ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 effect

Each 1.7 mL of solution contains 78.9 mg sorbitol (E 420).

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of skeletal related events (SREs) (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).

Treatment of adults and skeletally mature adolescents with giant cell tumour 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 hypercalcaemia is present (see section 4.4).

Patients treated with Wyost should be given the package leaflet and the patient reminder card.

Prevention of skeletal related events (SREs) in adults with advanced malignancies involving bone
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 tumour 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 tumour of bone did receive an additional 6 months of treatment following the surgery as per study protocol.

Patients with giant cell tumour 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 section 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).

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

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

Treatment of skeletally mature adolescents with giant cell tumour 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 hypocalcaemia (see section 4.4).

Unhealed lesions from dental or oral surgery.

4.4 Special warnings and precautions for use

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

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

Hypocalcaemia

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Wyost. Hypocalcaemia 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 hypocalcaemia occur (see section 4.8 for symptoms). Additional monitoring of calcium level should be considered during therapy in patients with risk factors for hypocalcaemia, or if otherwise indicated based on the clinical condition of the patient.

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

In the post-marketing setting, severe symptomatic hypocalcaemia (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 hypocalcaemia. The risk of developing hypocalcaemia 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. anaemia, 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 characterise 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.

Hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone and in patients with growing skeletons

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

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

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

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 tumour of bone or progression to metastatic disease is an infrequent event and a known risk in patients with giant cell tumour 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 tumour of bone patients treated with denosumab.

Excipients

This medicinal product contains 78.9 mg sorbitol in each vial. 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 studies, denosumab has been administered in combination with standard anti-cancer treatment and in patients 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 in 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.

Hypocalcaemia has very commonly been reported following denosumab administration, mostly within the first 2 weeks. Hypocalcaemia 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 (see sections 4.4 and section 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 tumour 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	Hypocalcaemia[1,2]
	Common	Hypophosphataemia
	Uncommon	Hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone[3]
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea
Gastrointestinal disorders	Very common	Diarrhoea
	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]
	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

Hypocalcaemia
A higher incidence of hypocalcaemia among patients treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical studies.

The highest incidence of hypocalcaemia was observed in a phase III study in patients with multiple myeloma. Hypocalcaemia 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 denosumab 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 studies in patients with advanced malignancies involving bone, hypocalcaemia 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 studies in patients with giant cell tumour of bone, hypocalcaemia was reported in 5.7% of patients. None of the adverse events was considered serious.

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

Osteonecrosis of the jaw (ONJ)
In clinical studies, 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 studies.

A higher incidence of ONJ among patients treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical studies. The highest incidence of ONJ was observed in a phase III study in patients with multiple myeloma. In the double-blind treatment phase of this study, 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 study, 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 studies 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 patients 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 patients were receiving or had received chemotherapy.

The studies in patients with breast or prostate cancer included a 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-randomised, 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 study 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 study in patients with giant cell tumour 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 study, median time on study 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 subjects 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 study programme overall, 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 programme 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 tumour 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 studies, 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 studies in patients with advanced malignancies involving bone, new primary malignancy was reported in 54/3 691 (1.5%) of patients treated with denosumab (median exposure of 13.8 months; range: 1.0 – 51.7) and 33/3 688 (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 tumour 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.

Paediatric population

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

Clinically significant hypercalcaemia after treatment discontinuation has been reported in the post-marketing setting in paediatric 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 hypocalcaemia in the absence of calcium supplementation. The risk of developing hypocalcaemia 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 hypocalcaemia despite calcium supplementation. The overall incidence of clinically significant hypocalcaemia 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 mineralisation, ATC code: M05BX04

Wyost is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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

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 studies 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

Anti-denosumab antibodies may develop during denosumab treatment. No apparent correlation of antibody development with pharmacokinetics, clinical response or adverse event has been observed.

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

Efficacy and safety of 120 mg denosumab SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV (intravenous) every 4 weeks were compared in three randomised, double-blind, active-controlled studies, in IV-bisphosphonate naïve patients with advanced malignancies involving bone: adults with breast cancer (Study 1), other solid tumours or multiple myeloma (Study 2), and castrate-resistant prostate cancer (Study 3). Within these active-controlled clinical studies, 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 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 tumours (see table 2).

