PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrEVENITY™

romosozumab injection

105 mg/1.17 mL solution for subcutaneous injection

Single-Use Prefilled Syringe

Professed Standard

Sclerostin Inhibitor

Bone Formation Agent

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, Ontario
L5N 0A4

Date of Approval:
Jun 17, 2019

Submission Control No: 197713

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EVENITY is indicated for:

- The treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture.

1.1 Pediatrics (< 18 years of age):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥ 65 years of age):

Of the 6544 postmenopausal women with osteoporosis treated with EVENITY in clinical studies, 5234 (80%) were ≥ 65 years old and 2390 (36.5%) were ≥ 75 years old.

2 CONTRAINDICATIONS

- EVENITY is contraindicated in patients who are hypersensitive to romosozumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Table 1 **Dosage Forms, Strengths, Composition and Packaging**.
- EVENITY is contraindicated in patients with hypocalcemia. Correct pre-existing hypocalcemia prior to initiating treatment with EVENITY (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Potential Risk of Myocardial Infarction, Stroke and Cardiovascular Death

- EVENITY may increase the risk of myocardial infarction, stroke, and cardiovascular death (see **WARNINGS AND PRECAUTIONS*, and Clinical Trial Adverse Reactions)***.
- EVENITY treatment is not recommended in patients with a history of myocardial infarction or stroke.
- Consider whether the benefits outweigh the risks in patients with other cardiovascular or cerebrovascular disease or associated risk factors.
- EVENITY treatment should be discontinued in patients that experience a myocardial infarction or stroke.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

EVENITY is administered subcutaneously.

EVENITY should be administered by a health care professional or an individual trained by a health care professional.

After initial training in proper subcutaneous injection technique, an individual may self-inject EVENITY if a physician determines that is appropriate and with medical follow-up as necessary.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of EVENITY is 210 mg administered once every month as two consecutive subcutaneous injections of 105 mg each using the single-dose prefilled syringes for 12 doses.

Patients should be adequately supplemented with calcium and vitamin D (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS** and **CLINICAL TRIALS**).

Limit duration of use to 12 monthly doses. When a patient has completed the 12 months of EVENITY therapy, and osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered (see **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**). In the absence of a follow on anti-resorptive therapy, bone mineral density (BMD) gains trend toward pre-treatment levels following cessation of EVENITY.

Health Canada has not authorized an indication for pediatric use.

No dosage adjustment may be required in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring hemodialysis; however, EVENITY should be used with caution (see **WARNINGS AND PRECAUTIONS, Renal Impairment**).

4.3 Administration

To administer the recommended dose of 210 mg, give two consecutive subcutaneous injections of 105 mg each.

Visually inspect EVENITY for particles and discolouration prior to administration. EVENITY is a clear to opalescent, colourless to light yellow solution. Do not use if the solution is cloudy or discoloured or contains particles.

Administer EVENITY in the abdomen, thigh, or upper arm subcutaneously. If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.

Comprehensive instructions for the administration of EVENITY are provided in the **Patient Medication Information – How to take EVENITY** section.

4.4 Missed Dose

If an EVENITY dose is missed, administer as soon as it can be rescheduled. Thereafter, EVENITY can be scheduled every month from the date of the last dose.

5 OVERDOSAGE

There is no experience with overdosage in clinical trials with EVENITY.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution for injection 105 mg/1.17 mL	Acetate, calcium, polysorbate 20, sodium hydroxide, sucrose, and water for injection

EVENITY is a sterile, preservative-free, clear to opalescent, colourless to light yellow solution, pH 5.2.

The elastomeric needle shield of the prefilled syringe is made from synthetic latex-free rubber.

EVENITY is provided as:

- Carton of two 105 mg (210 mg dose) single-use prefilled syringe in 1.17 mL of solution (90 mg/mL).

7 DESCRIPTION

EVENITY (romosozumab injection) is a humanized IgG2 monoclonal antibody with high affinity and specificity for sclerostin. By inhibiting sclerostin, romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption. Romosozumab has an approximate molecular weight of 149 kDa and is produced in a mammalian cell line (Chinese hamster ovary) by recombinant DNA technology.

8 WARNINGS AND PRECAUTIONS

Please see the **Serious Warnings and Precautions Box** at the beginning of Part I: Health Professional Information.

General

Patients should be adequately supplemented with calcium and vitamin D during EVENITY treatment (see **CONTRAINDICATIONS**, and **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism** -- ***Hypocalcemia***).

Bone

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing and has occurred in EVENITY-treated patients in clinical trials (see **Clinical Trial Adverse Reactions**).

Evaluate patients for risk factors for ONJ before starting treatment. A dental examination with appropriate preventative dentistry is recommended prior to treatment with EVENITY in patients with risk factors for ONJ. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, smoking, a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, invasive dental procedures (e.g. dental extractions, dental implants, and oral

surgery), and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, ill-fitting dentures, anemia, coagulopathy, and infection).

Patients should maintain good oral hygiene practices during treatment with EVENITY. Patients should receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with EVENITY.

For patients in whom invasive dental procedures cannot be avoided, the clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ during treatment with EVENITY should receive care by a dentist or an oral surgeon. Consider discontinuation of EVENITY treatment based on an individual benefit-risk assessment.

Atypical Femoral Fractures

Atypical low-energy or low-trauma fractures of the femoral shaft, which can occur spontaneously, have been reported in patients treated with EVENITY (see **Clinical Trial Adverse Reactions**).

