

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENOBY™ safely and effectively. See full prescribing information for ENOBY™.

### ENOBY™ (denosumab-qdpe) injection, for subcutaneous use

Initial U.S. Approval: 2025

ENOBY™ (denosumab-qdpe) is biosimilar\* to PROLIA® (denosumab).

**WARNING: SEVERE HYPOCALCEMIA IN PATIENTS WITH ADVANCED KIDNEY DISEASE**  
See full prescribing information for complete boxed warning.

- Patients with advanced chronic kidney disease are at greater risk of severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. (5.1)
- The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia. (5.1)
- Prior to initiating Enoby in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with Enoby in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD. (2.2, 5.1)

## INDICATIONS AND USAGE

- Enoby is a RANK ligand (RANKL) inhibitor indicated for treatment:
- of postmenopausal women with osteoporosis at high risk for fracture (1.1)
  - to increase bone mass in men with osteoporosis at high risk for fracture (1.2)
  - of glucocorticoid-induced osteoporosis in men and women at high risk for fracture (1.3)
  - to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer (1.4)
  - to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (1.5)

## DOSAGE AND ADMINISTRATION

- Pregnancy must be ruled out prior to administration of Enoby. (2.1)
- Before initiating Enoby in patients with advanced chronic kidney disease, including dialysis patients, evaluate for the presence of chronic kidney disease mineral and bone disorder with intact parathyroid hormone, serum calcium, 25(OH) vitamin D, and 1,25(OH)<sub>2</sub> vitamin D. (2.2, 5.1, 8.6)
- Enoby should be administered by a healthcare provider. (2.3)
- Administer 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen. (2.3)
- Instruct patients to take calcium 1000 mg daily and at least 400 IU vitamin D daily. (2.3)

## DOSAGE FORMS AND STRENGTHS

- Injection: 60 mg/mL solution in a single-dose pre-filled syringe (3)

## CONTRAINDICATIONS

- Hypocalcemia (4, 5.1)
- Pregnancy (4, 8.1)
- Known hypersensitivity to denosumab products (4, 5.3)

Known hypersensitivity to denosumab products (4, 5.3)

**WARNINGS AND PRECAUTIONS**

- Hypocalcemia: Pre-existing hypocalcemia must be corrected before initiating Enoby. May worsen, especially in patients with renal impairment. Adequately supplement all patients with calcium and vitamin D. Concomitant use of calcimimetic drugs may also worsen hypocalcemia. Evaluate for presence of chronic kidney disease mineral-bone disorder. Monitor serum calcium. (5.1)

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## FULL PRESCRIBING INFORMATION

**WARNING: SEVERE HYPOCALCEMIA IN PATIENTS WITH ADVANCED KIDNEY DISEASE**

- Patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m<sup>2</sup>), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. (See [Warnings and Precautions \(5.1\)](#).)
- The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia in these patients. (See [Warnings and Precautions \(5.1\)](#).)
- Prior to initiating Enoby in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with Enoby in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD. (See [Dosage and Administration \(2.2\)](#) and [Warnings and Precautions \(5.1\)](#).)

## INDICATIONS AND USAGE

- Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture**

Enoby is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures. (See [Clinical Studies \(14.1\)](#).)

- Treatment to Increase Bone Mass in Men with Osteoporosis**

Enoby is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. (See [Clinical Studies \(14.3\)](#).)

- Treatment of Glucocorticoid-Induced Osteoporosis**

Enoby is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. (See [Clinical Studies \(14.3\)](#).)

- Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer**

Enoby is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer. In these patients, denosumab also reduced the incidence of vertebral fractures. (See [Clinical Studies \(14.4\)](#).)

- Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer**

Enoby is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. (See [Clinical Studies \(14.5\)](#).)

## DOSAGE AND ADMINISTRATION

- Pregnancy Testing Prior to Initiation of Enoby**

Pregnancy must be ruled out prior to administration of Enoby. Perform pregnancy testing in all females of reproductive potential prior to administration of Enoby. Based on findings in animals, denosumab products can cause fetal harm when administered to pregnant women. (See [Use in Specific Populations \(8.1, 8.3\)](#).)

