HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OSENVELT safely and effectively. See full prescribing information for OSENVELT.

OSENVELT® (denosumab-bmwo) injection, for subcutaneous use
Initial U.S. Approval: 2025

OSENVELT® (denosumab-bmwo) is biosimilar* to XGEVA® (denosumab)

----------INDICATIONS AND USAGE----------
Osenvelt is a RANK ligand (RANKL) inhibitor indicated for:
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. (1.1)
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. (1.2, 14.3)
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Osenvelt should be administered by a healthcare provider. (2.1)
- Osenvelt is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally. (2.1)
- Multiple Myeloma and Bone Metastasis from Solid Tumors: Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen. (2.2)
- Giant Cell Tumor of Bone: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen. (2.3)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. (2.2, 2.3)
- Hypercalcemia of Malignancy: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4.1)
- Known clinically significant hypersensitivity to denosumab products (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Drug Products with Same Active Ingredient: Patients receiving Osenvelt should not receive other denosumab products concomitantly. (5.1)
- Hypersensitivity reactions including anaphylaxis may occur. Discontinue permanently if a clinically significant reaction occurs. (5.2)
- Hypocalcemia: Denosumab products can cause severe symptomatic hypocalcemia. Fatal cases have been reported with denosumab products use. Correct hypocalcemia prior to initiating Osenvelt. Monitor calcium levels during therapy, especially in the first weeks of initiating therapy, and adequately supplement all patients with calcium and vitamin D. (5.3)
- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving denosumab products. Perform an oral examination prior to starting Osenvelt. Monitor for symptoms. Avoid invasive dental procedures during treatment with Osenvelt. (5.4)
- Atypical femoral fracture: Evaluate patients with thigh or groin pain to rule out a femoral fracture. (5.5)
- Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons: Monitor patients for signs and symptoms of hypercalcemia, and manage as clinically appropriate. (5.6, 8.4)
- Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation: When Osenvelt treatment is discontinued, evaluate the individual patient's risk for vertebral fractures. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------
- Bone Metastasis from Solid Tumors: Most common adverse reactions (≥ 25%) were fatigue/asthenia, hypophosphatemia, and nausea. (6.1)
- Multiple Myeloma: Most common adverse reactions (≥ 10%) were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. (6.1)
- Giant Cell Tumor of Bone: Most common adverse reactions (≥ 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. (6.1)
- Hypercalcemia of Malignancy: Most common adverse reactions (> 20%) were nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact CELLTRION USA, Inc. at 1-800-560-9414 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric patients: Recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone. (8.4)
- Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia. Adequately supplement with calcium and vitamin D. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Osenvelt has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 01/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma and Bone Metastasis from Solid Tumors

Osenvelt is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

1.2 Giant Cell Tumor of Bone

Osenvelt is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity *[see Clinical Trials (14.2)]*.

1.3 Hypercalcemia of Malignancy

Osenvelt is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Osenvelt should be administered by a healthcare provider.

Osenvelt is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally.

2.2 Multiple Myeloma and Bone Metastasis from Solid Tumors

The recommended dose of Osenvelt is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.3)]*.

2.3 Giant Cell Tumor of Bone

The recommended dose of Osenvelt is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and*

Precautions (5.3)].

2.4 Hypercalcemia of Malignancy

The recommended dose of Osenvelt is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

2.5 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Osenvelt is a clear, colorless to pale yellow solution. Do not use if the solution is discolored or cloudy or if the solution contains particles or foreign particulate matter.

Prior to administration, Osenvelt may be removed from the refrigerator and brought to room temperature up to 25°C (77°F) by standing in the original carton. This generally takes 15 to 30 minutes. Do not warm Osenvelt in any other way *[see How Supplied/Storage and Handling (16)]*.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-dose or entry.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/1.7 mL (70 mg/mL) of clear, colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Osenvelt *[see Warnings and Precautions (5.3)]*.

4.2 Hypersensitivity

Osenvelt is contraindicated in patients with known clinically significant hypersensitivity to denosumab products *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Patients receiving Osenvelt should not receive other denosumab products concomitantly.