Any patient who presents with new or unusual thigh, hip or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Assess patients presenting with an atypical femur fracture for symptoms and signs of fracture in the contralateral limb. Consider interruption of EVENITY treatment based on an individual benefit-risk assessment.

Cardiovascular

Myocardial Infarction, Stroke, and Cardiovascular Death

In a randomized controlled trial in postmenopausal women at high risk of fracture, major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, were reported more often in EVENITY-treated patients compared to patients treated with alendronate (see **SERIOUS WARNINGS AND PRECAUTIONS BOX** and **Clinical Trial Adverse Reactions**).

EVENITY treatment is not recommended in patients with a history of myocardial infarction or stroke. Consider whether the benefits outweigh the risks in patients with other cardiovascular or cerebrovascular disease or associated risk factors. During EVENITY treatment, patients that develop symptoms suggestive of myocardial infarction or stroke should undergo a prompt medical evaluation. EVENITY treatment should be discontinued in patients that experience a myocardial infarction or stroke.

Driving and Operating Machinery

No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving EVENITY.

Endocrine and Metabolism

Hypocalcemia

Hypocalcemia has occurred in patients receiving EVENITY. Correct hypocalcemia prior to initiating EVENITY treatment.

Patients should be adequately supplemented with calcium and vitamin D during EVENITY treatment. Monitor patients for signs and symptoms of hypocalcemia (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] of 15 to 29 mL/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcemia. In these patients, monitor serum calcium levels and ensure adequate supplementation with calcium and vitamin D. Instruct these patients about the symptoms of hypocalcemia and the importance of calcium and vitamin D supplementation.

Hepatic Impairment

The safety and effectiveness of EVENITY have not been studied in patients with hepatic impairment.

Immune

Hypersensitivity

Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash and urticaria have occurred in EVENITY-treated patients. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of EVENITY (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Renal Impairment

Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcemia (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS– Endocrine and Metabolism: *Hypocalcemia***).

8.1 Special Populations

8.1.1 Pregnant Women

EVENITY is not indicated for use in women of reproductive potential and may cause fetal harm when administered to a pregnant woman based on findings in animal studies.

In reproductive and developmental toxicity studies in rats, maternal-fetal transfer of romosozumab was demonstrated and bone developmental changes and skeletal malformations including syndactyly and polydactyly were observed (see **NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicology**).

8.1.2 Breast-feeding

EVENITY is not indicated for use in nursing women. In animal studies where pregnant rats were given weekly doses of romosozumab from 6 weeks before cohabitation through mating and lactation at 10, 60, or 300 mg/kg (equivalent to 1.5, 19 or 56 times the clinical exposure following a monthly subcutaneous dose of 210 mg, based on AUC comparison), romosozumab was dose-dependently present in the serum of offspring on postnatal day 21 at 0.01 to 2.4 times maternal exposure due to gestational and/or lactational exposure.

8.1.3 Fertility

No data are available on the effect of EVENITY on human fertility. Animal studies in female and male rats did not show any effects on fertility endpoints at doses up to 300 mg/kg (100-fold the clinical dose) (see **NON-CLINICAL TOXICOLOGY**).

8.1.4 Pediatrics (< 18 years of age)

The safety and effectiveness of EVENITY has not been studied in pediatric patients. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.1.5 Geriatrics (≥ 65 years of age)

Of the 6544 postmenopausal women with osteoporosis treated with EVENITY in clinical studies, 5234 (80%) were ≥ 65 years old and 2390 (36.5%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

In Study 1 (FRAME) during the 12-month double-blind treatment period, the incidence of all-cause mortality was 0.7% (24/3576) in the placebo group and 0.8% (29/3581) in the EVENITY group. The incidence of non-fatal serious adverse events was 8.3% in the placebo group and 9.1% in the EVENITY group. The percentage of patients who withdrew from the study due to adverse events was 1.1% in the placebo group and 1.1% in the EVENITY group. The most common adverse reactions reported with EVENITY (greater than or equal to 5% and at a higher incidence than placebo) were arthralgia (13.1%) and headache (6.6%). The most common adverse reaction leading to discontinuation of EVENITY was arthralgia (6 patients [0.2%] in the placebo group and 5 patients [0.1%) in the EVENITY group).

In Study 2 (ARCH) during the 12-month double-blind treatment period, the incidence of all-cause mortality was 1.1% (22/2014) in the alendronate group and 1.5% (30/2040) in the EVENITY group. The incidence of non-fatal serious adverse events was 13.3% in the alendronate group and 11.9% in the EVENITY group. The percentage of patients who withdrew from the study due to adverse events was 1.2% in the alendronate group and 1.2% in the EVENITY group. The most common adverse reactions reported with EVENITY (greater than or equal to 5%) were arthralgia (8.1%) and headache (5.2%).

9.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment of Postmenopausal Osteoporosis in Women at High Risk of Fracture

Study 1 (FRAME) (placebo-controlled)

The safety of EVENITY in the treatment of postmenopausal osteoporosis in women at high risk of fracture was demonstrated in a multicenter, randomized, double-blind, placebo-controlled study of 7180 postmenopausal women aged 55 to 90 years (mean age of 71 years).

A total of 3581 and 3576 patients received at least 1 dose of EVENITY and placebo, respectively, administered once every month during the 12-month double-blind study period. Patients received at least 500 mg calcium and 600 international units (IU) vitamin D supplementation daily. Most patients (77%) received a loading dose of 50,000 to 60,000 IU of vitamin D within one week of randomization if their serum 25-hydroxyvitamin D concentrations were 40 ng/mL or less.