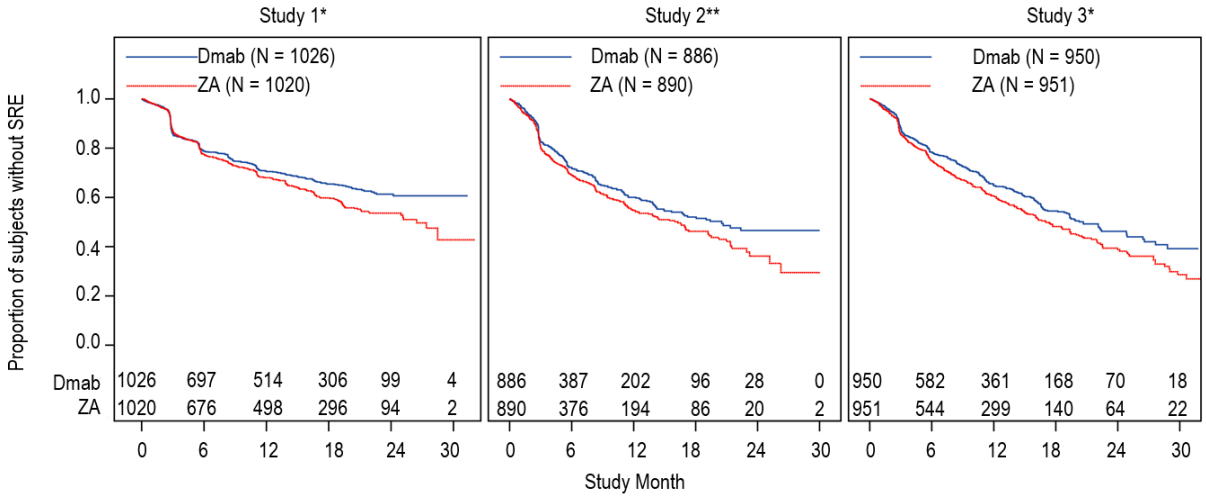
Table 2. Efficacy results in patients with advanced malignancies involving bone

	Study 1 breast cancer		**Study 2 other solid tumours** 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 patients (%)	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	
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

	Study 1 breast cancer		Study 2 other solid tumours** or multiple myeloma		Study 3 prostate cancer		Combined advanced cancer	
	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid	Denosumab	zoledronic acid
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 = hypercalcaemia 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, gastrointestinal/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 randomised
* = Statistically significant for superiority; ** = Statistically significant for non-inferiority

Disease progression and overall survival with bone metastases from solid tumours

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 tumours 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 tumours or multiple myeloma) examined overall survival for the 3 tumour 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 tumour 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 analyses. 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 = 0.0002).