5.2 Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with use of denosumab products. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Osenvelt therapy permanently *[see Contraindications (4.2) and Adverse Reactions (6.2)]*.

5.3 Hypocalcemia

Denosumab products can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to Osenvelt treatment. Monitor calcium levels, throughout Osenvelt therapy, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare provider for symptoms of hypocalcemia *[see Contraindications (4.1), Adverse Reactions (6.1, 6.2), and Patient Counseling Information (17)]*.

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/min and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake *[see Adverse Reactions (6.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.4 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving denosumab products, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with cancer, the incidence of ONJ was higher with longer duration of exposure *[see Adverse Reactions (6.1)]*. Seventy-nine percent of patients with ONJ had a history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor.

Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections. Similarly, for denosumab-treated patients with multiple myeloma that developed ONJ, 58% had a history of invasive dental procedures as a predisposing factor.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of Osenvelt and

periodically during Osenvelt therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Osenvelt. Consider temporary discontinuation of Osenvelt therapy if an invasive dental procedure must be performed. There are no data available to suggest the optimal duration of treatment interruption.

Patients who are suspected of having or who develop ONJ while on Osenvelt should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Clinical judgment of the treating healthcare provider should guide the management plan of each patient based on individual risk/benefit assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Atypical femoral fracture has been reported with denosumab products *[see Adverse Reactions (6.1)]*. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

During Osenvelt treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Osenvelt therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons

Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in denosumab product-treated patients with giant cell tumor of bone and patients with growing skeletons. Hypercalcemia has been reported within the first year after treatment discontinuation. After treatment is discontinued, monitor patients for signs and symptoms of hypercalcemia, assess serum calcium periodically, reevaluate the patient's calcium and vitamin D supplementation requirements and manage patients as clinically appropriate *[see Adverse Reactions (6) and Use in Specific Populations (8.4)]*.

5.7 Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab products. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures.

When Osenvelt treatment is discontinued, evaluate the individual patient's risk for vertebral fractures *[see Patient Counseling Information (17)]*.

5.8 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, denosumab products can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of denosumab to cynomolgus monkeys throughout pregnancy at a dose 25-fold higher than the recommended human dose of denosumab based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Osenvelt. Advise pregnant women and females of reproductive potential that exposure to Osenvelt during pregnancy or within 5 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Osenvelt *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.2)]*
- Hypocalcemia *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.4)]*
- Atypical Subtrochanteric and Diaphyseal Femoral Fracture *[see Warnings and Precautions (5.5)]*
- Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and in patients with growing skeletons *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]*
- Multiple vertebral fractures (MVF) following treatment discontinuation *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Bone Metastasis from Solid Tumors

The safety of denosumab was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14.1)]* in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of denosumab. In Studies 20050136, 20050244, and 20050103, patients were randomized to receive either 120 mg of denosumab every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were 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. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to denosumab was 12 months (range: 0.1-41) and median duration on-study was 13 months (range: 0.1-41). Of patients who received denosumab, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18-93). Seventy-five percent of patients who received denosumab received concomitant chemotherapy.

The most common adverse reactions in patients (incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1). The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation of denosumab were osteonecrosis and hypocalcemia.

Table 1. Selected[a] Adverse Reactions of Any Severity (Studies 20050136, 20050244, and 20050103)

Body System	Denosumab n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving denosumab in Studies 20050136, 20050244, and 20050103, and meeting one of the following criteria:

- At least 1% greater incidence in denosumab-treated patients, or
- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (US Prescribing Information for zoledronic acid)

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 - 8.5 mg/dL (2.075 - 2.125 mmol/L) for calcium and 2.2 - 2.8 mg/dL (0.71 - 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with denosumab and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.
- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15% of patients treated with denosumab and 7% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phases of Studies 20050136, 20050244, and 20050103, ONJ was confirmed in 1.8% of patients in the denosumab group (median exposure of 12.0 months; range: 0.1-41) and 1.3% of patients in the zoledronic acid group. The trials in patients with breast (Study 20050136) or prostate (Study 20050103) cancer included an open-label extension treatment phase where patients were offered denosumab 120 mg once every 4 weeks (median overall exposure of 14.9 months; range: 0.1-67.2). The patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ was 1.1% during the first year of treatment, 3.7% in the second year, and 4.6% per year thereafter. The median time to ONJ was 20.6 months (range: 4-53) *[see Warnings and Precautions (5.4)]*.