Study 2 (ARCH) (alendronate-controlled)

The safety of EVENITY in the treatment of postmenopausal osteoporosis in women at high risk of fracture was demonstrated in a multicenter, randomized, double-blind, alendronate-controlled study of 4093 postmenopausal women aged 55 to 90 years (mean age of 74 years).

A total of 2040 and 2014 patients received at least 1 dose of EVENITY and alendronate, respectively, with EVENITY administered once every month during the 12-month double-blind study period. A total of 3462 patients received at least 1 dose of alendronate in the open-label period. Patients received at least 500 mg calcium and 600 IU vitamin D supplementation daily. Most patients (74%) received a loading dose of 50,000 to 60,000 IU of vitamin D within one week of randomization if their serum 25-hydroxyvitamin D concentrations were 40 ng/mL or less.

Table 2 below summarizes the adverse events reported during the first 12 months of Study 1 (FRAME) and Study 2 (ARCH).

Table 2. Adverse Events Reported in Women with Post-Menopausal Osteoporosis at High Risk for Fracture in ≥ 2% of patients in EVENITY Group in Either Study and More Frequently in the EVENITY Group than the Placebo Group in Study 1 (FRAME) (First 12 Months Analysis)

	Study 1 (FRAME)		Study 2 (ARCH)	
SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N = 3576) n (%)	EVENITY 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg PO QW (N = 2014) n (%)	EVENITY 210 mg SC QM (N = 2040) n (%)
EYE DISORDERS				
Cataract	54 (1.5)	70 (2.0)	36 (1.8)	49 (2.4)
GASTROINTESTINAL DISORDERS				
Dyspepsia	60 (1.7)	70 (2.0)	50 (2.5)	54 (2.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Asthenia	79 (2.2)	84 (2.3)	53 (2.6)	50 (2.5)
Oedema peripheral	67 (1.9)	86 (2.4)	38 (1.9)	34 (1.7)
INFECTIONS AND INFESTATIONS				
Nasopharyngitis	67 (1.9)	73 (2.0)	43 (2.1)	41 (2.0)
METABOLISM AND NUTRITION DISORDERS				
Dyslipidaemia	74 (2.1)	81 (2.3)	28 (1.4)	23 (1.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	434 (12.1)	468 (13.1)	194 (9.6)	166 (8.1)
Muscle spasms	140 (3.9)	163 (4.6)	81 (4.0)	70 (3.4)
Neck pain	54 (1.5)	80 (2.2)	42 (2.1)	34 (1.7)
NERVOUS SYSTEM DISORDERS				
Headache	208 (5.8)	235 (6.6)	110 (5.5)	106 (5.2)
Paraesthesia	62 (1.7)	72 (2.0)	34 (1.7)	29 (1.4)
PSYCHIATRIC DISORDERS				
Insomnia	68 (1.9)	72 (2.0)	36 (1.8)	34 (1.7)
Depression	45 (1.3)	48 (1.3)	42 (2.1)	42 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Cough	117 (3.3)	130 (3.6)	55 (2.7)	74 (3.6)

QM: Monthly; PO: by mouth; SC: subcutaneously

Major Adverse Cardiovascular Events (MACE)

During the 12-month double-blind treatment period of Study 1 (FRAME), myocardial infarction was reported in 9 (0.3%) EVENITY-treated patients and 8 (0.2%) placebo-treated patients. Stroke was reported in 8 (0.2%) EVENITY-treated patients and 10 (0.3%) placebo-treated patients. Cardiovascular death was reported in 17 (0.5%) EVENITY-treated patients and 15 (0.4%) placebo-treated patients. These events were reported in patients with and without a history of myocardial infarction or stroke. Overall, positively-adjudicated MACE (defined as non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) were reported in 30 (0.8%) EVENITY-treated patients and 29 (0.8%) placebo-treated patients (hazard ratio: 1.03 [95% confidence interval (0.62, 1.72)]) for EVENITY compared to placebo.

During the 12-month double-blind treatment period of Study 2 (ARCH), myocardial infarction was reported in 16 (0.8%) EVENITY-treated patients and 5 (0.2%) alendronate-treated patients. Stroke was reported in 13 (0.6%) EVENITY-treated patients and 7 (0.3%) alendronate-treated patients. Cardiovascular death was reported in 17 (0.8%) EVENITY-treated patients and 12 (0.6%) alendronate-treated patients. These events were reported in patients with and without a history of myocardial infarction or stroke. Overall, positively-adjudicated MACE were reported in 41 (2.0%) EVENITY-treated patients and 22 (1.1%) alendronate-treated patients (hazard ratio: 1.87 [95% confidence interval (1.11, 3.14)]) for EVENITY compared to alendronate (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, WARNINGS AND PRECAUTIONS)**.

The adverse reactions described below are from the combined 12-month controlled treatment periods of Study 1 (FRAME) (placebo-controlled) and Study 2 (ARCH) (alendronate-controlled) (n = 11, 211).