- Laboratory Testing in Patients with Advanced Chronic Kidney Disease Prior to Initiation of Enoby**

In patients with advanced chronic kidney disease [i.e., estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup>], including dialysis-dependent patients, evaluate for the presence of chronic kidney disease mineral and bone disorder (CKD-MBD) with intact parathyroid hormone (PTH), serum calcium, 25(OH) vitamin D, and 1,25(OH)<sub>2</sub> vitamin D, prior to decisions regarding Enoby treatment. Consider also assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present. (See [Warnings and Precautions \(5.1\)](#).)

- Recommended Dosage**

Enoby should be administered by a healthcare provider.

The recommended dose of Enoby is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Enoby via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. (See [Warnings and Precautions \(5.1\)](#).)

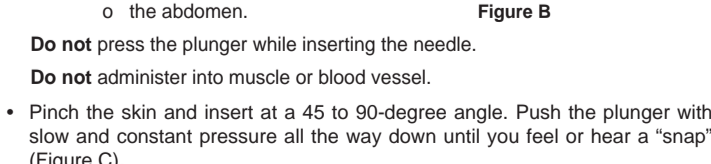
- Preparation and Administration**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Enoby is a clear to slightly opalescent, 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, Enoby may be removed from the refrigerator and brought to room temperature up to 25°C (77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Enoby in any other way. (See [How Supplied/Storage and Handling \(16\)](#).)

**Instructions for Administration of Enoby Pre-filled Syringe with Needle Safety Guard**  
**IMPORTANT:** In order to minimize accidental needlesticks, the Enoby single-dose pre-filled syringe has a clear safety guard that activates automatically to cover the needle after the injection is given.

**DO NOT** attempt to activate the clear safety guard prior to administering the injection. It will lock in place and prevent injection.



Step 1: Remove Gray Needle Cap (Figure A)



Step 2: Administer Subcutaneous Injection

- Choose an injection site (Figure B).
- The recommended injection sites for Enoby include:
  - the upper arm OR
  - the upper thigh OR
  - the abdomen.

Do not press the plunger while inserting the needle.

Do not administer into muscle or blood vessel.

- Pinch the skin and insert at a 45 to 90-degree angle. Push the plunger with slow and constant pressure all the way down until you feel or hear a "snap" (Figure C).



Figure C

- Same Active Ingredient: Patients receiving Enoby should not receive other denosumab products concomitantly. (5.2)
- Hypersensitivity including anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs. (5.3)
- Osteonecrosis of the jaw: Has been reported with denosumab products. Monitor for symptoms. (5.4)
- Atypical femoral fractures: Have been reported. Evaluate patients with thigh or groin pain to rule out a femoral fracture. (5.5)
- Multiple vertebral fractures have been reported following treatment discontinuation. Patients should be transitioned to another antiresorptive agent if Enoby is discontinued. (5.6)
- Serious infections including skin infections: May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis. (5.7)
- Dermatologic reactions: Dermatitis, rashes, and eczema have been reported. Consider discontinuing Enoby if severe symptoms develop. (5.8)
- Severe bone, joint, muscle pain may occur. Discontinue use if severe symptoms develop. (5.9)
- Suppression of bone turnover: Significant suppression has been demonstrated. Monitor for consequences of bone over-suppression. (5.10)

## ADVERSE REACTIONS

- Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials. (6.1)
- Male osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis. (6.1)
- Glucocorticoid-induced osteoporosis: Most common adverse reactions (> 3% and more common than active-control group) were: back pain, hypertension, bronchitis, and headache. (6.1)
- Bone loss due to hormone ablation for cancer: Most common adverse reactions (> 10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](#).

**USE IN SPECIFIC POPULATIONS**

- Pregnant women and females of reproductive potential: Denosumab products may cause fetal harm when administered to pregnant women. Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Enoby. (8.1, 8.3)
- Pediatric patients: Enoby is not approved for use in pediatric patients. (8.4)
- Renal impairment: No dose adjustment is necessary in patients with renal impairment with an eGFR >30 mL/min/1.73 m<sup>2</sup>, including dialysis-dependent patients, are at greater risk of severe hypocalcemia. The presence of underlying chronic kidney disease-mineral bone disorder markedly increases the risk of hypocalcemia. (5.1, 8.6)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