In a placebo-controlled clinical trial with an extension treatment phase evaluating denosumab for the prevention of bone metastases 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 (number of events per 100 patient years) of confirmed ONJ was 1.1% during the first year of treatment, 3% in the second year, and 7% per year thereafter.

Atypical Subtrochanteric and Diaphyseal Fracture

In the clinical trial program, atypical femoral fracture has been reported in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and after treatment was discontinued *[see Warnings and Precautions (5.5)]*.

Multiple Myeloma

The safety of denosumab was evaluated in an international, randomized (1:1), double-blind, active-controlled trial of patients with newly diagnosed multiple myeloma with treatment through disease progression *[see Clinical Trials (14.2)]*. In this trial, patients received 120 mg denosumab every 4 weeks as a subcutaneous injection (n = 850) or 4 mg (dose adjusted for renal function) of zoledronic acid intravenously (IV) every 4 weeks by IV infusion (n = 852). Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were 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. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to denosumab was 16 months (range: 1-50) and median duration on-study was 17 months (range: 0-49). Of patients who received denosumab, 46% were female, 83% were White, 13% Asian, 3% Black or African American, and 4% Hispanic/Latino. The median age of the patients randomized to denosumab was 63 years (range: 29-91) and all patients who received denosumab received concomitant anti-myeloma chemotherapy.

The adverse reaction profile of denosumab in patients with multiple myeloma, Study 20090482, was similar to that observed in Studies 20050136, 20050244, and 20050103. The most common adverse reactions (incidence ≥ 10%) were diarrhea (34%), nausea (32%), anemia (22%), back pain (21%), thrombocytopenia (19%), peripheral edema (17%), hypocalcemia (16%), upper respiratory tract infection (15%), rash (14%), and headache (11%). The most common serious adverse reaction (incidence ≥ 5%) was pneumonia (8%). The most common adverse reaction resulting in discontinuation of denosumab (≥ 1%) was osteonecrosis of the jaw.

Hypocalcemia and Hypophosphatemia

Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) and severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 2% and 21% patients treated with denosumab, respectively.

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phase of Study 20090482, ONJ was confirmed in 4.1% of patients in the denosumab group (median exposure of 16 months; range: 1-50) and 2.8% of patients in the zoledronic acid group (median 15 months, range: 1-45 months). At the completion of the double-blind treatment phase of Study 20090482, the patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ in the denosumab group (median exposure of 19.4 months; range: 1-52) was 2% during the first year of treatment, 5% in the second year, and 4.5% per year thereafter. The median time to ONJ was 18.7 months (range: 1-44) *[see Warnings and Precautions (5.4)]*.

Giant Cell Tumor of Bone

The safety of denosumab was evaluated in two single-arm trials (Study 20062004 and Study 20040215) *[see Clinical Trials (14.3)]* in which a total of 548 adult or skeletally mature adolescent patients with giant cell tumor of bone received at least 1 dose of denosumab. Patients received 120 mg denosumab subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Patients receiving concurrent bisphosphonate therapy were excluded from enrollment in both studies. 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 enrollment in Study 20040215. During the trial, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

Of the 548 patients who received denosumab, 467 patients were treated with denosumab for ≥ 1 year, 323 patients for ≥ 2 years, and 255 patients for ≥ 3 years. The median number of doses received was 33 (range: 4-138 doses) and the median number of months on-study was 60 (range: 0-140 months). Fifty-seven percent of the enrolled patients were women and 82% were White. The median age was 33 years (range: 13-83 years); a total of 19 patients were skeletally mature adolescents (12 to <17 years of age).