Hypocalcemia

Across both trials, hypocalcemia adverse events were reported in 2 (<0.1%) EVENITY-treated patients and 1 (< 0.1%) control-treated patients. Decreases in albumin adjusted serum calcium to below the lower limit of normal (8.3 mg/dL) were reported in 14 (0.2%) EVENITY-treated patients and 10 (0.2%) control-treated patients. No patient receiving EVENITY developed serum calcium < 7.5 mg/dL. The nadir in albumin-adjusted serum calcium level occurred by month 1 after EVENITY dosing in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Hypersensitivity

Across both trials, hypersensitivity reactions were reported in 364 (7%) EVENITY-treated patients and 365 (7%) control-treated patients. Reported reactions included angioedema (EVENITY:3 [< 0.1%]; control: 3 [< 0.1 %]), erythema multiforme (EVENITY: 1 [< 0.1%]; control: 0 [0%]), dermatitis (EVENITY: 32 [1%]; control: 42 [1%]), rash (EVENITY: 60 [1%]; control: 53 [1%]), and urticaria (EVENITY: 23 [0.4%]; control: 27 [0.5%]) (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Osteonecrosis of the jaw

Across both trials, osteonecrosis of the jaw occurred in one patient during treatment with EVENITY (see **WARNINGS AND PRECAUTIONS**).

Atypical femoral fractures

Across both trials, atypical femoral fracture occurred in one patient during treatment with EVENITY (see **WARNINGS AND PRECAUTIONS**).

Injection Site Reactions

Across both trials, injection site reactions occurred in 278 (5%) EVENITY-treated patients and 157 (3%) control-treated patients. The most commonly reported injection site reactions were pain (EVENITY: 94 [1.7%]; control: 70 [1.3%]) and erythema (EVENITY: 80 [1.4%]; control: 14 [0.3%]). Injection site reactions resulted in discontinuation of treatment in 7 (0.1%) EVENITY-treated patients and 3 (<0.1%) control-treated patients.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of romosozumab has been evaluated using a screening immunoassay for the detection of binding anti-romosozumab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

Of the 5914 postmenopausal women dosed with 210 mg monthly EVENITY, 1072 (18.1%) developed anti-romosozumab binding antibodies. Of these, 50 (4.7%) had antibodies classified as neutralizing. Antibodies to romosozumab were generally not associated with changes in efficacy and safety of EVENITY.

9.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

<u>Hypocalcemia</u>

Hypocalcemia was observed in EVENITY-treated patients (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Endocrine and Metabolism: Hypocalcemia and ADVERSE REACTIONS – Clinical Trial Adverse Drug Reactions: Hypocalcemia)**.

Serum phosphorous

During the double-blind period of Study 1 (FRAME), median serum phosphorous concentrations were decreased by 5% in EVENITY-treated patients and 0% in placebo-treated patients after 1 month. Median serum phosphorous concentrations remained decreased in EVENITY-treated patients for up to 12 months. During this time, 5 (0.1%) EVENITY-treated patients and 4 (0.1%) placebo-treated patients had a grade 3 (<2.0-1.0 mg/dL) below-normal phosphorus result; no grade 4 (<1.0 mg/dL) results were reported.

Alkaline phosphatase

During the double-blind period of Study 1 (FRAME), median serum alkaline phosphatase levels were increased by 29% in EVENITY-treated patients and returned to baseline by month 9. There were no increases in serum alkaline phosphatase levels in placebo-treated patients. No EVENITY-treated patients and 1 (< 0.1%) placebo-treated patient had a grade 3 (>5 – 20.0 x

ULN) above-normal alkaline phosphatase result; no grade 4 (>20.0 x ULN) results were reported.

Intact parathyroid hormone (iPTH)

During the double-blind period of Study 1 (FRAME), after two weeks of treatment, median serum iPTH levels increased by 37% in a subset of EVENITY-treated patients and by 5% in a subset of placebo-treated patients. The median serum iPTH remained above baseline levels in EVENITY-treated patients at 12 months.

Study 3 (STRUCTURE) (Women transitioning from alendronate therapy)

A multicentre, randomized, open-label study enrolled post-menopausal women with a mean age of 71 years (range 56 to 90 years) at high risk of fracture. A percentage of 99.5% of patients had been treated with alendronate in the past year, and all patients had been treated with bisphosphonates in the past 3 years (90.4% alendronate). In the EVENITY-treated patients (n=218), the types and subject incidence of adverse events reported after one year were not meaningfully different from those reported in patients in other clinical studies that had not transitioned from alendronate

9.4 Less Common Clinical Trial Adverse Drug Reactions

Listing 1 The following adverse events were reported in EVENITY-treated patients in Study 1 (FRAME) and Study 2 (ARCH) at frequencies < 2% and ≥ 0.1%; and for events reported in Study 1 (FRAME), more frequently in EVENITY-treated versus placebo-treated patients

BLOOD AND LYMPHATIC SYSTEM DISORDERS: leukopenia, neutrophilia

CARDIAC DISORDERS: atrial fibrillation, cardiac failure, mitral valve incompetence, tachycardia, tricuspid valve, incompetence, coronary artery disease, myocardial ischemia, acute myocardial infarction, ventricular extrasystoles, cardiomegaly, angina unstable, hypertensive heart disease, bradycardia, sinus bradycardia, bundle branch block left, left ventricular hypertrophy

EAR AND LABYRINTH DISORDERS: excessive cerumen production

ENDOCRINE DISORDERS: hypothyroidism, hyperthyroidism

EYE DISORDERS: glaucoma, dry eye, conjunctival hemorrhage, macular degeneration, eye pain, ocular hyperaemia, eye pruritus