Clinical efficacy in patients with multiple myeloma

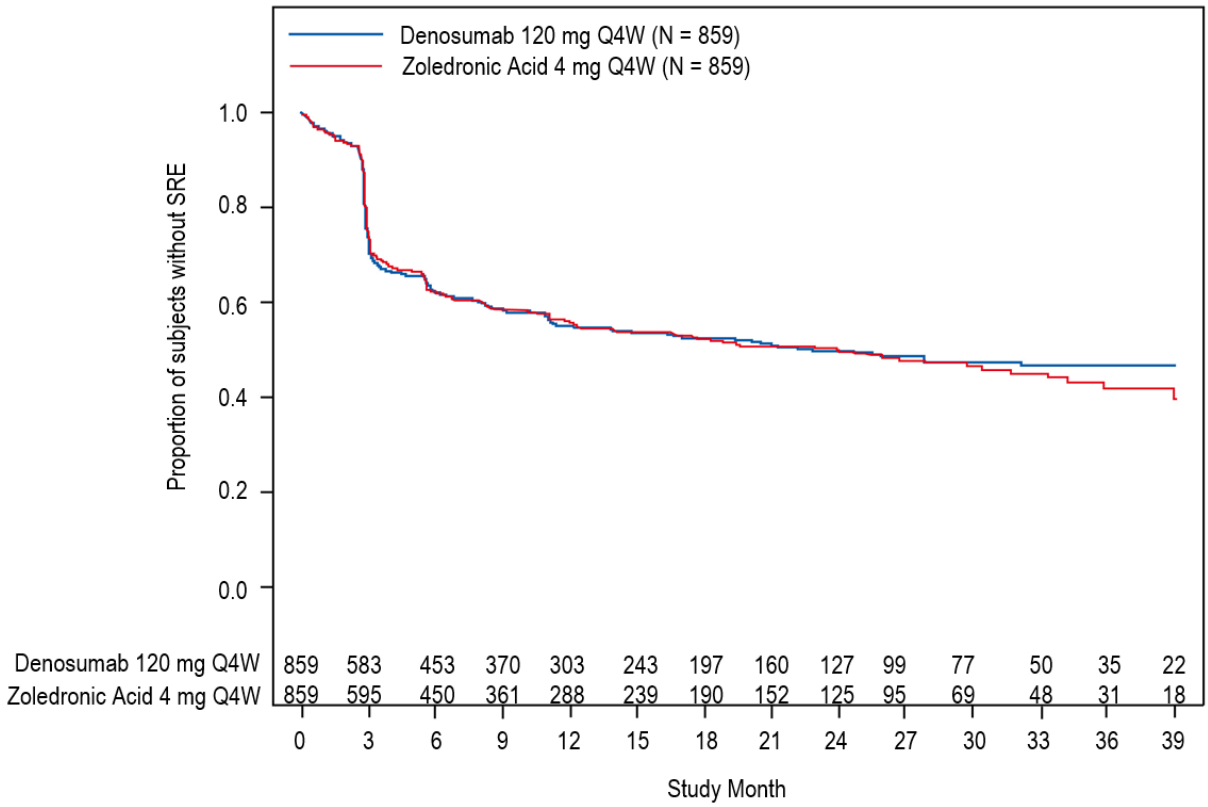
Denosumab was evaluated in an international, randomised (1:1), double-blind, active-controlled study comparing denosumab with zoledronic acid in patients with newly diagnosed multiple myeloma, Study 4.

In this study, 1 718 multiple myeloma patients with at least one bone lesion were randomised 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 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 utilised/planned to utilise 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 randomised

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)
Hazard ratio (95% CI)	0.98 (0.85, 1.14)	

	Denosumab (N = 859)	Zoledronic Acid (N = 859)
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 = hypercalcaemia of malignancy

Clinical efficacy and safety in adults and skeletally mature adolescents with giant cell tumour of bone

The safety and efficacy of denosumab was studied in two phase II open-label, single-arm studies (Studies 5 and 6) that enrolled 554 patients with giant cell tumour of bone that was either unresectable or for which surgery would be associated with severe morbidity and a prospective, multicentre, open-label, phase IV study (study 7) that provided long-term safety follow-up for patients who completed study 6. Patients received 120 mg denosumab subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15. Patients who discontinued denosumab then entered the safety follow-up phase for a minimum of 60 months. Retreatment with denosumab while in safety follow-up was allowed for patients 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 tumour of bone. The main outcome measure of the study 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 tumour 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 tumour 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 patients with giant cell tumour 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 patients 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.

Study 7 enrolled 85 adult patients who were previously enrolled and completed study 6. Patients were allowed to receive denosumab treatment for GCTB, and all patients were followed for 5 years. The primary objective was to evaluate the long-term safety profile of denosumab in patients with giant cell tumour of the bone.

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with the reference medicinal product containing denosumab in one or more subsets of the paediatric population in the prevention of SREs in patients with bone metastases and subsets of the paediatric population below the age of 12 in the treatment of giant cell tumour of bone (see section 4.2 for information on paediatric use).

In Study 6, denosumab has been evaluated in a subset of 28 adolescent patients (aged 13 – 17 years) with giant cell tumour 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 patients with surgically unsalvageable disease (n = 14) had disease recurrence during initial treatment. Thirteen of the 14 patients 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 patients 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 patients with multiple myeloma who received 120 mg every 4 weeks, median trough levels varied by less than 8% between months 6 and 12. In patients with giant cell tumour 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 patients 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 tumour 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.

Paediatric population

In skeletally-mature adolescents (12 – 17 years of age) with giant cell tumour 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 patients with GCTB.

5.3 Preclinical safety data

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

In mouse bone metastasis models of oestrogen 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 tumour growth. When OPG-Fc was combined with hormonal therapy (tamoxifen) or chemotherapy (docetaxel) in these models, there was additive inhibition of skeletal tumour growth in breast, and prostate or lung cancer respectively. In a mouse model of mammary tumour induction, RANK-Fc reduced hormone-induced proliferation in mammary epithelium and delayed tumour 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 foetal harm during a period equivalent to the first trimester, although foetal 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 haematopoiesis, 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 mineralisation 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.