The common adverse reaction profile of denosumab in patients with giant cell tumor of bone was generally similar to that reported in Studies 20050136, 20050244, and 20050103. The most common adverse reactions in patients (incidence ≥ 10%) were arthralgia, back pain, pain in extremity, fatigue,

headache, nausea, nasopharyngitis, musculoskeletal pain, toothache, vomiting, hypophosphatemia, constipation, diarrhea, and cough. The most frequent serious adverse reactions were osteonecrosis of the jaw (3.6%), bone giant cell tumor (1.5%), anemia (1.1%), pneumonia (0.9%), and back pain (0.9%). The most frequent adverse reactions resulting in discontinuation of denosumab was osteonecrosis of the jaw (incidence of 3.6%). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Hypocalcemia and Hypophosphatemia

- Moderate to severe hypocalcemia (corrected serum calcium less than 8 mg/dL or less than 2 mmol/L) occurred in 5% of patients treated with denosumab.
- Severe hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L) occurred in 20% of patients treated with denosumab.

Osteonecrosis of the Jaw (ONJ)

In the pooled analysis of Study 20062004 and Study 20040215, ONJ was confirmed in 7% of patients who received denosumab (median number of doses received: 33; range: 4-138 doses).

Study 20140114 (NCT03301857) was a 5-year long term follow-up study for patients (n = 85) who completed Study 20062004. In Study 20062004 and Study 20140114 combined, ONJ was confirmed in 7% of patients who received denosumab (median time on trial 62.2 months (range 0 - 173). The combined patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ was 0.2% 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 1.5% thereafter *[see Warnings and Precautions (5.4)]*.

Atypical Subtrochanteric and Diaphyseal Fracture

In the pooled analysis of Study 20062004 and Study 20040215, atypical femoral fracture was observed in 0.9% of patients who received denosumab (median number of doses received: 33; range: 4-138 doses).

In Study 20062004 and Study 20140114, the combined incidence of confirmed atypical femoral fracture was 1.3% of patients who received denosumab *[see Warnings and Precautions (5.5)]*.

Hypercalcemia Following Treatment Discontinuation

In the pooled safety population, 0.7% of patients experienced serious adverse events of hypercalcemia > 30 days following treatment discontinuation that was recurrent in some patients *[see Warnings and Precautions (5.6)]*.

Hypercalcemia of Malignancy

Denosumab was evaluated in an open-label, single-arm trial (Study 20070315) in which 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy were enrolled *[see Clinical Trials (14.4)]*.

The adverse reaction profile of denosumab in patients with hypercalcemia of malignancy was similar to that reported in Studies 20050136, 20050244, 20050103, 20062004, and 20040215. Adverse reactions occurring in greater than 20% of patients were nausea (30%), dyspnea (27%), decreased appetite (24%), headache (24%), peripheral edema (24%), vomiting (24%), anemia (21%), constipation (21%), and diarrhea (21%). The following adverse reactions of Grade 3 or greater severity related to study therapy were reported on-study: fatigue (3%) and infection (6%). Grade 3 laboratory abnormalities included hypomagnesemia (3%), hypokalemia (3%), and hypophosphatemia (76%) of patients. No deaths on-study were related to denosumab therapy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of denosumab products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases *[see Contraindications (4.1) and Warnings and Precautions (5.3)]*.
- Hypercalcemia: Severe symptomatic hypercalcemia following treatment discontinuation can occur *[see Adverse Reactions (6) and Warnings and Precautions (5.6)]*.
- Hypersensitivity, including anaphylactic reactions *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*.
- Musculoskeletal pain, including severe musculoskeletal pain. Positive re-challenge has been reported.
- Lichenoid drug eruptions (e.g., lichen planus-like reactions).
- Alopecia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, denosumab products can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are insufficient data

with denosumab products use in pregnant women to inform any drug associated risks for adverse developmental outcomes. *In utero* denosumab exposure from cynomolgus monkeys dosed monthly with denosumab throughout pregnancy at a dose 25-fold higher than the recommended human dose of denosumab based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality; and absent lymph nodes, abnormal bone growth, and decreased neonatal growth *[see Data]*.