\*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 ENOBY has been demonstrated for the condition(s) of use of (e.g., indication(s), dosing regimen(s), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

**Issued: 09/2025**

**6 ADVERSE REACTIONS**

- Clinical Trials Experience
- Postmarketing Experience

**8 USE IN SPECIFIC POPULATIONS**

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential
- Pediatric Use
- Geriatric Use
- Renal Impairment

**11 DESCRIPTION**

- CLINICAL PHARMACOLOGY**
  - Mechanism of Action
  - Pharmacokinetics
  - Pharmacodynamics
  - Immunogenicity
- NONCLINICAL TOXICOLOGY**
  - Carcinogenesis, Mutagenesis, Impairment of Fertility
  - Animal Toxicology and/or Pharmacology
- CLINICAL STUDIES**
  - Treatment of Postmenopausal Women with Osteoporosis
  - Treatment to Increase Bone Mass in Men with Osteoporosis
  - Treatment of Glucocorticoid-Induced Osteoporosis
  - Treatment of Bone Loss in Men with Prostate Cancer
  - Treatment of Bone Loss in Women with Breast Cancer

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

- Sections or subsections omitted from the full prescribing information are not listed.

**6 ADVERSE REACTIONS**

- Clinical Trials Experience
- Postmarketing Experience

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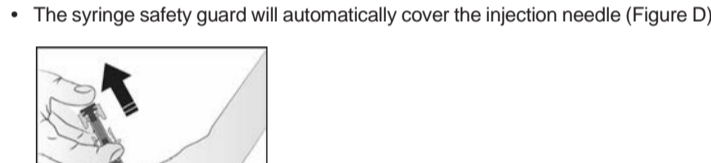
**16 HOW SUPPLIED/STORAGE AND HANDLING**

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**Step 3: Release Plunger and Dispose of Syringe**

- Keeping the pre-filled syringe at the injection site, release the thumb from the plunger and lift syringe.
- The syringe safety guard will automatically cover the injection needle (Figure D).



**Figure D**

- Immediately dispose of the syringe and needle cap in the nearest sharps container.
- Do not put the needle cap back on the used syringe.

**3 DOSAGE FORMS AND STRENGTHS**

- Injection: 60 mg/mL clear to slightly opalescent, colorless to pale yellow solution in a single-dose pre-filled syringe.

**4 CONTRAINDICATIONS**

Enoby is contraindicated in:

- Patients with hypocalcemia: Pre-existing hypocalcemia must be corrected prior to initiating therapy with Enoby. (See [Warnings and Precautions \(5.1\)](#).)
- Pregnant women: Denosumab products may cause fetal harm when administered to a pregnant woman. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Enoby. (See [Use in Specific Populations \(8.1\)](#).)
- Patients with hypersensitivity to denosumab products: Enoby is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria. (See [Warnings and Precautions \(5.3\)](#), [Adverse Reactions \(6.2\)](#).)

**5 WARNINGS AND PRECAUTIONS**

- Severe Hypocalcemia and Mineral Metabolism Changes**

Denosumab products can cause severe hypocalcemia and fatal cases have been reported. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Enoby. Adequately supplement all patients with calcium and vitamin D. (See [Dosage and Administration \(2.1\)](#), [Contraindications \(4\)](#), and [Adverse Reactions \(6.1\)](#).)

In patients with advanced chronic kidney disease who are predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, treatment with other calcium-lowering drugs), assess serum calcium and mineral levels (phosphorus and magnesium) before 14 days after Enoby injection. In some postmarketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

**Patients with Advanced Chronic Kidney Disease**

Patients with advanced chronic kidney disease [i.e., eGFR < 30 mL/min/1.73 m<sup>2</sup>] including dialysis-dependent patients are at greater risk for severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. The presence of underlying chronic kidney disease-mineral bone disorder (CKD-MBD, renal osteodystrophy) markedly increases the risk of hypocalcemia. Concomitant use of calcimimetic drugs may also worsen hypocalcemia risk.

