Wyost®

1. NAME OF THE MEDICINAL PRODUCT

Wyost 120 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL).

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.

Excipient with known effects:

Each 1.7 mL of solution contains 78 mg sorbitol
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to slightly yellowish or slightly brownish solution with a pH between 4.9 and 5.5 and an osmolality of 245 – 345 mOsmol/kg

Patient safety information Card
The marketing of Wyost is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

Wyost is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Xgeva. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. Information regarding biosimilar products can be found on the website of the Ministry of Health:

https://www.gov.il/he/Departments/General/biosimilar.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours. Treatment of adult and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

4.2 Posology and method of administration

Wyost should be administered under the responsibility of a healthcare professional.

Posology

Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcemia is present (see section 4.4).

Patients treated with Wyost should be given the package leaflet and the 'patient safety information card'.

Prevention of skeletal related events in adults with multiple myeloma and in adults with bone metastases from solid tumors
The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.

Giant cell tumor of bone
The recommended dose of Wyost is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.

Patients in the phase II study who underwent complete resection of giant cell tumor of bone did receive an additional 6 months of treatment following the surgery as per study protocol.

Patients with giant cell tumor of bone should be evaluated at regular intervals to determine whether they continue to benefit from treatment. In patients whose disease is controlled by Wyost, the effect of interruption or cessation of treatment has not been evaluated, however limited data in these patients does not indicate a rebound effect upon cessation of treatment.

Renal impairment
No dose adjustment is required in patients with renal impairment (see sections 4.4 for recommendations relating to monitoring of calcium, 4.8 and 5.2).

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 (see section 5.2).

Pediatric population
The safety and efficacy of Wyost have not been established in pediatric patients (age < 18) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumor of bone.

Wyost is not recommended in pediatric patients (age < 18) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumor of bone (see section 4.4).

Treatment of skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, the posology is the same as in adults.

Inhibition of receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition (see section 5.3).

Method of administration
For subcutaneous use.

For instructions for use, handling and disposal, see section 6.6.

4.3 Contraindications

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

Severe, untreated hypocalcemia (see section 4.4).

Unhealed lesions from dental or oral surgery.

4.4 Special warnings and precautions for use

Calcium and vitamin D supplementation
Supplementation with calcium and vitamin D is required in all patients unless hypercalcemia is present (see section 4.2).

Hypocalcemia
Pre-existing hypocalcemia must be corrected prior to initiating therapy with Wyost. Hypocalcemia can occur at any time during therapy with Wyost. Monitoring of calcium levels should be conducted (i) prior to the initial dose of Wyost, (ii) within two weeks after the initial dose, (iii) if suspected symptoms of hypocalcemia occur (see section 4.8 for symptoms). Additional monitoring of calcium level should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated based on the clinical condition of the patient.

Patients should be encouraged to report symptoms indicative of hypocalcemia. If hypocalcemia occurs while receiving Wyost, additional calcium supplementation and additional monitoring may be necessary.

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

Renal impairment
Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. The risk of developing hypocalcemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients.

Osteonecrosis of the jaw (ONJ)
ONJ has been reported commonly in patients receiving denosumab (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.

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., anemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, pre-existing 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 Wyost 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 Wyost 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 co-morbid 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 Wyost 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.

Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and in patients with growing skeletons

Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in denosumab -treated patients with giant cell tumor of bone weeks to months following treatment discontinuation.

After treatment is discontinued, monitor patients for signs and symptoms of hypercalcemia, consider periodic assessment of serum calcium and re-evaluate the patient's calcium and vitamin D supplementation requirements (see section 4.8).

Denosumab is not recommended in patients with growing skeletons (see section 4.2). Clinically significant hypercalcemia has also been reported in this patient group weeks to months following treatment discontinuation.

Multiple vertebral fractures (MVF) following treatment discontinuation

Cases of multiple vertebral fractures (MVF) have occurred rarely following discontinuation of denosumab in patients participating in ongoing clinical trials. These fractures were not due to bone metastases and occurred approximately 1 year following discontinuation of treatment with denosumab , particularly in post-menopausal women with malignancies with risk factors such as osteoporosis or prior (non-vertebral or vertebral) fractures.

Consistent with the pharmacological properties of denosumab , effects on bone are known to be reversible and bone turnover increases after denosumab is discontinued.

Advise patients not to interrupt denosumab therapy without their physician's advice.