GASTROINTESTINAL DISORDERS: dental caries, irritable bowel syndrome, chronic gastritis, dry mouth, loose tooth, diverticulum, gingival pain, gastritis erosive, aphthous ulcer, odynophagia, gastric polyps, mouth ulceration, oesophagitis, gastrointestinal haemorrhage, gastric disorder, ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: injection site pain, injection site erythema, non-cardiac chest pain, injection site pruritus, chest pain, injection site bruising, injection site swelling, injection site rash, drug intolerance, injection site haematoma, chest discomfort, cyst, feeling hot, face oedema, injection site urticaria

IMMUNE SYSTEM DISORDERS: hypersensitivity

INFECTIONS AND INFESTATIONS: pneumonia, cystitis, pharyngitis, sinusitis, rhinitis, conjunctivitis, herpes zoster, gingivitis, respiratory tract infection, viral infection, oral herpes, onychomycosis, tonsillitis, laryngitis, upper respiratory tract infection bacterial, conjunctivitis

bacterial, tooth infection, tooth abscess, helicobacter infection, otitis externa, oral candidiasis, diverticulitis, acute sinusitis, herpes simplex, bacterial vaginosis, otitis media, genital herpes, diarrhoea infectious, infected skin ulcer, tonsillitis bacterial, gastroenteritis bacterial, skin infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: limb injury, tooth fracture, wound, arthropod bite, road traffic accident, humerus fracture, tendon rupture, craniocerebral injury, anaemia postoperative, excoriation

INVESTIGATIONS: weight decreased, body height decreased

METABOLISM AND NUTRITION DISORDERS: hypercholesterolaemia, diabetes mellitus, hyperglycaemia, hypokalaemia, type 2 diabetes mellitus, hyponatraemia, hyperuricaemia, hypertriglyceridaemia, glucose tolerance impaired, hypoglycaemia, carbohydrate intolerance, diabetes mellitus inadequate control, dehydration

MUSCOSKELETAL AND CONNECTIVE TISSUE DISORDERS: bone pain, tendonitis, muscle contracture, bursitis, intervertebral disc disorder, arthritis, musculoskeletal stiffness, groin pain, synovial cyst, flank pain, plantar fasciitis, foot deformity, scoliosis, pain in jaw, musculoskeletal discomfort, joint stiffness, intervertebral disc degeneration

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): skin papilloma, lipoma, lung neoplasm malignant, colon adenoma

NERVOUS SYSTEM DISORDERS: sciatica, hypoaesthesia, tension headache, tremor, neuralgia, amnesia, transient ischaemic attack, balance disorder, burning sensation, radiculopathy, cerebral atrophy, epilepsy, carotid arteriosclerosis, cerebral arteriosclerosis, polyneuropathy, loss of consciousness, memory impairment, transient ischemic attack, amnesia, cerebrovascular disorder, tremor, cerebral arteriosclerosis, Parkinson's disease, vertebrobasilar insufficiency

PRODUCT ISSUES: device failure

PSYCHIATRIC DISORDERS: depression

RENAL AND URINARY DISORDERS: renal cyst, dysuria, chronic kidney disease, nephrolithiasis, haematuria, renal failure, hypertonic bladder

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: breast pain, uterine prolapse, atrophic vulvovaginitis, cystocele vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: dyspnoea, asthma, epistaxis, productive cough, dysphonia, pulmonary hypertension, bronchitis chronic, rhinorrhoea pulmonary hypertension

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: rash, alopecia, erythema, seborrhoeic dermatitis, skin disorder, xeroderma, night sweats, dermal cyst, rash generalised

SURGICAL AND MEDICAL PROCEDURES: Tooth extraction

VASCULAR DISORDERS: peripheral venous disease, arteriosclerosis, aortic arteriosclerosis, hypertensive crisis, peripheral arterial occlusive disease, phlebitis

10 DRUG INTERACTIONS

10.1 Overview

No drug interaction studies have been conducted with EVENITY.

10.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

10.3 Drug-Food Interactions

Interactions with food have not been established.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

EVENITY (romosozumab) is a humanized monoclonal antibody (IgG2) that inhibits the action of sclerostin, a regulatory factor in bone metabolism. Romosozumab increases bone formation and, to a lesser extent, decreases bone resorption. Animal studies showed that romosozumab stimulates new bone formation on trabecular and cortical bone surfaces by stimulating osteoblastic activity resulting in increases in trabecular and cortical bone mass and improvements in bone structure and strength.

11.2 Pharmacodynamics

In a clinical study of postmenopausal women with osteoporosis, EVENITY increased the bone formation marker procollagen type 1 N-telopeptide (P1NP) with a peak increase from baseline of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to concentrations seen with placebo at month 9 and a decline from baseline to approximately 15% below the concentration seen with placebo at month 12. EVENITY decreased the bone resorption marker type-1 collagen C-telopeptide (CTX) with a maximal reduction from baseline of approximately 55% relative to placebo 2 weeks after initiating treatment. CTX remained below concentrations seen with placebo at month 12.

In a clinical study of postmenopausal women with low bone mineral density, after discontinuation of EVENITY P1NP levels returned to baseline within 12 months; after discontinuation of EVENITY CTX levels increased above baseline levels within 3 months and returned toward baseline levels by month 12.

11.3 Pharmacokinetics

Romosozumab exhibited nonlinear pharmacokinetics with exposure increasing greater than dose proportionally (eg. 550-fold increase in mean area under the concentration-time curve from time 0 to infinity (AUC_{inf}) for the 100-fold increase in subcutaneous doses ranging from 0.1 to 10 mg/kg [0.03 to 3.3 times the approved recommended dosage for a 70 kg woman]).