To minimize the risk of hypocalcemia in patients with advanced chronic kidney disease, evaluate for the presence of chronic kidney disease mineral and bone disorder with intact parathyroid hormone (PTH), serum calcium, 25(OH) vitamin D, and 1,25(OH)<sub>2</sub> vitamin D prior to decisions regarding Enoby treatment. Consider also assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present. Monitor serum calcium weekly for the first 4 weeks after Enoby administration, and more frequently if patients have advanced chronic kidney disease, including those who are dialysis-dependent, and the symptoms of hypocalcemia and the importance of maintaining serum calcium levels with adequate calcium and activated vitamin D supplementation. Treatment during Enoby administration and discontinuation should be supervised by a healthcare provider who is experienced in diagnosis and management of CKD-MBD.

**5.2 Drug Products with Same Active Ingredient**

Patients receiving Enoby should not receive other denosumab products concomitantly.

**5.3 Hypersensitivity**

Clinically significant hypersensitivity including anaphylaxis has been reported with denosumab products. Symptoms have included hypotension, dyspnea, throat tightness, and wheezing. In some postmarketing cases, hypocalcemia or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Enoby. (See [Contraindications \(4\)](#), [Adverse Reactions \(6.2\)](#).)

**5.4 Osteonecrosis of the Jaw (ONJ)**

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. It has been reported in patients receiving denosumab products. (See [Adverse Reactions \(6.1\)](#).) A routine dental exam should be performed by the prescriber prior to initiation of Enoby treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Enoby in patients with risk factors for ONJ, such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), chronic administration of bisphosphonate drugs associated with ONJ, periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures. Good oral hygiene practices should be maintained during Enoby treatment. In some postmarketing cases, hypocalcemia with ONJ may increase the risk of developing ONJ. The risk of ONJ may increase with duration of exposure to denosumab products.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ while on Enoby should receive care by a dentist or oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Enoby therapy should be considered based on individual benefit-risk assessment.

**5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures**

Atypical low energy or low trauma fractures of the shaft have been reported in patients receiving 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. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with antiresorptive agents.

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 Enoby 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. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Enoby therapy should be considered, pending a benefit-risk assessment, on an individual basis.

**5.6 Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation**

Following discontinuation of denosumab treatment, fracture risk increases, including the risk of multiple vertebral fractures. Treatment with denosumab results in significant suppression of bone turnover and cessation of denosumab treatment results in increased bone turnover above pretreatment values 9 months after the last dose of denosumab. Bone turnover then returns to pretreatment values 24 months after the last dose of denosumab. In addition, bone mineral density (BMD) returns to pretreatment values within 18 months after the last injection. (See [Clinical Pharmacology \(12.2\)](#), [Clinical Studies \(14.1\)](#).)

New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of denosumab. Prior vertebral fracture was a predictor of multiple vertebral fractures following treatment discontinuation. Evaluate an individual's benefit-risk before initiating treatment with Enoby.

If Enoby treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy. (See [Adverse Reactions \(6.1\)](#).)

**5.7 Serious Infections**

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the denosumab group than in the placebo group. (See [Adverse Reactions \(6.1\)](#).) Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with denosumab. Endocarditis was also reported more frequently in denosumab-treated patients. The incidence of opportunistic infections was similar between placebo and denosumab groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with Enoby. In patients who develop serious infections while on Enoby, prescribers should assess the need for continued Enoby therapy.

## 5.8 Dermatologic Adverse Reactions

In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the denosumab group compared to the placebo group. Most of these events were not specific to the injection site. (See [Adverse Reactions \(6.1\)](#).) Consider discontinuing Enoby if severe symptoms develop.

## 5.9 Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking denosumab products. (See [Adverse Reactions \(6.2\)](#).) The time to onset of symptoms varied from one day to several months after starting denosumab products. Consider discontinuing use if severe symptoms develop. (See [Patient Counseling Information \(17\)](#).)

## 5.10 Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with denosumab resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. (See [Clinical Pharmacology \(12.2\)](#), [Clinical Studies \(14.1\)](#).) The significance of these findings and the effect of long-term treatment with denosumab products are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with denosumab may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

**5.11 Hypocalcemia in Pediatric Patients with Osteogenesis Imperfecta**

Enoby is not approved for use in pediatric patients. Hypocalcemia has been reported in pediatric patients with osteogenesis imperfecta treated with denosumab products. Some cases required hospitalization. (See [Use in Specific Populations \(8.4\)](#).)