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.

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

Acetic acid, glacial*
Sorbitol (E 420)
Polysorbate 20
Sodium hydroxide (for pH adjustment)*
Hydrochloric acid (for pH adjustment)
Water for injections
* 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

3 years.

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 (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap.

Packs of 1, 3 or 4 vials. Not all pack sizes may be marketed.

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 ºC) 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. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1812/001
EU/1/24/1812/002
EU/1/24/1812/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharmaceutical Manufacturing LLC
Kolodvorska cesta 27
1234 Menges
Slovenia

Name and address of the manufacturer responsible for batch release

Lek Pharmaceuticals d.d.
Verovškova ulica 57
1526 Ljubljana
Slovenia

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Wyost 120 mg solution for injection
denosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: acetic acid, glacial, sorbitol (E 420), polysorbate 20, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection

1 single use vial
3 single use vials
4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1812/001 1 single use vial
EU/1/24/1812/002 3 single use vials
EU/1/24/1812/003 4 single use vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wyost

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Wyost 120 mg injection
denosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.7 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Wyost 120 mg solution for injection
denosumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with Wyost.

What is in this leaflet

1. What Wyost is and what it is used for
2. What you need to know before you use Wyost
3. How to use Wyost
4. Possible side effects
5. How to store Wyost
6. Contents of the pack and other information

1. What Wyost is and what it is used for

Wyost contains denosumab, a protein (monoclonal antibody) that works to slow down bone destruction caused by cancer spreading to the bone (bone metastasis) or by giant cell tumour of bone.

Wyost is used in adults with advanced cancer to prevent serious complications caused by bone metastasis (e.g. fracture, pressure on the spinal cord or the need to receive radiation therapy or surgery).

Wyost is also used to treat giant cell tumour of bone, which cannot be treated by surgery or where surgery is not the best option, in adults and adolescents whose bones have stopped growing.

2. What you need to know before you use Wyost

Do not use Wyost

- if you are allergic to denosumab or any of the other ingredients of this medicine (listed in section 6).

Your healthcare professional will not administer Wyost to you if you have a very low level of calcium in your blood which has not been treated.

Your healthcare professional will not administer Wyost to you if you have unhealed wounds from dental or oral surgery.

Warnings and precautions

Talk to your doctor before using Wyost

Calcium and vitamin D supplementation
You should take calcium and vitamin D supplements while being treated with Wyost unless your blood calcium is high. Your doctor will discuss this with you. If the level of calcium in your blood is low, your doctor may decide to give you calcium supplements before you start treatment with Wyost.

Low calcium levels in the blood
Please tell your doctor immediately if you have spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion or loss of consciousness while being treated with Wyost. You may have low levels of calcium in your blood.

Renal impairment
Tell your doctor if you have or have had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium, especially if you do not take calcium supplements.

Problems with your mouth, teeth or jaw
A side effect called osteonecrosis of the jaw (bone damage in the jaw) has been reported commonly (may affect up to 1 in 10 people) in patients receiving denosumab injections for cancer-related conditions. Osteonecrosis of the jaw can also occur after stopping treatment.

It is important to try to prevent osteonecrosis of the jaw developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take:

- Before receiving treatment, tell your doctor/nurse (healthcare professional) if you have any problems with your mouth or teeth. Your doctor should delay the start of your treatment if you have unhealed wounds in your mouth from dental procedures or oral surgery. Your doctor may recommend a dental examination before you start treatment with Wyost.
- While being treated, you should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Wyost.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Patients undergoing chemotherapy and/or radiotherapy, taking steroids or anti-angiogenic medicines (used to treat cancer), undergoing dental surgery, who do not receive routine dental care, have gum disease or who are smokers, may have a higher risk of developing osteonecrosis of the jaw.

Unusual thigh bone fractures
Some people have developed unusual fractures in their thigh bone while being treated with denosumab. Contact your doctor if you experience new or unusual pain in your hip, groin, or thigh.