When denosumab

treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

Others

Patients being treated with Wyost should not be treated concomitantly with other denosumab containing medicinal products (for osteoporosis indications).

Patients being treated with Wyost should not be treated concomitantly with bisphosphonates.

Malignancy in giant cell tumor of bone or progression to metastatic disease is an infrequent event and a known risk in patients with giant cell tumor of bone. Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis. Available clinical data does not suggest an increased risk of malignancy in giant cell tumor of bone patients treated with denosumab.

Excipients

This medicinal product contains 78.9 mg sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol sodium (23 mg) per 120 mg dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In clinical trials, denosumab has been administered in combination with standard anti-cancer treatment and in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in trough serum concentration and

pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTx/Cr) by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure.

4.6 Fertility, pregnancy and lactation

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).

Wyost is not recommended during pregnancy 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 Wyost. Any effects of Wyost 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. A risk to the newborns/infants cannot be excluded. Knockout mouse studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision must be made on whether to abstain from breast-feeding or to abstain from Wyost therapy, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of therapy for the woman.

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).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Overall safety profile is consistent in all approved indications for Wyost.

Hypocalcemia has very commonly been reported following denosumab administration, mostly within the first 2 weeks. Hypocalcemia can be severe and symptomatic (see section 4.8 - description of selected adverse reactions). The decreases in serum calcium were generally appropriately managed by calcium and vitamin D supplementation. The most common adverse reactions with denosumab are musculoskeletal pain. Cases of osteonecrosis of the jaw (ONJ) (see sections 4.4 and 4.8 – Description of selected adverse reactions) have been commonly observed in patients taking denosumab.

Tabulated list of adverse reactions

The following convention has been used for the classification of the adverse reactions based on incidence rates in four phase III, two phase II clinical studies and post-marketing experience (see table 1): 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), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in patients with advanced malignancies involving bone, multiple myeloma, or with giant cell tumor of bone

MedDRA system organ class	Frequency category	Adverse reactions
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	New primary malignancy[1]
Immune system disorders	Rare	Drug hypersensitivity[1]
	Rare	Anaphylactic reaction[1]
Metabolism and nutrition disorders	Very common	Hypocalcemia[1, 2]

MedDRA system organ class	Frequency category	Adverse reactions
	Common	Hypophosphatemia
	Uncommon	Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone[3]
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnea
Gastrointestinal disorders	Very common	Diarrhea
	Common	Tooth extraction
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Lichenoid drug eruptions[1]
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[1]
	Common	Osteonecrosis of the jaw[1]
	Uncommon	Atypical femoral fracture[1]
	Rare	Multiple vertebral fractures following treatment discontinuation[3]
	Not known	Osteonecrosis of the external auditory canal[3,4]

[1] See section Description of selected adverse reactions
[2] See section Other special populations
[3] See section 4.4
[4] Class effect

Description of selected adverse reactions

Hypocalcemia
A higher incidence of hypocalcemia among subjects treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical trials.

The highest incidence of hypocalcemia was observed in a phase III trial in patients with multiple myeloma. Hypocalcemia was reported in 16.9% of patients treated with denosumab and 12.4% of patients treated with zoledronic acid. A grade 3 decrease in serum calcium levels was experienced in 1.4% of patients treated with XGEVA and 0.6% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.4% of patients treated with denosumab and 0.1% of patients treated with zoledronic acid.

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcemia was reported in 9.6% of patients treated with denosumab and 5.0% of patients treated with zoledronic acid.

A grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with denosumab and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with denosumab and 0.2% of patients treated with zoledronic acid (see section 4.4).

In two phase II single-arm clinical trials in patients with giant cell tumor of bone, hypocalcemia was reported in 5.7% of patients. None of the adverse events was considered serious.

In the post-marketing setting, severe symptomatic hypocalcemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy. Examples of clinical manifestations of severe symptomatic hypocalcemia have included QT interval prolongation, tetany, seizures and altered mental status (including coma) (see section 4.4). Symptoms of hypocalcemia in clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

Osteonecrosis of the jaw (ONJ)
In clinical trials, the incidence of ONJ was higher with longer duration of exposure; ONJ has also been diagnosed after stopping treatment with denosumab with the majority of cases occurring within 5 months after the last dose. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure were excluded from the clinical trials.