## 6 ADVERSE REACTIONS

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

- Severe Hypocalcemia and Mineral Metabolism Changes (See [Warnings and Precautions \(5.1\)](#))
- Hypersensitivity (See [Warnings and Precautions \(5.3\)](#))
- Osteonecrosis of the Jaw (See [Warnings and Precautions \(5.4\)](#))
- Atypical Subtrochanteric and Diaphyseal Femoral Fractures (See [Warnings and Precautions \(5.5\)](#))
- Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation (See [Warnings and Precautions \(5.6\)](#))
- Serious Infections (See [Warnings and Precautions \(5.7\)](#))
- Dermatologic Adverse Reactions (See [Warnings and Precautions \(5.8\)](#))

The most common adverse reactions reported with denosumab products in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

The most common adverse reactions reported with denosumab products in men with osteoporosis are back pain, arthralgia, and nasopharyngitis.

The most common adverse reactions reported with denosumab products in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache.

The most common (per patient incidence > 10%) adverse reactions reported with denosumab products in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of denosumab products in patients with postmenopausal osteoporosis are back pain and constipation.

## 6.1 Clinical Trials Experience

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

**Treatment of Postmenopausal Women with Osteoporosis**

The safety of denosumab in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to denosumab administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the denosumab group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the denosumab group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and denosumab groups, respectively. The most common adverse reactions reported with denosumab in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the denosumab-treated women than in the placebo-treated women are shown in the table below.

**Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients**

Preferred Term	Denosumab (N = 3886) n (%)	Placebo (N = 3876) n (%)
Back pain	1347 (34.7)	1340 (34.6)
Pain in extremity	453 (11.7)	

## Absorption

Following subcutaneous administration, the median time to maximum denosumab concentration ( $T_{max}$ ) was 10 days (range: 3 to 21 days).

## Distribution

The mean volume of distribution for denosumab was 5.2 L (SD = 1.7 L).

## Elimination

Serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46).

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable differences in pharmacokinetics with age (in postmenopausal women), race, or body weight (36 to 140 kg).

## Seminal Fluid Pharmacokinetic Study

Serum and seminal fluid concentrations of denosumab were measured in 12 healthy male volunteers (age range: 43-65 years). After a single 60 mg subcutaneous administration of denosumab, the mean ( $\pm$  SD)  $C_{max}$  values in the serum and seminal fluid samples were 6170 ( $\pm$  2070) and 100 ( $\pm$  81.9) ng/mL, respectively, resulting in a maximum seminal fluid concentration of approximately 2% of serum levels. The median (range)  $T_{1/2}$  values in the serum and seminal fluid samples were 2.0 (1.9 to 2.1) and 2.1 (2.0 to 4.9) days, respectively. Among the subjects, the highest denosumab concentration in seminal fluid was 301 ng/mL at 22 days post-dose. On the first day of measurement (10 days post-dose), nine of eleven subjects had quantifiable concentrations in semen. On the last day of measurement (106 days post-dose), five subjects still had quantifiable concentrations of denosumab in seminal fluid, with a mean ( $\pm$  SD) seminal fluid concentration of 21.1 ( $\pm$  36.5) ng/mL across all subjects (n = 12).

## Drug Interactions

In a study of 19 postmenopausal women with low BMD and rheumatoid arthritis treated with etanercept (50 mg subcutaneous injection once weekly), a single dose of denosumab (60 mg subcutaneous injection) was administered 7 days after the previous dose of etanercept. No clinically significant changes in the pharmacokinetics of etanercept were observed.

## Cytochrome P450 substrates

In a study of 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered 2 weeks after a single-dose of denosumab (60 mg subcutaneous injection), which approximates the  $T_{max}$  of denosumab. Denosumab did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab does not alter the pharmacokinetics of drugs metabolized by CYP3A4 in postmenopausal women with osteoporosis.

## Specific Populations

**Gender:** Mean serum denosumab concentration-time profiles observed in a study conducted in healthy men  $\geq$  50 years were similar to those observed in a study conducted in postmenopausal women using the same dose regimen.

**Age:** The pharmacokinetics of denosumab were not affected by age across all populations studied; whose ages ranged from 28 to 87 years.