Apprise pregnant women of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a "knockout mouse"). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy starting at gestational day 20 and at a pharmacologically active dose 25-fold higher than the recommended human dose of denosumab based on body weight, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia, and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab *in utero*; however, development and lactation have not been fully evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node

agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.

8.2 Lactation

Risk Summary

There is no information regarding the presence of denosumab products in human milk, the effects on the breastfed child, or the effects on milk production. Denosumab was detected in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio) and maternal mammary gland development was normal, with no impaired lactation. However, pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Osenvelt treatment and any potential adverse effects on the breastfed child from Osenvelt or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on findings in animals and its mechanism of action, denosumab products can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Osenvelt treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Osenvelt.

8.4 Pediatric Use

The safety and efficacy of Osenvelt have not been established in pediatric patients except in skeletally mature adolescents (aged 12-16 years) with giant cell tumor of bone. Osenvelt is recommended only for treatment of skeletally mature adolescents (aged 12-16 years) with giant cell tumor of bone *[see Indications and Usage (1.2)]*. Clinically significant hypercalcemia after treatment discontinuation has been reported in pediatric patients with growing skeletons who received denosumab products for giant cell tumor of bone or for unapproved indications *[see Adverse Reactions (6.2) and Warnings and*

Precautions (5.6)].

Denosumab was studied in an open-label trial that enrolled a subset of 19 adolescent patients (aged 12-16 years) with giant cell tumor of bone who had reached skeletal maturity, defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus), and had a body weight ≥ 45 kg *[see Indications and Usage (1.2) and Clinical Trials (14.3)].* A total of one of five (20%) evaluable adolescent patients had an objective response by retrospective independent assessment of radiographic response according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The adverse reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults *[see Adverse Reactions (6.1) and Clinical Trials (14.3)]*.

Animal Data

Treatment with denosumab products may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed *in utero* to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)].*

8.5 Geriatric Use

Of the total number of patients in clinical studies that received denosumab (n = 2841) in Studies 20050136, 20050244, and 20050103, 1271 (44%) were ≥ 65 years old, while 473 patients (17%) were ≥ 75 years old. Of the 859 patients in Study 20090482 that received denosumab, 387 patients (45%) were ≥ 65 years old, while 141 patients (16%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between older and younger patients.

8.6 Renal Impairment

Two clinical trials were conducted in patients without cancer and with varying degrees of renal function.

In one study, patients (N = 55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a

second study, patients (N = 32) with severe renal dysfunction (creatinine clearance less than 30 mL/min and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, greater risk of developing hypocalcemia was observed with increasing renal impairment, and with inadequate/no calcium supplementation. Hypocalcemia was mild to moderate in severity in 96% of patients. Monitor calcium levels and calcium and vitamin D intake *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of denosumab products.

11 DESCRIPTION

Denosumab-bmwo is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab-bmwo has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Osenvelt (denosumab-bmwo) injection is a sterile, preservative-free, clear, colorless to pale yellow solution for subcutaneous use.

Each single-dose vial of Osenvelt contains 120 mg denosumab-bmwo, 0.44 mg acetic acid, 0.17 mg polysorbate 20, 1.78 mg sodium acetate, 79.9 mg sorbitol, and Water for Injection. The pH is 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Denosumab products bind to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Denosumab products prevent RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

12.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx/Cr was 82% within 1 week following initiation of denosumab 120 mg administered subcutaneously. In Studies 20050136,

20050244, and 20050103, the median reduction in uNTx/Cr from baseline to Month 3 was approximately 80% in 2075 denosumab-treated patients.

In a phase 3 study of patients with newly diagnosed multiple myeloma who received subcutaneous doses of denosumab 120 mg every 4 weeks (Q4W), median reductions in uNTx/Cr of approximately 75% were observed by week 5. Reductions in bone turnover markers were maintained, with median reductions of 74% to 79% for uNTx/Cr from weeks 9 to 49 of continued 120 mg Q4W dosing.