A higher incidence of ONJ among subjects treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical trials. The highest incidence of ONJ was observed in a phase III trial in patients with multiple myeloma. In the double-blind treatment phase of this trial, ONJ was confirmed in 5.9% of patients treated with denosumab (median exposure of 19.4 months; range: 1 - 52) and in 3.2% of patients treated with zoledronic acid. At the completion of the double-blind treatment phase of this trial, the patient-year adjusted incidence of confirmed ONJ in the denosumab group (median exposure of 19.4 months; range: 1 - 52), was 2.0 per 100 patient-years during the first year of treatment, 5.0 in the second year, and 4.5 thereafter. The median time to ONJ was 18.7 months (range: 1 - 44).

In the primary treatment phases of three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with denosumab (median exposure of 12.0 months; range: 0.1 – 40.5) and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most (81% in both treatment groups) had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. Most subjects were receiving or had received chemotherapy.

The trials in patients with breast or prostate cancer included an denosumab extension treatment phase (median overall exposure of 14.9 months; range: 0.1 – 67.2). ONJ was confirmed in 6.9% of patients with breast cancer and prostate cancer during the extension treatment phase.

The patient-year adjusted overall incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.7 in the second year and 4.6 thereafter. The median time to ONJ was 20.6 months (range: 4 - 53).

A non-randomized, retrospective, observational study in 2,877 patients with cancer treated with denosumab or zoledronic acid in Sweden, Denmark, and Norway showed that 5-year incidence proportions of medically confirmed ONJ were 5.7% (95% CI: 4.4, 7.3; median follow-up time of 20 months [range: 0.2-60]) in a cohort of patients receiving denosumab and 1.4% (95% CI: 0.8, 2.3; median follow-up time of 13 months [range: 0.1-60]) in a separate cohort of patients receiving zoledronic acid. Five-year incidence proportion of ONJ in patients switching from zoledronic acid to denosumab was 6.6% (95% CI: 4.2, 10.0; median follow-up time of 13 months [range: 0.2-60]).

In a phase III trial in patients with non-metastatic prostate cancer (a patient population for which denosumab is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.0 in the second year, and 7.1 thereafter.

In a long-term phase II open-label clinical trial in patients with giant cell tumor of bone (Study 6, see section 5.1), ONJ was confirmed in 6.8% of patients, including one adolescent (median number of 34 doses; range: 4 – 116). At the completion of the trial, median time on trial including safety follow-up phase was 60.9 months (range: 0 – 112.6). The patient-year adjusted incidence of confirmed ONJ was 1.5 per 100 patient-years overall (0.2 per 100 patient-years during the first year of treatment, 1.5 in the second year, 1.8 in the third year, 2.1 in the fourth year, 1.4 in the fifth year, and 2.2 thereafter). The median time to ONJ was 41 months (range: 11 - 96).

Study 7 was conducted to continue to follow patients with GCTB who were treated in study 6 for an additional 5 or more years. ONJ was reported in 6 patients (11.8%) of the 51 exposed patients with median total 42 doses of denosumab. Three of these cases of ONJ were medically confirmed.

Drug related hypersensitivity reactions
In the post-marketing setting, events of hypersensitivity, including rare events of anaphylactic reactions, have been reported in patients receiving denosumab.

Atypical fractures of the femur
In the clinical trial program, atypical femoral fractures have been reported uncommonly in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued (see section 4.4).

In the clinical trial program for GCTB, atypical femoral fractures have been reported commonly in patients treated with denosumab. In study 6, incidence of confirmed AFF was 0.95% (5/526) in patients with giant cell tumor of bone. In the follow-up study 7, the incidence of confirmed AFF was 3.9% (2/51) of patients exposed to denosumab.

Musculoskeletal pain

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

New primary malignancy
In the primary double-blind treatment phases of four phase III active-controlled clinical trials in patients with advanced malignancies involving bone, new primary malignancy was reported in 54/3691 (1.5%) of patients treated with denosumab (median exposure of 13.8 months; range: 1.0–51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0-50.8).

The cumulative incidence at one year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively.

No treatment-related pattern in individual cancers or cancer groupings was apparent.

In patients with giant cell tumor of bone, incidence of new malignancy, including malignancies involving the bone and outside the bone was 3.8% (20/526) in study 6. In the follow-up study 7, the incidence was 11.8% (6/51) of patients exposed to denosumab.

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

Pediatric population

Denosumab was studied in an open-label trial that enrolled 28 skeletally mature adolescents with giant cell tumor of bone. Based on these limited data, the adverse event profile appeared to be similar to adults.

