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

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

Excipients with known effect

Each 1.7 mL of solution contains 78.2 mg sorbitol (E420) and 0.17 mg polysorbate 20 (E432).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to slightly yellow solution and may contain trace amounts of translucent to white proteinaceous particles.

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 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

Bilprevda 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 Bilprevda should be given the package leaflet and the patient reminder card.

Prevention of skeletal related events in adults with advanced malignancies involving bone

The recommended dose of Bilprevda 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 Bilprevda 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 Bilprevda, 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).

Paediatric population

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

Bilprevda 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 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.

The administration of the 120 mg/1.7 mL vial should only be performed by a healthcare professional.

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 Bilprevda. Hypocalcaemia can occur at any time during therapy with Bilprevda. Monitoring of calcium levels should be conducted (i) prior to the initial dose of Bilprevda, (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 Bilprevda, 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 Bilprevda 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 Bilprevda 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 Bilprevda 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).

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

Patients being treated with Bilprevda 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.

Warnings for excipients

This medicinal product contains sorbitol and polysorbate 20. The additive effect of concomitantly administered products containing sorbitol (or fructose) and polysorbate 20, and dietary intake of sorbitol (or fructose) and polysorbate 20 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 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).

Bilprevda is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with Bilprevda. Any effects of Bilprevda 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 Bilprevda 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

Bilprevda 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 denosumab.

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 section 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 1Adverse 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]

MedDRA system organ class	Frequency category	Adverse reactions
	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 trials.

The highest incidence of hypocalcaemia was observed in a phase III trial 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 trials 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 trials 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 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 patients 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 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 trials 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 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 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 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 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 trial 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 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 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 trial 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Bilprevda is a biosimilar medicinal product. Detailed information is available on the MHRA website.

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), 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

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 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 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 tumours (see table 2).

Table 2Efficacy results in patients with advanced malignancies involving bone

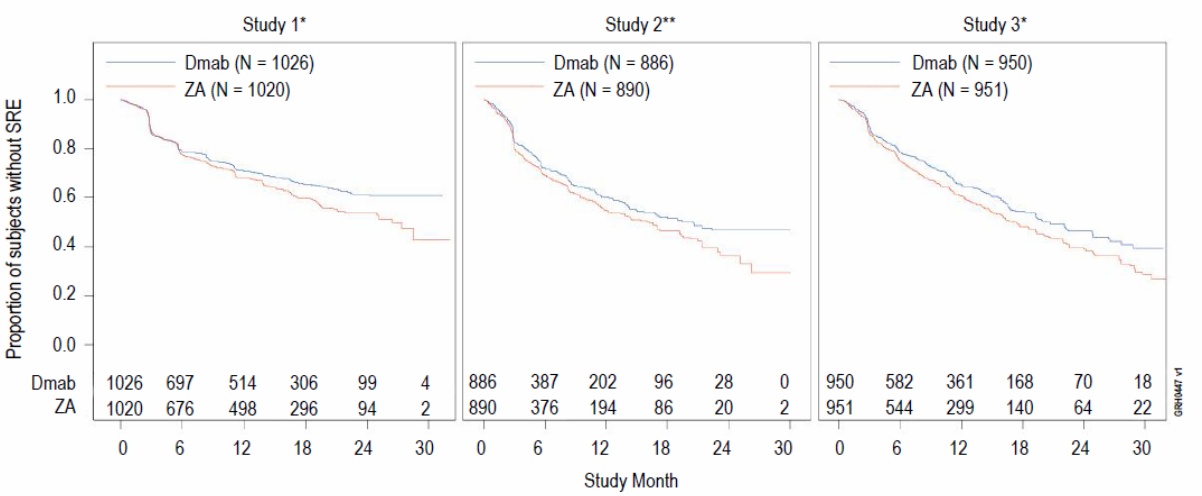
	Study 1 breast cancer		**Study 2 other solid tumours** or multiple myeloma**		**Study 3 prostate cancer**		**Combined advanced cancer**	
	Denosumab	**zoledronic acid**	**Denosumab**	**zoledronic acid**	**Denosumab**	**zoledronic acid**	**Denosumab**	**zoledronic acid**
N	**1 026**	**1 020**	**886**	**890**	**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

	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**
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
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 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 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 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 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 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

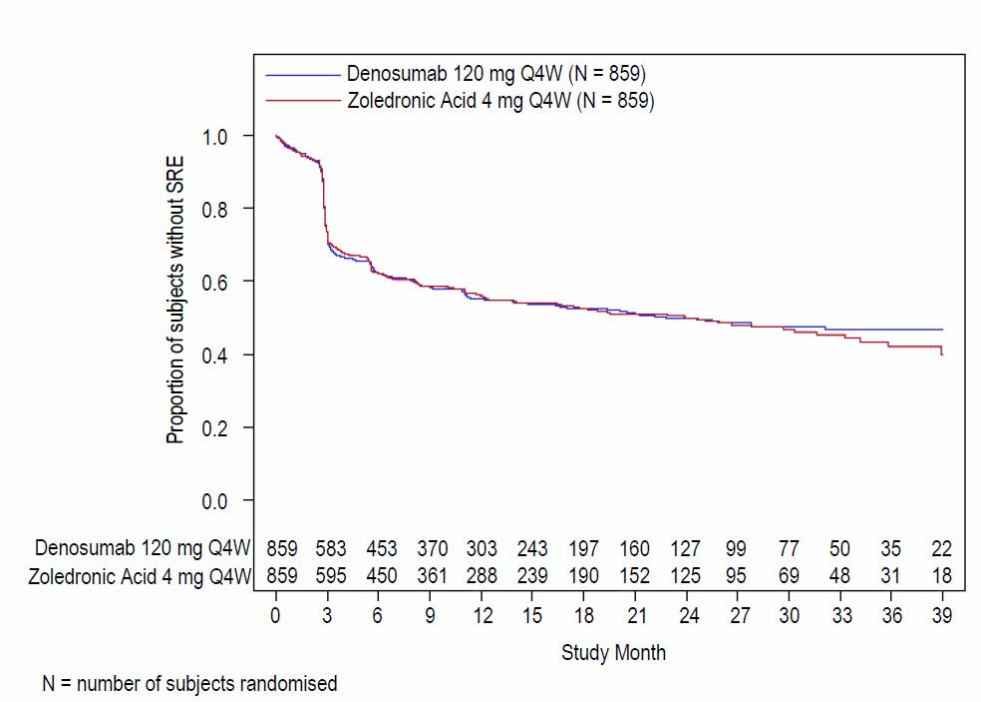


Table 3Efficacy results for denosumab compared to zoledronic acid in patients with newly diagnosed multiple myeloma

	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)	
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		

	Denosumab (N = 859)	**Zoledronic Acid (N = 859)**
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 trials (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. 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 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 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 licensing authority has waived the obligation to submit the results of studies with denosumab in all subsets of the paediatric population in the prevention of skeletal related events 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 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*

Sodium hydroxide (for pH adjustment)*

Sorbitol (E420)

Polysorbate 20 (E432)

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

24 months

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 bromobutyl rubber stopper aluminium-plastic combination caps.

Pack sizes of one.

6.6 Special precautions for disposal

- Before administration, the Bilprevda solution should be inspected visually. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured.
- Do not shake.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25ºC) 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

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Chełmska 30/34

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8 MARKETING AUTHORISATION NUMBER(S)

PL 59642/0004

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10 DATE OF REVISION OF THE TEXT

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