In adult and skeletally mature adolescent patients with giant cell tumor of bone who received subcutaneous doses of denosumab 120 mg Q4W with a 120 mg loading dose on Days 8 and 15, median reductions in uNTx/Cr from baseline were 84% at Week 13 and 82% at Week 25.

12.3 Pharmacokinetics

Following subcutaneous administration, bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses.

With multiple subcutaneous doses of 120 mg once every 4 weeks, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months. A mean (± standard deviation) serum steady-state trough concentration of 20.5 (± 13.5) mcg/mL was achieved by 6 months. The mean elimination half-life was 28 days.

In patients with newly diagnosed multiple myeloma who received 120 mg every 4 weeks, denosumab concentrations appear to reach steady-state by month 6. In patients with giant cell tumor of bone, after administration of subcutaneous doses of 120 mg once every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy, mean (± standard deviation) serum trough concentrations on Day 8, 15, and one month after the first dose were 19.0 (± 24.1), 31.6 (± 27.3), 36.4 (± 20.6) mcg/mL, respectively. Steady-state was achieved in 3 months after initiation of treatment with a mean serum trough concentration of 23.4 (± 12.1) mcg/mL.

Special Populations

Body Weight: A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.

Age, Gender and Race: The pharmacokinetics of denosumab was not affected by age, gender, and race.

Pediatrics: In skeletally-mature adolescent patients (12 to 16 years of age) with giant cell tumor of bone (GCTB) who received 120 mg every 4 weeks with a 120 mg loading dose on Days 8 and 15, the pharmacokinetics of denosumab were comparable to those observed in adult patients with GCTB.
Hepatic Impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab products.

Renal Impairment: In clinical trials of 87 patients with varying degrees of renal dysfunction, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab *[see Use in Specific Populations (8.6)]*.

Drug Interactions

No formal drug-drug interaction trials have been conducted with denosumab. There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy and were not altered by concomitant chemotherapy and/or hormone therapy.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of denosumab or of other denosumab products. Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with denosumab for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based *in vitro* biological assay. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of denosumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

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

Mutagenicity

The genotoxic potential of denosumab products has not been evaluated.

Impairment of Fertility

Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 6.5- to 25-fold higher than the recommended human dose of 120 mg subcutaneously administered once every 4 weeks, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab products are inhibitors of osteoclastic bone resorption via inhibition of RANKL.

Because 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, OPG-Fc and RANK-Fc, provided additional information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

14 CLINICAL TRIALS

14.1 Bone Metastasis from Solid Tumors

The safety and efficacy of denosumab for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing denosumab with zoledronic acid. In all three trials, patients were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Study 20050136 (NCT00321464) enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 6 weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within 6 weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were White, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Study 20050244 (NCT00330759) enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was 7 for both denosumab and zoledronic acid.

Study 20050103 (NCT00321620) enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10 ng/mL, and 14% received chemotherapy within 6 weeks prior to randomization. Median age was 71 years and 86% of patients were White. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Denosumab delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases (Table 2). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials.

Table 2. Efficacy Results for Denosumab Compared to Zoledronic Acid

	Study 20050136 Metastatic Breast Cancer		Study 20050244 Metastatic Solid Tumors or Multiple Myeloma		Study 20050103 Metastatic CRPC[a]	
	Denosumab N = 1026	Zoledronic Acid N = 1020	Denosumab N = 886	Zoledronic Acid N = 890	Denosumab N = 950	Zoledronic Acid N = 951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value[e]	0.001		0.145		0.009	

[a] CRPC = castrate-resistant prostate cancer.
[b] NR = not reached.
[c] Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d] All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e] Adjusted p-values are presented.

14.2 Multiple Myeloma

The efficacy of denosumab for the prevention of skeletal-related events in newly diagnosed multiple myeloma patients with treatment through disease progression, was evaluated in Study 20090482 (NCT01345019), an international, randomized (1:1), double-blind, active-controlled, noninferiority trial comparing denosumab with zoledronic acid. In this trial, patients were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In this trial, the main efficacy outcome measure was noninferiority of time to first skeletal-related event (SRE). Additional efficacy outcome measures were superiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Study 20090482 enrolled 1718 newly diagnosed multiple myeloma patients with bone lesions.