Clinically significant hypercalcemia after treatment discontinuation has been reported in the post-marketing setting in pediatric patients (see section 4.4).

Other special populations

Renal impairment
In a clinical study of patients without advanced cancer with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis, there was a greater risk of developing hypocalcemia in the absence of calcium supplementation. The risk of developing hypocalcemia during denosumab treatment is greater with increasing degree of renal impairment. In a clinical study in patients without advanced cancer, 19% of patients with severe renal impairment (creatinine clearance < 30 mL/min) and 63% of patients receiving dialysis developed hypocalcemia despite calcium supplementation. The overall incidence of clinically significant hypocalcemia was 9%.

Accompanying increases in parathyroid hormone have also been observed in patients receiving denosumab with severe renal impairment or receiving dialysis. Monitoring of calcium levels and adequate intake of calcium and vitamin D is especially important in patients with renal impairment (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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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 and 120 mg weekly for 3 weeks.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
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 metastatic bone disease and multiple myeloma. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

Giant cell tumors of bone are characterized by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumor of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumor stroma is replaced with non-proliferative, differentiated, densely woven new bone.

Pharmacodynamic effects

In phase II clinical studies of patients with advanced malignancies involving bone, subcutaneous (SC) dosing of denosumab administered either every 4 weeks (Q4W) or every 12 weeks resulted in a rapid reduction in markers of bone resorption (uNTx/Cr, serum CTx [cross-linked C-telopeptide of type I collagen]), with median reductions of approximately 80% for uNTx/Cr occurring within
1 week regardless of prior bisphosphonate therapy or baseline uNTx/Cr level. In phase III clinical trials of patients with advanced malignancies involving bone, median uNTx/Cr reductions of approximately 80% were maintained through 49 weeks of denosumab treatment (120 mg every Q4W).

Immunogenicity

In clinical studies, neutralizing antibodies have not been observed for denosumab in advanced cancer patients or giant cell tumor of bone patients. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 3 years tested positive for non-neutralizing binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

Clinical efficacy and safety in patients with bone metastases from solid tumors

Efficacy and safety of 120 mg denosumab SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks were compared in three randomized, double-blind, active-controlled studies, in IV-bisphosphonate naïve patients with advanced malignancies involving bone: adults with breast cancer (study 1), other solid tumors or multiple myeloma (study 2), and castrate-resistant prostate cancer (study 3). Within these active-controlled clinical trials, safety was evaluated in 5,931 patients. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure, were not eligible for inclusion in these studies. The primary and secondary endpoints evaluated the occurrence of one or more skeletal related events (SREs). In studies demonstrating superiority of denosumab to zoledronic acid, patients were offered open-label denosumab in a pre-specified 2-year extension treatment phase. An SRE was defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.

Denosumab reduced the risk of developing a SRE, and developing multiple SREs (first and subsequent) in patients with bone metastases from solid tumors (see table 2).

Table 2: Efficacy results in patients with advanced malignancies involving bone

	Study 1 breast cancer		**Study 2 other solid tumors** or multiple myeloma**		**Study 3 prostate cancer**		**Combined advanced cancer**	
	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid
N	1,026	1,020	886	890	950	951	2,862	2,861
First SRE								
Median time (months)	NR	26.4	20.6	16.3	20.7	17.1	27.6	19.4
Difference in median time (months)	NA		4.2		3.5		8.2	
HR (95% CI)/RRR (%)	0.82 (0.71, 0.95)/18		0.84 (0.71, 0.98)/16		0.82 (0.71, 0.95)/18		0.83 (0.76, 0.90)/17	
Non-inferiority/Superiority p-values	< 0.0001†/0.0101†		0.0007†/0.0619†		0.0002†/0.0085†		< 0.0001/< 0.0001	
Proportion of subjects (%)	30.7	36.5	31.4	36.3	35.9	40.6	32.6	37.8
First and subsequent SRE*								
Mean number/patient	0.46	0.60	0.44	0.49	0.52	0.61	0.48	0.57
Rate ratio (95% CI)/RRR (%)	0.77 (0.66, 0.89)/23		0.90 (0.77, 1.04)/10		0.82 (0.71, 0.94)/18		0.82 (0.75, 0.89)/18	