**Race:** The pharmacokinetics of denosumab were not affected by race.

**Renal Impairment:** In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not necessary.

**Hepatic Impairment:** No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab products.

## 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). No neutralizing antibodies were observed. A corroborated study 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.

### 13.2 Mutagenicity

The genotoxic potential of denosumab products has not been evaluated.

### 13.3 Impairment of Fertility

Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 10- to 50-fold higher than the recommended human dose of 60 mg subcutaneously administered once every 6 months, 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.

In ovariectomized monkeys, once-monthly treatment with denosumab suppressed bone turnover and increased BMD and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone.

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, namely OPG-Fc, provided additional information on the pharmacodynamics of denosumab products. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobuloalveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborated 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 STUDIES

**14.1 Treatment of Postmenopausal Women with Osteoporosis**  
The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline BMD T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive subcutaneous injections of either placebo (N = 3906) or denosumab 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

### Effect on Vertebral Fractures

Denosumab significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years (p < 0.0001), as shown in Table 3. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the denosumab-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

**Table 3. The Effect of Denosumab on the Incidence of New Vertebral Fractures in Postmenopausal Women**

	Proportion of Women with Fracture (%) <sup>a</sup>		Absolute Risk Reduction (%) <sup>b</sup> (95% CI)	Relative Risk Reduction (%) <sup>b</sup> (95% CI)
	Placebo N = 3961 (%)	Denosumab N = 3702 (%)		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

<sup>a</sup> Event rates based on crude rates in each interval.

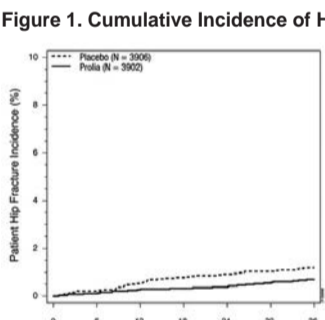
<sup>b</sup> Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

Denosumab was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

### Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for denosumab-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years (p = 0.04) (see Figure 1).

**Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years**



N = number of subjects randomized

### Effect on Nonvertebral Fractures

Treatment with denosumab resulted in a significant reduction in the incidence of nonvertebral fractures (see Table 4).

**Table 4. The Effect of Denosumab on the Incidence of Nonvertebral Fractures at Year 3**

	Proportion of Women with Fracture (%) <sup>a</sup>		Absolute Risk Reduction (%) <sup>b</sup> (95% CI)	Relative Risk Reduction (%) <sup>b</sup> (95% CI)
	Placebo N = 3906 (%)	Denosumab N = 3902 (%)		
Nonvertebral fracture <sup>c</sup>	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)*

<sup>a</sup> Event rates based on Kaplan-Meier estimates at 3 years.

<sup>b</sup> Excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges.

<sup>c</sup> p-value = 0.01.

### Effect on Bone Mineral Density (BMD)

Treatment with denosumab significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After denosumab discontinuation, BMD returned to approximately baseline levels within 12 months.

### Bone Histology and Histomorphometry

A total of 115 transilic crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in denosumab group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with denosumab resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

### 14.2 Treatment to Increase Bone Mass in Men with Osteoporosis

The efficacy and safety of denosumab in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck were also enrolled if there was a history of prior fragility fracture. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study. The 242 men enrolled in the study ranged in age from 31 to 84 years with a mean age of 65 years. Men were randomized to receive SC injections of either placebo (n = 121) or denosumab 60 mg (n = 121) once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

### Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline 0-1 year. Secondary efficacy variables included percent change in total hip, and femoral neck BMD from baseline to 1 year.

Treatment with denosumab significantly increased BMD at 1-year. The treatment differences in BMD at 1-year were 4.8% (+0.9% placebo, +5.7% denosumab; (95% CI: 4.0, 5.6); p < 0.0001) at the lumbar spine, 2.0% (+0.3% placebo, +2.4% denosumab) at the total hip, and 2.2% (0.0% placebo, +2.1% denosumab) at femoral neck. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, BMD, testosterone concentrations, and level of bone turnover.