Randomization was stratified by a history of prior SRE (yes or no), the anti-myeloma agent being utilized/planned to be utilized in first-line therapy (novel therapy-based or non-novel therapy-based [novel therapies include bortezomib, lenalidomide, or thalidomide]), intent to undergo autologous PBSC transplantation (yes or no), stage at diagnosis (International Staging System I or II or III) and region Japan (yes or no). At study enrollment, 96% of the patients were receiving or planning to receive novel therapy-based first-line anti-myeloma therapy, 55% of the patients intended to undergo autologous PBSC transplantation, 61% of patients had a previous SRE, 32% were at ISS stage I, 38% were at ISS stage II and 29% were at ISS Stage III, and 2% were enrolled from Japan. Median age was 63 years, 82% of patients were White, and 46% of patients were women. The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.

Denosumab was noninferior to zoledronic acid in delaying the time to first SRE following randomization (HR = 0.98, 95% CI, 0.85-1.14). The results for overall survival (OS) were comparable between denosumab and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

Table 3. Efficacy Results for Denosumab Compared to Zoledronic Acid

	Study 20090482 Multiple Myeloma	
	Denosumab N = 859	**Zoledronic Acid N = 859**
First On-study SRE		
Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
Components of First SRE		
Radiation to Bone	47 (5.5)	62 (7.2)
Pathological Fracture	342 (39.8)	338 (39.3)
Surgery to Bone	37 (4.3)	48 (5.6)
Spinal Cord Compression	6 (0.7)	4 (0.5)
Median Time to SRE (months) (95% CI)	22.8 (14.7, NE[a])	24 (16.6, 33.3)
Hazard Ratio (95% CI)	0.98 (0.85, 1.14)	

[a] NE = not estimable

14.3 Giant Cell Tumor of Bone

The safety and efficacy of denosumab for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials [Study 20040215 (NCT00396279) and Study 20062004 (NCT00680992)] that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg denosumab subcutaneously every 4 weeks with a

loading dose on Days 8 and 15 of the first cycle of therapy. 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 20040215 was a single-arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study enrollment. Patients enrolled in Study 20040215 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during denosumab treatment.

Study 20062004 was a parallel-cohort, proof of concept, and safety trial conducted in 535 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Study 20062004 enrolled 19 patients who were 12-16 years of age *[see Use in Specific Populations (8.4)].* Patients enrolled into one of three cohorts: Cohort 1 enrolled 268 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 252 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 15 patients who previously participated in Study 20040215. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

A retrospective interim analysis concluded by an independent review committee evaluated objective response in 187 patients enrolled and treated in Study 20040215 and Study 20062004 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Study 20040215 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Study 20062004). The primary efficacy outcome measure was objective response rate using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.

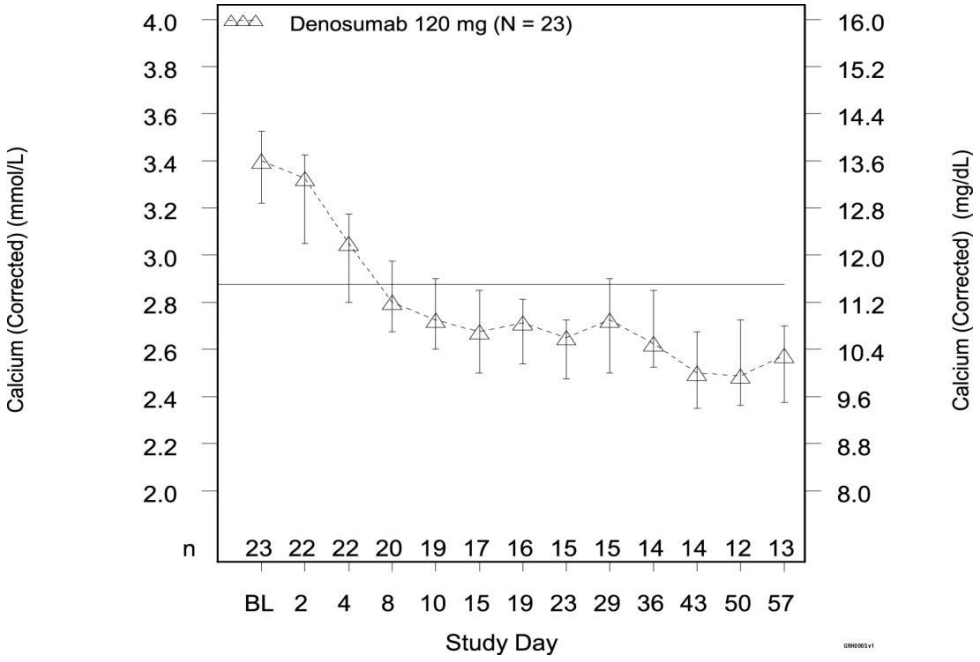
The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2-44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

