcohol wipe.
3. To avoid bending the needle, gently pull the cover from needle straight off without twisting, as shown in pictures 1 and 2 below.

Do not touch the needle or push the plunger.



4. Pinch the clean injection site skin and insert the needle fully into the skin.
5. Push the plunger with a slow constant pressure, always keeping the skin pinched. Push the plunger until all content from the syringe is injected.
6. Remove the needle from skin.
7. Do not rub the injection site. If needed, you may cover the injection site with adhesive.
8. Only use one prefilled syringe for one injection.

   Do not use any denosumab solution that is left in the syringe.

Disposing of used syringes

- Do not put the cover back on used needles.
- Keep used syringes out of the reach and sight of children.
- The used syringe should be disposed of in accordance with the local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS

Intas Pharmaceuticals Limited

Plot No. 423/P/A, Sarkhej - Bavla Highway, Village: Moraiya,

Taluka: Sanand, District: Ahmedabad 382 213, Gujarat, India

8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0279

9. DATE OF FIRST REGISTRATION

19th July, 2022

10. DATE OF REVISION