The presence of anti-romosozumab binding antibodies decreased romosozumab exposure up to 22%. The presence of neutralizing antibodies decreased romosozumab exposure up to 63% (see **ADVERSE REACTIONS**).

Absorption

Administration of a single dose of 210 mg EVENITY in healthy male and female subjects (n = 90, age range 21 to 65 years) resulted in a mean (standard deviation [SD]) maximum serum concentration (C_{max}) of 22.2 (5.8) mcg/mL and a mean AUC_{inf} of 389 (127) mcg*day/mL.The median time to maximum romosozumab concentration (T_{max}) was 5 days (range: 2 to 7 days).

Following a 210 mg subcutaneous dose, bioavailability was estimated to be 81% based on population pharmacokinetic (popPK) analyses.

Steady-state concentrations were achieved by month 3 with minimal accumulation (less than 2-fold) following the monthly administration of 210 mg to postmenopausal women. The mean trough serum romosozumab concentrations at months 3, 6, 9, and 12 ranged from 8 to 13 mcg/mL.

Distribution

The volume of distribution at steady-state was estimated to be 3.92 L based on popPK model estimates for a patient of 61 kg of body weight.

Metabolism

The metabolic pathway of romosozumab has not been characterized. As a humanized IgG2 monoclonal antibody, romosozumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Elimination

Romosozumab exhibited nonlinear pharmacokinetics with the clearance of romosozumab decreasing as the dose increased. The estimated mean systematic clearance (CL/F) of romosozumab was 0.38 mL/hr/kg, following a single subcutaneous administration of 3 mg/kg (the approved recommended dosage for a 70 kg woman). The mean effective $t_{1/2}$ was 12.8 days after 3 doses of 3 mg/kg (the approved recommended dosage for a 70 kg woman) every 4 weeks.

Special Populations

Based on a population pharmacokinetic analysis, age (20-89 years), gender, race, prior alendronate exposure, or disease state (low bone mass or osteoporosis) had no clinically meaningful effects on pharmacokinetics (< 20% change in exposure at steady state). Romosozumab exposure decreased with increasing body weight. This decrease had a minimal impact on lumbar spine BMD gain (< 20% change) based on exposure-response analyses.

Renal Impairment: Following a single 210 mg dose of romosozumab in a clinical study of 16 patients with severe renal impairment or ESRD requiring hemodialysis, mean C_{max} and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects. Mean romosozumab exposure was similar between patients with ESRD requiring hemodialysis and healthy subjects. No dosage adjustment may be required in these patient populations; however, EVENITY should be used with caution (see **WARNINGS AND PRECAUTIONS, Renal Impairment**).

Hepatic Impairment: No clinical studies have been conducted to evaluate the effect of hepatic impairment.

12 STORAGE, STABILITY, AND DISPOSAL

Refrigerate at 2°C to 8°C in the original carton.

If removed from the refrigerator, EVENITY should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days.

Protect EVENITY from direct light and do not expose to temperatures above 25°C.

Do not freeze.

Do not store EVENITY in extreme heat or cold.

Do not shake.

13 SPECIAL HANDLING INSTRUCTIONS

Prior to subcutaneous administration, allow EVENITY to sit at room temperature for at least 30 minutes before injecting for patient's comfort. Do not warm in any other way.

Visually inspect the solution for particles and discolouration. Do not use if the solution is discoloured, cloudy, or contains particles.

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

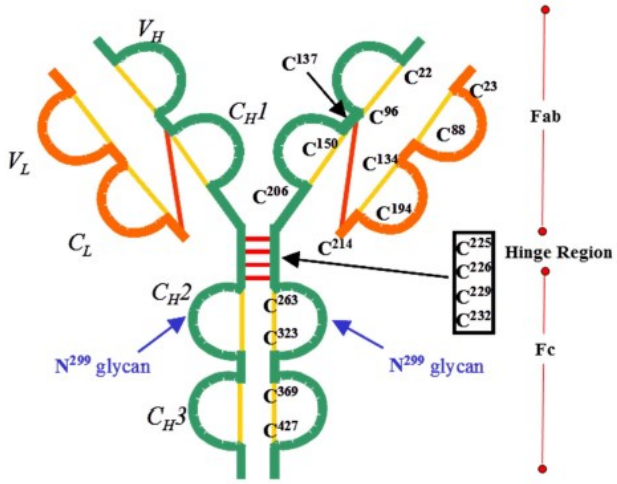
Drug Substance

Proper name: romosozumab

Molecular mass: 149 kDa (approximate)

Structural formula:

Figure 1. Schematic of Romosozumab Structure



Heavy chains are shown in green and light chains are shown in orange

V_H is the variable domain of the heavy chain

C_H1, C_H2, and C_H3 are the constant domains of the heavy chain

V_L is the variable domain of the light chain

C_L is the constant domain of the light chain

Product Characteristics

Romosozumab is a humanized IgG2 monoclonal antibody with high affinity and specificity for sclerostin. Romosozumab has an approximate molecular weight of 149 kDa and is produced in a mammalian cell line (Chinese hamster ovary) by recombinant DNA technology.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Table 3. Summary of Patient Demographics for Clinical Trials in Postmenopausal Women with Osteoporosis