### Bone Histology and Histomorphometry

A total of 29 transilic crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in denosumab group, 12 specimens in placebo group). Of the biopsies obtained, 29 (100%) were adequate for qualitative histology and, in denosumab patients, 6 (35%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 6% had no tetracycline label present at the month 12 biopsy, while 100% of placebo-treated patients had double label present. When compared to placebo, treatment with denosumab resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

### 14.3 Treatment of Glucocorticoid-Induced Osteoporosis

The efficacy and safety of denosumab in the treatment of patients with glucocorticoid-induced osteoporosis was assessed in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind, parallel-group, active-controlled study (NCT 01575873) of 795 patients (70% women and 30% men) aged 20 to 94 years (mean age of 63 years) treated with greater than or equal to 7.5 mg/day prednisone (or equivalent) for < 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-initiating subpopulation; n = 290) or < 3 months prior to study enrollment and initiating glucocorticoid treatment for a total of at least 6 months (glucocorticoid-continuing subpopulation; n = 505). Enrolled patients < 50 years of age were required to have a history of osteoporotic fracture. Enrolled patients  $\geq$  50 years of age who were in the glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of  $\leq$  -2.0 at the lumbar spine, total hip, or femoral neck, or a BMD T-score  $\leq$  -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Patients were randomized (1:1) to receive either an oral daily bisphosphonate (active-control, risedronate 5 mg once daily) (n = 397) or denosumab 60 mg subcutaneously once every 6 months (n = 398) over 1 year. Randomization was stratified by gender within each subpopulation. Patients received at least 1000 mg calcium and 800 IU vitamin D supplementation daily.

### Effect on Bone Mineral Density (BMD)

In the glucocorticoid-initiating subpopulation, denosumab significantly increased lumbar spine BMD compared to the active-control at one year (Active-control 0.8%, denosumab 3.8%) with a treatment difference of 2.9% (p < 0.001). In the glucocorticoid-continuing subpopulation, denosumab significantly increased lumbar spine BMD compared to active-control at one year (Active-control 2.3%, denosumab 4.4%) with a treatment difference of 2.2% (p < 0.001). Consistent effects on lumbar spine BMD were observed regardless of gender, race, geographic region, menopausal status, and baseline age, lumbar spine BMD T-score, and glucocorticoid dose within each subpopulation.

### Bone Histology

Bone biopsy specimens were obtained from 17 patients (11 in the active-control treatment group and 6 in the denosumab treatment group) at Month 12. Of the biopsies obtained, 17 (100%) were adequate for qualitative histology. Qualitative assessments showed bone of normal architecture and quality without mineralization defects or bone marrow abnormality. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with active-control, 100% of biopsies had tetracycline label present at the month 12 biopsy and 100% of biopsies had double label present and (67%) had no tetracycline label present at the 12-month biopsy. Evaluation of full quantitative histomorphometry including bone remodeling rates was not possible in the glucocorticoid-induced osteoporosis population treated with denosumab. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

### 14.4 Treatment of Bone Loss in Men with Prostate Cancer

The efficacy and safety of denosumab in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0 or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive subcutaneous injections of either placebo (n = 734) or denosumab 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs.  $\geq$  70 years) and duration of ADT at trial entry ( $\leq$  6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

### Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in denosumab-treated patients as compared to placebo-treated patients (-1.0% placebo, +5.6% denosumab; treatment difference 6.7% (95% CI: 6.2, 7.1); p < 0.0001).

With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% denosumab) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% denosumab) at the total hip, and 4.9% (-1.8% placebo, +3.0% denosumab) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.

### Effect on Vertebral Fractures

Denosumab significantly reduced the incidence of new vertebral fractures at 3 years (p = 0.0125), as shown in Table 5.

**Table 5. The Effect of Denosumab on the Incidence of New Vertebral Fractures in Men with Nonmetastatic Prostate Cancer**

	Proportion of Men with Fracture (%) <sup>a</sup>		Absolute Risk Reduction (%) <sup>b</sup> (95% CI)	Relative Risk Reduction (%) <sup>b</sup> (95% CI)
	Placebo N = 673 (%)	Denosumab N = 679 (%)		
0-1 Year	1.9	0.3	1.6 (0.5, 2.8)	85 (33, 97)
0-2 Years	3.3	1.0	2.2 (0.7, 3.8)	69 (27, 66)
0-3 Years	3.9	1.5	2.4 (0.7, 4.1)	62 (22, 81)

<sup>a</sup> Event rates based on crude rates in each interval.