Superiority p-value	0.0012†		0.1447†		0.0085†		< 0.0001	
	Study 1 breast cancer		**Study 2 other solid tumors** or multiple myeloma**		**Study 3 prostate cancer**		**Combined advanced cancer**	
	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid
SMR per Year	0.45	0.58	0.86	1.04	0.79	0.83	0.69	0.81
First SRE or HCM								
Median time (months)	NR	25.2	19.0	14.4	20.3	17.1	26.6	19.4
HR (95% CI)/RRR (%)	0.82 (0.70, 0.95)/18		0.83 (0.71, 0.97)/17		0.83 (0.72, 0.96)/17		0.83 (0.76, 0.90)/17	
Superiority p-value	0.0074		0.0215		0.0134		< 0.0001	
First radiation to bone								
Median time (months)	NR	NR	NR	NR	NR	28.6	NR	33.2
HR (95% CI)/RRR (%)	0.74 (0.59, 0.94)/26		0.78 (0.63, 0.97)/22		0.78 (0.66, 0.94)/22		0.77 (0.69, 0.87)/23	
Superiority p-value	0.0121		0.0256		0.0071		< 0.0001	

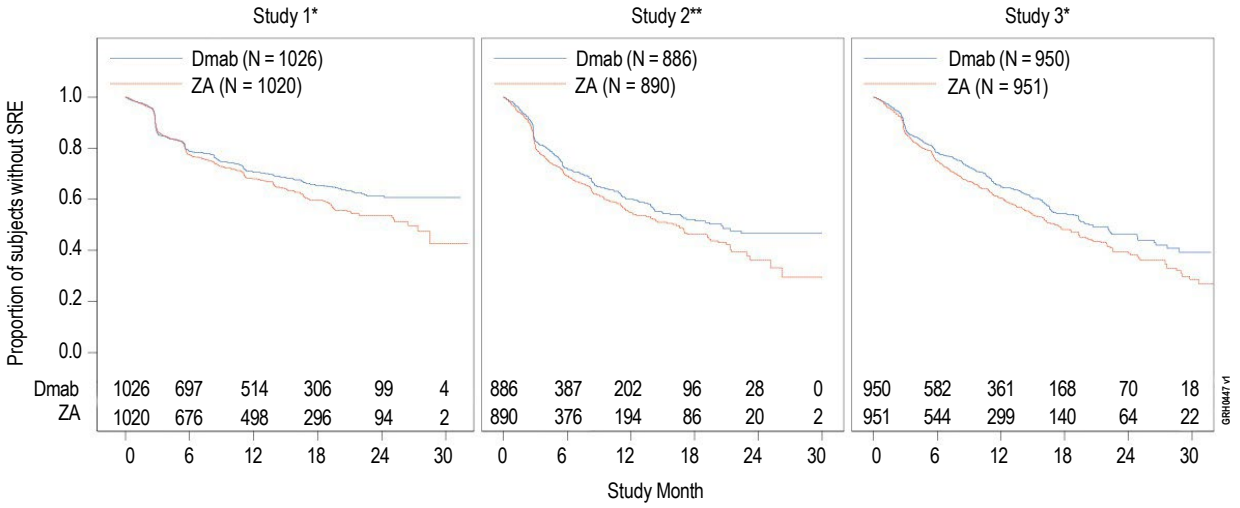
NR = not reached; NA = not available; HCM = hypercalcemia of malignancy; SMR = skeletal morbidity rate; HR = hazard ratio; RRR = relative risk reduction;

† Adjusted p-values are presented for studies 1, 2 and 3 (first SRE and first and subsequent SRE endpoints);

* Accounts for all skeletal events over time; only events occurring ≥ 21 days after the previous event are counted;

** Including non-small cell lung cancer (NSCLC), renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, GI/genitourinary cancer and others, excluding breast and prostate cancer.

Figure 1. Kaplan-Meier plots of time to first on-study SRE



Dmab = Denosumab 120 mg Q4W
ZA = Zoledronic Acid 4 mg Q4W
N = Number of subjects randomized
* = Statistically significant for superiority; ** = Statistically significant for non-inferiority

Disease progression and overall survival with bone metastases from solid tumors

Disease progression was similar between denosumab and zoledronic acid in all three studies and in the pre-specified analysis of all three studies combined.