14.4 Hypercalcemia of Malignancy

The safety and efficacy of denosumab was demonstrated in an open-label, single-arm trial [Study 20070315 (NCT00896454)] that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy. Patients received denosumab subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

In this trial, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of denosumab therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after denosumab administration. Efficacy data are summarized in Figure 1 and Table 4. Concurrent chemotherapy did not appear to affect response to denosumab.

Figure 1. Corrected Serum Calcium by Visit in Responders (Median and Interquartile Range)



N = Number of responders who received ≥ 1 dose of investigational product
n = Number of responders who had no missing data at baseline and the time point of interest

Table 4. Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N = 33	**Proportion (%) (95% CI)**
All Responders (CSC ≤ 11.5 mg/dL) by Day 10	21	63.6 (45.1, 79.6)

All Responders by Day 57	23	69.7 (51.3, 84.4)
Complete Responders (CSC ≤ 10.8 mg/dL) by Day 10	12	36.4 (20.4, 54.9)
All Complete Responders by Day 57	21	63.6 (45.1, 79.6)

Median time to response (CSC ≤ 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC ≤ 10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Osenvelt (denosumab-bmwo) injection is a clear, colorless to pale yellow solution supplied in a single-dose vial.

120 mg/1.7 mL (70 mg/mL) in a single-dose vial	1 vial per carton	NDC 72606-038-01

Storage and Handling

Store Osenvelt refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Prior to administration, Osenvelt may be allowed to reach room temperature up to 25°C (77°F) in the original carton. Osenvelt may be stored at temperatures up to a maximum 25°C (77°F) for a single period of up to 63 days but not exceeding the original expiry date. If necessary, the product may be returned to the refrigerator once within 63 days and provided this does not exceed the original expiry date. It must be used after subsequent removal from refrigeration. Discard Osenvelt if not used or returned to refrigerator within the 63 days. Do not use Osenvelt after the expiry date printed on the label.

Protect Osenvelt from direct light and heat.

Avoid vigorous shaking of Osenvelt.

17 PATIENT COUNSELING INFORMATION

Drug Products with Same Active Ingredient

Advise patients that if they receive Osenvelt, they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.1)]*.

Hypersensitivity

Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur. Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab products *[see Warnings and Precautions (5.2) and Contraindications (4.2)]*.

Hypocalcemia

Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Osenvelt *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Osenvelt and to inform their dentist prior to dental procedures that they are receiving Osenvelt. Patients should avoid invasive dental procedures during treatment with Osenvelt and inform their healthcare provider or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.4)]*.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Advise patients to report new or unusual thigh, hip, or groin pain *[see Warnings and Precautions (5.5)]*.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons

Advise patients to report nausea, vomiting, headache, and decreased alertness following treatment discontinuation *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]*.

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Advise patients that after treatment with Osenvelt is stopped there may be an increased risk of having broken bones in the spine especially in patients who have had a fracture or who have had osteoporosis. Advise patients not to interrupt Osenvelt therapy without their physician's advice *[see Warnings and Precautions (5.7)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that Osenvelt can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of Osenvelt *[see Use in Specific Populations (8.3)]*.

OSENVELT® (denosumab-bmwo)

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