<sup>b</sup> Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group and ADT duration variables.

### 14.5 Treatment of Bone Loss in Women with Breast Cancer

The efficacy and safety of denosumab in the treatment of bone loss in women receiving adjuvant (AJ) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo (n = 125) or denosumab 60 mg (n = 127) once every 6 months for a total of 4 doses administered as randomized by duration of adjuvant AJ therapy at trial entry ( $\leq$  6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AJ therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

### Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in denosumab-treated patients as compared to placebo-treated patients (6.0% placebo, +4.8% denosumab; treatment difference 5.5% (95% CI: 4.8, 6.3); p < 0.0001).

With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% denosumab) at the lumbar spine, 4.7% (-1.0% placebo, +3.8% denosumab) at the total hip, and 3.6% (-0.8% placebo, +2.8% denosumab) at the femoral neck.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

Enoby (denosumab-qbde) injection is a clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose prefilled syringe with a safety guard. The prefilled syringe is not made with natural rubber latex.

60 mg/mL in a single-dose prefilled syringe	1 per carton	NDC 0143-9165-01
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### Storage and Handling

Store Enoby 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, Enoby may be allowed to reach room temperature up to 25°C (77°F) in the original container. Once removed from the refrigerator, Enoby must not be exposed to temperatures above 25°C (77°F) and must be used within 30 days. Discard Enoby if not used within the 30 days. Do not use Enoby after the expiry date printed on the label.

Protect Enoby from direct light and heat.

Avoid vigorous shaking of Enoby.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Hypocalcemia

Advise the patient to adequately supplement with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Enoby [see *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.0)]. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

### Severe Hypocalcemia in Patients with Advanced Chronic Kidney Disease

Advise patients with advanced chronic kidney disease, including those who are dialysis-dependent, about the symptoms of hypocalcemia and the importance of maintaining serum calcium levels with adequate calcium and activated vitamin D supplementation. Advise these patients to have their serum calcium measured weekly for the first month after Enoby administration and monthly thereafter [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.6)].

### Drug Products with Same Active Ingredient

Advise patients that if they receive Enoby, they should not receive other denosumab products concomitantly [see *Warnings and Precautions* (5.2)].

### 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 allergic hypersensitivity reactions that they should not receive denosumab products [see *Warnings and Precautions* (5.3), *Contraindications* (4)].

### Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Enoby and to inform their dentist prior to dental procedures that they are receiving Enoby. Patients should inform their physician 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 Fractures

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

### Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Advise patients not to interrupt Enoby therapy without talking to their physician [see *Warnings and Precautions* (5.6)].

### Serious Infections

Advise patients to seek prompt medical attention if they develop signs or symptoms of infections, including cellulitis [see *Warnings and Precautions* (5.7)].

### Dermatologic Adverse Reactions

Advise patients to seek prompt medical attention if they develop signs or symptoms of dermatologic reactions (such as dermatitis, rashes, and eczema) [see *Warnings and Precautions* (5.8)].

### Musculoskeletal Pain

Inform patients that severe bone, joint, and/or muscle pain have been reported in patients taking denosumab products. Patients should report severe symptoms if they develop [see *Warnings and Precautions* (5.9)].

### Pregnancy/Nursing

Counsel females of reproductive potential to use effective contraceptive measure to prevent pregnancy during treatment and for at least 5 months after the last dose of Enoby. Advise the patient to contact their physician immediately if pregnancy occurs during the treatment. Advise patients not to take Enoby while pregnant or breastfeeding. If a patient wishes to start breastfeeding after treatment, advise her to discuss the appropriate timing with her physician [see *Contraindications* (4), *Use in Specific Populations* (8.1)].

### Schedule of Administration

Advise patients that if a dose of Enoby is missed, the injection should be administered as soon as convenient. Thereafter, schedule injections every 6 months from the date of the last injection.

### Enoby™ (denosumab-qbde)

#### Manufactured by:

Hikma Pharmaceuticals USA Inc.

2 Esterbrook Lane

Cherry Hill, NJ 08003 USA

U.S. License No. 2356

Product of Hungary

Prolia® is a registered trademark of Amgen Inc.

Medication Guide Enoby™ (eh-noé-bee) (denosumab-qbde)	
Injection, for subcutaneous use	