In studies 1, 2 and 3, overall survival was balanced between denosumab and zoledronic acid in patients with advanced malignancies involving bone: patients with breast cancer (hazard ratio and 95% CI was 0.95 [0.81, 1.11]), patients with prostate cancer (hazard ratio and 95% CI was 1.03 [0.91, 1.17]), and patients with other solid tumors or multiple myeloma (hazard ratio and 95% CI was 0.95 [0.83, 1.08]). A post-hoc analysis in study 2 (patients with other solid tumors or multiple myeloma) examined overall survival for the 3 tumor types used for stratification (non-small cell lung cancer, multiple myeloma, and other). Overall survival was longer for denosumab in non-small cell lung cancer (hazard ratio 95% CI of 0.79 [0.65, 0.95]; n = 702) and longer for zoledronic acid in multiple myeloma (hazard ratio 95% CI of 2.26 [1.13, 4.50]; n = 180) and similar between denosumab and zoledronic acid in other tumor types (hazard ratio 95% CI of 1.08 (0.90, 1.30); n = 894). This study did not control for prognostic factors and anti-

neoplastic

treatments. In a combined pre-specified analysis from studies 1, 2 and 3, overall survival was similar between denosumab and zoledronic acid (hazard ratio and 95% CI 0.99 [0.91, 1.07]).

Effect on pain

The time to pain improvement (i.e. ≥ 2-point decrease from baseline in Brief Pain Inventory-Short Form (BPI-SF) worst pain score) was similar for denosumab and zoledronic acid in each study and the integrated analyzes. In a post-hoc analysis of the combined dataset, the median time to worsening pain (> 4-point worst pain score) in patients with mild or no pain at baseline was delayed for denosumab compared to zoledronic acid (198 versus 143 days) (p-value = 0.0002).

Clinical efficacy in patients with multiple myeloma

Denosumab was evaluated in an international, randomized (1:1), double-blind, active-controlled study comparing denosumab with zoledronic acid in patients with newly diagnosed multiple myeloma, study 4.

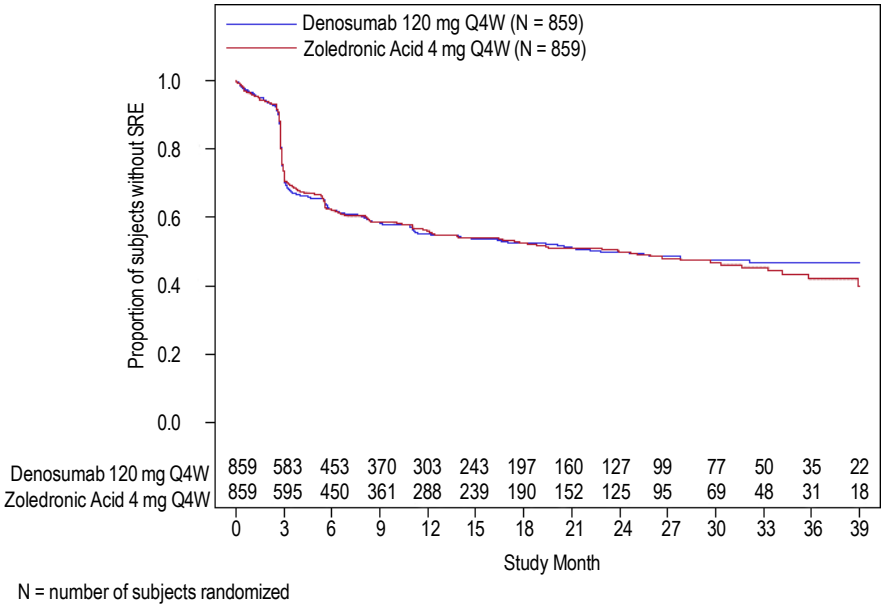
In this study, 1,718 multiple myeloma patients with at least one bone lesion were randomized to receive 120 mg denosumab subcutaneously every 4 weeks (Q4W) or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose-adjusted for renal function). The primary outcome measure was demonstration of non-inferiority of time to first on-study skeletal related event (SRE) as compared to zoledronic acid. Secondary outcome measures included superiority of time to first SRE, superiority of time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.

Across both study arms, 54.5% of patients intended to undergo autologous PBSC transplantation, 95.8% patients utilized/planned to utilize a novel anti-myeloma agent (novel therapies include bortezomib, lenalidomide, or thalidomide) in first-line therapy, and 60.7% of patients had a previous SRE. The number of patients across both study arms with ISS stage I, stage II, and stage III at diagnosis were 32.4%, 38.2%, and 29.3%, respectively.

The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.

Efficacy results from study 4 are presented in figure 2 and table 3.