Study #	Trial design	Dosage, route of administration and duration*	Number of Women Involved in First 12 Months of Treatment	Mean age in Years (Range in Years)	Gender
Study 1 (FRAME)	Phase 3, multicentre, multinational, randomized, double-blind, placebo-controlled, parallel-group study	EVENITY 210 mg or placebo SC injection once every month for 12 months followed by denosumab 60 mg SC every 6 months, 36 month duration	7180 EVENITY: 3589 Placebo: 3591	70.9 (55 to 90)	Female
Study 2 (ARCH)	Phase 3, multicentre, multinational, randomized, double-blind, alendronate-controlled, superiority study	EVENITY 210 mg SC injection once every month or oral weekly alendronate for 12 months followed by alendronate, 36 month median duration	4093 EVENITY: 2046 Alendronate: 2047	74.3 (55 to 90)	Female

*After the 12-month double blind study period, women in both arms transitioned to open-label denosumab 60 mg subcutaneous every 6 months for 12 months for Study 1 FRAME or open-label alendronate for Study 2 ARCH while remaining blinded to initial treatment assignment

Study 1 (FRAME) was a randomized, double-blind, placebo-controlled study of 7180 postmenopausal women aged 55 to 90 years (mean age of 70.9 years with bone mineral density (BMD) T-score less than or equal to −2.5 at the total hip or femoral neck.

Women were randomized to receive subcutaneous injections of either EVENITY (N = 3589) or placebo (N = 3591) once every month for 12 months with daily supplementation of 500 to 1000 mg calcium and 600 to 800 international units vitamin D. After the 12-month treatment period, women in both arms transitioned to open-label anti-resorptive therapy (denosumab) for 12 months while remaining blinded to their initial treatment.

The coprimary efficacy endpoints were new vertebral fracture at month 12 and month 24.

Study 2 (ARCH) was a randomized, double-blind, alendronate-controlled study of 4093 postmenopausal women aged 55 to 90 years (mean age of 74.3 years) with BMD T-score less than or equal to −2.5 at the total hip or femoral neck and either one moderate or severe vertebral fracture or two mild vertebral fractures, or BMD T-score less than or equal to -2.0 at the total hip or femoral neck and either two moderate or severe vertebral fractures or a recent history (ie. within the last 24 months) of a proximal femur fracture.

Women were randomized (1:1) to receive either monthly subcutaneous injections of EVENITY (N = 2046) or weekly oral alendronate dose (70 mg) (N = 2047) for 12 months, with daily supplementation of 500 to 1000 mg calcium and 600 to 800 international units vitamin D. After the 12-month treatment period, women in both arms transitioned to open-label alendronate while remaining blinded to their initial treatment.

The primary efficacy endpoints were the incidence of morphometric vertebral fracture at 24 months and time to the first clinical fracture through the primary analysis period. Clinical fracture was a composite endpoint of nonvertebral fracture and symptomatic vertebral fracture.

This was an event-driven trial, and the primary analysis was performed when all women who remained on the study had completed the month 24 study visit and clinical fracture events were confirmed for at least 330 women.

15.2 Clinical Study Results

15.2.1 Clinical Trial Results for Study 1 FRAME

Effect on Fractures

EVENITY significantly reduced the incidence of new vertebral fractures through month 12 ($p < 0.001$). In addition, the reduction in fracture risk persisted through the second year in women who received EVENITY during the first year and transitioned to denosumab compared to those who transitioned from placebo to denosumab (month 24; $p < 0.001$) (see Table 4). The incidence of nonvertebral fractures was not statistically significant when comparing EVENITY-treated women to placebo-treated women at month 12 or month 24.

Table 4. Effect of EVENITY on the Incidence and Risk of Fractures in Study 1 (FRAME)

	Placebo/ Denosumab (N = 3591) n/N1 (%)	EVENITY/ Denosumab (N = 3589) n/N (%)	Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)	p-value[b]
New vertebral fracture through Month 12	73/3591 (2.0)	20/3589 (0.6)	1.47 (0.84, 2.09)	72 (49, 85)	<0.001
New vertebral fracture thorough Month 24	125/3591 (3.5)	30/3589 (0.8)	2.67 (1.78, 3.55)	76 (60, 86)	<0.001

N= Number of subjects randomized

[a] Absolute and relative risk reductions are based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture strata.

[b] P-value is based on logistic regression model for new vertebral fracture adjusting for age and prevalent vertebral fracture strata.

Missing fracture status is imputed by multiple imputation for patients without observed fracture.

Effect on Bone Mineral Density (BMD)

In a sensitivity analysis at month 12, the treatment differences between EVENITY and placebo in BMD were 11.2% at the lumbar spine, 5.2% at the total hip, and 4.7% at the femoral neck. At month 24, the treatment differences between EVENITY followed by denosumab and placebo followed by denosumab in BMD were 9.4% at the lumbar spine, 4.6% at the total hip, and 4.3% at the femoral neck.

After EVENITY discontinuation, BMD returns to approximately baseline levels within 12 months in the absence of follow-on antiresorptive therapy.

Effect on Bone Histology and Histomorphometry

A total of 154 transiliac crest bone biopsy specimens were obtained from 139 women at month 2, month 12, and/or month 24. All biopsies obtained were adequate for qualitative histology and 138 (89.6%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments from patients treated with EVENITY showed normal bone architecture and quality at all time points. There was no evidence of woven bone, mineralization defects, or marrow fibrosis.