High calcium levels in the blood after stopping treatment with Wyost
Some patients with giant cell tumour of the bone have developed high calcium levels in the blood weeks to months after stopping treatment. Your doctor will monitor you for signs and symptoms of high levels of calcium, after you stop receiving Wyost.

Children and adolescents

Wyost is not recommended for children and adolescents under 18 years of age except for adolescents with giant cell tumour of the bone whose bones have stopped growing. The use of denosumab has not been studied in children and adolescents with other cancers that have spread to bone.

Other medicines and Wyost

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. It is especially important that you tell your doctor if you are being treated with

- another medicine containing denosumab
- a bisphosphonate

You should not take Wyost together with other medicines containing denosumab or bisphosphonates.

Pregnancy and breast-feeding

Denosumab has not been tested in pregnant women. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Wyost is not recommended for use if you are pregnant. Women of child-bearing potential should use effective methods of contraception while being treated with Wyost and for at least 5 months after stopping treatment with Wyost.

If you become pregnant during treatment with Wyost or less than 5 months after stopping treatment with Wyost, please inform your doctor.

It is unknown whether denosumab is excreted in human milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding or whether to stop taking Wyost, considering the benefit of breast-feeding to the baby and the benefit of Wyost to the mother.

If you are nursing during treatment with Wyost, please inform your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

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

Wyost contains sorbitol

This medicine contains 78.9 mg sorbitol in each vial.

Wyost contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 120 mg dose, that is to say essentially ‘sodium-free’.

3. How to use Wyost

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

The recommended dose of Wyost is 120 mg administered once every 4 weeks, as a single injection under the skin (subcutaneous). Wyost will be injected into your thigh, abdomen or upper arm. If you

are being treated for giant cell tumour of bone, you will receive an additional dose 1 week and 2 weeks after the first dose.

Do not shake.

You should also take calcium and vitamin D supplements while being treated with Wyost unless you have an excess of calcium in the blood. Your doctor will discuss this with you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately if you develop any of these symptoms while being treated with Wyost (may affect more than 1 in 10 people):
- spasms, twitches, cramps in your muscles, numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion or loss of consciousness. These could be signs that you have low calcium levels in the blood. Low calcium in the blood may also lead to a change in heart rhythm called QT prolongation, which is seen by electrocardiogram (ECG).

Please tell your doctor and dentist immediately if you experience any of these symptoms while being treated with Wyost or after stopping treatment (may affect up to 1 in 10 people):
- persistent pain in the mouth and/or jaw, and/or swelling or non-healing of sores in the mouth or jaw, discharge, numbness or feeling of heaviness in the jaw, or loosening of a tooth could be signs of bone damage in the jaw (osteonecrosis).

Very common side effects (may affect more than 1 in 10 people):
- bone, joint, and/or muscle pain which is sometimes severe,
- shortness of breath,
- diarrhoea.

Common side effects (may affect up to 1 in 10 people):
- low phosphate levels in the blood (hypophosphataemia),
- removal of a tooth,
- excessive sweating,
- in patients with advanced cancer: development of another form of cancer.

Uncommon side effects (may affect up to 1 in 100 people):
- high calcium levels in the blood (hypercalcaemia) after stopping treatment in patients with giant cell tumour of the bone,
- new or unusual pain in your hip, groin or thigh (this may be an early indication of a possible fracture of the thigh bone),
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions).

Rare side effects (may affect up to 1 in 1 000 people):
- allergic reactions (e.g. wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin). In rare cases allergic reactions may be severe.

Not known (frequency cannot be estimated from the available data):
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Wyost

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

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

The vial may be left outside the refrigerator to reach room temperature (up to 25 °C) before injection. This will make the injection more comfortable. Once your vial has been left to reach room temperature (up to 25 °C), it must be used within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Wyost contains
- The active substance is denosumab. Each vial contains 120 mg of denosumab in 1.7 mL of solution (corresponding to 70 mg/mL).
- The other ingredients are acetic acid, glacial, sorbitol (E 420), polysorbate 20, sodium hydroxide, hydrochloric acid and water for injections.

What Wyost looks like and contents of the pack

Wyost is a solution for injection (injection).

Wyost is a clear to slightly opalescent, colourless to slightly yellowish or slightly brownish solution.

Each pack contains 1, 3 or 4 single use vials. Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only:

- 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 ºC) 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 product or waste material should be disposed of in accordance with local requirements.