Figure 2. Kaplan-Meier plot for time to first on-study SRE in patients with newly diagnosed multiple myeloma



N = number of subjects randomized

Table 3: Efficacy results for denosumab compared to zoledronic acid in patients with newly diagnosed multiple myeloma

	denosumab **(N = 859)**	**Zoledronic Acid (N = 859)**
First SRE		
Number of patients who had SREs (%)	376 (43.8)	383 (44.6)

Median time to SRE (months)	22.8 (14.7, NE)	23.98 (16.56, 33.31)
	denosumab **(N = 859)**	**Zoledronic Acid (N = 859)**
Hazard ratio (95% CI)	0.98 (0.85, 1.14)	
First and subsequent SRE		
Mean number of events/patient	0.66	0.66
Rate ratio (95% CI)	1.01 (0.89, 1.15)	
Skeletal morbidity rate per year	0.61	0.62
First SRE or HCM		
Median time (months)	22.14 (14.26, NE)	21.32 (13.86, 29.7)
Hazard ratio (95% CI)	0.98 (0.85, 1.12)	
First radiation to bone		
Hazard ratio (95% CI)	0.78 (0.53, 1.14)	
Overall survival		
Hazard ratio (95% CI)	0.90 (0.70, 1.16)	

NE = not estimable
HCM = hypercalcemia of malignancy

Clinical efficacy and safety in adults and skeletally mature adolescents with giant cell tumor of bone
The safety and efficacy of denosumab was studied in two phase II open-label, single-arm trials (studies 5 and 6) that enrolled 554 patients with giant cell tumor of bone that was either unresectable or for which surgery would be associated with severe morbidity. Patients received 120 mg denosumab subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15. Patients who discontinued XGEVA then entered the safety follow-up phase for a minimum of 60 months. Retreatment with XGEVA while in safety follow-up was allowed for subjects who initially demonstrated a response to denosumab (e.g., in the case of recurrent disease).

Study 5 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumor of bone. The main outcome measure of the trial was response rate, defined as either at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells), or a lack of progression of the target lesion by radiographic measurements in cases where histopathology was not available.

Of the 35 patients included in the efficacy analysis, 85.7% (95% CI: 69.7, 95.2) had a treatment response to denosumab. All 20 patients (100%) with histology assessments met response criteria. Of the remaining 15 patients, 10 (67%) radiographic measurements showed no progression of the target lesion.

Study 6 enrolled 535 adult or skeletally mature adolescents with giant cell tumor of bone. Of these patients, 28 were aged 12-17 years. Patients were assigned to one of three cohorts: cohort 1 included patients with surgically unsalvageable disease (e.g., sacral, spinal, or multiple lesions, including pulmonary metastases); cohort 2 included patients with surgically salvageable disease whose planned surgery was associated with severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); cohort 3 included patients previously participating in study 5 and rolled over into this study. The primary objective was to evaluate the safety profile of denosumab in subjects with giant cell tumor of bone. The secondary outcome measures of the study included time to disease progression (based on investigator assessment) for cohort 1 and proportion of patients without any surgery at month 6 for cohort 2.

In cohort 1 at the final analysis, 28 of the 260 treated patients (10.8%) had disease progression. In cohort 2, 219 of the 238 (92.0%; 95% CI: 87.8%, 95.1%) evaluable patients treated with denosumab had not undergone surgery by month 6. Of the 239 subjects in cohort 2 with baseline target lesion location or on-study location not in lungs or soft tissue, a total of 82 subjects (34.3%) were able to avoid on-study surgery. Overall, efficacy results in skeletally mature adolescents were similar to those observed in adults.

Effect on pain

In the final analysis cohorts 1 and 2 combined, a clinically meaningful reduction in worst pain (i.e. ≥ 2-point decrease from baseline) was reported for 30.8% of patients at risk (i.e. those who had a worst pain score of ≥ 2 at baseline) within 1 week of treatment, and ≥ 50% at week 5. These pain improvements were maintained at all subsequent evaluations.

Pediatric population

In study 6, denosumab has been evaluated in a subset of 28 adolescent patients (aged 13-17 years) with giant cell tumor of bone who had reached skeletal maturity defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg. One adolescent subject with surgically unsalvageable disease (N=14) had disease recurrence during initial treatment. Thirteen of the 14 subjects with surgically salvageable disease whose planned surgery was associated with severe morbidity had not undergone surgery by month 6.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration, bioavailability was 62%.

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

In subjects with advanced cancer, who received multiple doses of 120 mg every 4 weeks an approximate 2-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months, consistent with time-independent pharmacokinetics. In subjects with multiple myeloma who received 120 mg every 4 weeks, median trough levels varied by less than 8% between months 6 and 12. In subjects with giant cell tumor of bone who received 120 mg every 4 weeks with a loading dose on days 8 and 15, steady-state levels were achieved within the first month of treatment. Between weeks 9 and 49, median trough levels varied by less than 9%. In subjects who discontinued 120 mg every 4 weeks, the mean half-life was 28 days (range: 14 to 55 days).

A population pharmacokinetic analysis did not indicate clinically significant changes in the systemic exposure of denosumab at steady-state with respect to age (18 to 87 years), race/ethnicity (Blacks, Hispanics, Asians and Caucasians explored), gender or solid tumor types or patients with multiple myeloma. Increasing body weight was associated with decreases in systemic exposure, and vice versa. The alterations were not considered clinically-relevant, since pharmacodynamic effects based on bone turnover markers were consistent across a wide range of body weight.

Linearity/non-linearity

Denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, but approximately dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher. The non-linearity is likely due to a saturable target-mediated elimination pathway of importance at low concentrations.

Renal impairment

In studies of denosumab (60 mg, n = 55 and 120 mg, n = 32) in patients without advanced cancer but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus dose adjustment for renal impairment is not required. There is no need for renal monitoring with denosumab dosing.

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.

Elderly

No overall differences in safety or efficacy were observed between geriatric patients and younger patients. Controlled clinical studies of denosumab in patients with advanced malignancies involving bone over age 65 revealed similar efficacy and safety in older and younger patients. No dose adjustment is required in elderly patients.

Pediatric population

In skeletally-mature adolescents (12-17 years of age) with giant cell tumor of bone who received 120 mg every 4 weeks with a loading dose on days 8 and 15, the pharmacokinetics of denosumab were similar to those observed in adult subjects with GCTB.

5.3 Preclinical safety data

Since the biological activity of denosumab in animals is specific to non-human primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, such as OPG-Fc and RANK-Fc, were used to evaluate the pharmacodynamic properties of denosumab in rodent models.

In mouse bone metastasis models of estrogen receptor positive and negative human breast cancer, prostate cancer and non-small cell lung cancer, OPG-Fc reduced osteolytic, osteoblastic, and osteolytic/osteoblastic lesions, delayed formation of *de novo* bone metastases, and reduced skeletal tumor growth. When OPG-Fc was combined with hormonal therapy (tamoxifen) or chemotherapy (docetaxel) in these models, there was additive inhibition of skeletal tumor growth in breast, and prostate or lung cancer respectively. In a mouse model of mammary tumor induction, RANK-Fc reduced hormone-induced proliferation in mammary epithelium and delayed tumor formation.

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 single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 2.7 to 15 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.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester of pregnancy, denosumab doses resulting in 9 times greater systemic exposure than the recommended human dose did not induce maternal toxicity or fetal harm during a period equivalent to the first trimester, although fetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at systemic exposures 12-fold higher than the human dose, 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 labor; adverse maternal effects occurred infrequently during labor. 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.

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 remodeling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

In preclinical studies knockout mice lacking RANK or RANKL had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) and exhibited impairment of lymph node formation. Neonatal RANK/RANKL knockout mice exhibited decreased body weight, reduced bone growth, altered growth plates and lack of tooth eruption. Reduced bone growth, altered growth plates and impaired tooth eruption were also seen in studies of neonatal rats administered RANKL inhibitors, and these changes were partially reversible when dosing of RANKL inhibitor was discontinued. Adolescent primates dosed with denosumab at 2.7 and 15 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
Acetic acid, glacial
Polysorbate 20
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once removed from the refrigerator, Wyost 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

1.7 mL solution in a single use vial (type I glass) with stopper and seal (aluminum) with flip-off cap.

Pack sizes of one vial

6.6 Special precautions for disposal and other handling

- Before administration, the Wyost solution should be inspected visually. Do not inject the solution if it is cloudy or contains visible particles.
- Do not shake.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.
- The entire contents of the vial should be injected.
- A 27 gauge needle is recommended for the administration of denosumab.

- The vial should not be re-entered.

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

7. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS

Sandoz Pharmaceuticals Israel LTD

P.O. BOX 9015, TEL AVIV, ISRAEL
Israel

8. MARKETING AUTHORIZATION NUMBER

178-85-38242-00

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