Histomorphometry assessments on biopsies at months 2 and 12 compared the effect of EVENITY with placebo (15 specimens at month 2 and 39 specimens at month 12 in the EVENITY group, 14 specimens at month 2 and 31 specimens at month 12 in the placebo group). After 2 months of EVENITY treatment, increases in histomorphometric indices consistent with bone formation at trabecular and endocortical surfaces were observed. These effects on bone formation were accompanied by decreases in indices consistent with bone resorption. After 12 months of EVENITY treatment, indices of both bone formation and resorption were decreased and bone volume, and trabecular and cortical thickness, were increased.

15.2.2 Clinical Trial Results for Study 2 ARCH

Effect on Fractures

EVENITY reduced the incidence of new vertebral fracture at 24 months (see Table 5).

Table 5. Effect of EVENITY on the Incidence of New Vertebral Fractures in Study 2 (ARCH)

	Alendronate Alone (N = 2047) n/N1 (%)	EVENITY Followed by Alendronate (N = 2046) n/N1 (%)	Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)[a]	p-value[b]
New vertebral fracture through Month 24	243/2047 (11.9%)	127/2046 (6.2%)	5.79 (3.51, 8.06	48 (34, 60)	<0.001

N= Number of subjects randomized

a. Absolute and relative risk reductions are based on the Mantel-Haenszel method adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.

b. P-value is based on logistic regression model for new vertebral fracture) adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.

Missing fracture status is imputed by multiple imputation for patients without observed fracture.

EVENITY significantly reduced the risk of clinical fracture through the end of the primary analysis period (see Table 6). This was an event-driven trial and the duration of follow-up varied across subjects. The median duration of subject follow-up for the primary analysis period was 33 months. Subjects with nonvertebral fracture comprised 83% of the subjects with clinical fracture during the primary analysis period.

Table 6. Effect of EVENITY on the Risk of Clinical Fractures in Study 2 (ARCH)

	Proportion of Women with Fracture (%)[a]		Hazard Ratio (95% CI)[c]	p-value[c]
	Alendronate Alone (N = 2047)	EVENITY Followed by Alendronate (N = 2046)		
Clinical fracture through primary analysis period[b]	13.0%	9.7%	0.73 (0.61, 0.88)	<0.001

N = Number of subjects randomized

a. % = number of subjects who had a fracture through the primary analysis period/N*100%; the duration of follow-up varied across subjects.

b. Primary analysis period ended when clinical fracture events were confirmed for at least 330 subjects and all subjects completed the month 24 study visit. The median duration (range) of follow-up for the primary analysis period was 33 (0, 56) months

c. Hazard ratio and P-value are based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline

EVENITY followed by alendronate also significantly reduced the risk of nonvertebral fracture through the primary analysis period (with a median follow-up of 33 months), with a hazard ratio of 0.81 (95% CI: 0.66, 0.99; p = 0.04) compared to alendronate alone.

Effect on Bone Mineral Density (BMD)

EVENITY significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with alendronate at month 12. The treatment differences in BMD were 7.4% at the lumbar spine, 2.9% at the total hip, and 2.8% at the femoral neck.

Twelve months of treatment with EVENITY followed by 12 months of treatment with alendronate significantly increased BMD compared with alendronate alone. The BMD increase with EVENITY over alendronate observed at month 12 was maintained at month 24. The treatment differences in BMD at month 24 were 6.8% at the lumbar spine, 3.2% at the total hip, and 3.2% at the femoral neck.

15.3 Treatment of Osteoporosis in Women Transitioning From Bisphosphonate Therapy (Study 3 STRUCTURE)

An open-label study enrolled post-menopausal women with a mean age of 71 years (range 56 to 90 years) at high risk of fracture. A percentage of 99.5% of patients had been treated with alendronate in the past year, and all patients had been treated with bisphosphonates in the past 3 years (90.4% alendronate). This study evaluated safety and BMD changes through 12 months of treatment with EVENITY compared with 12 months of treatment with teriparatide. In the EVENITY-treated patients (n=218) at Month 12 this therapy increased BMD from baseline by 9.8% at the lumbar spine, 2.9% at the total hip, and 3.2% at the femoral neck. The incidence of fractures was not evaluated in this study.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

No adverse effects were noted in rats and monkeys after 26 once-weekly subcutaneous romosozumab doses up to 100 mg/kg, equivalent to systemic exposures of 38 and 93 times, respectively, the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg EVENITY (based on AUC comparison).

Bone safety studies of up to 12-month duration were conducted in ovariectomized rats and monkeys with once-weekly romosozumab doses yielding exposures ranging from 1 to 22 times the systemic exposure in humans given monthly doses of 210 mg, based on AUC comparison. Romosozumab increased bone mass and improved cancellous bone microarchitecture and cortical bone geometry by increasing bone formation on periosteal, endocortical, and trabecular surfaces, and decreasing bone resorption on trabecular and endocortical surfaces. The increases in bone mass were significantly correlated with increases in bone strength. In rats and monkeys, bone quality was maintained at all skeletal sites at doses ranging from 1 to 22 times human exposure, and slightly improved in vertebrae at 19 to 22 times human exposure. There was no evidence of mineralization defects, osteoid accumulation, or woven bone formation.

Carcinogenicity

In a rat carcinogenicity study, once-weekly romosozumab doses of 3, 10 or 50 mg/kg were administered by subcutaneous injection to Sprague-Dawley rats from 8 weeks up to 98 weeks of age, resulting in systemic exposures that were up to 19 times the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg EVENITY (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with trabecular and cortical bone thickening at all doses. There were no effects of romosozumab on mortality and romosozumab did not cause significant increases in tumor incidence in male or female rats.

Genotoxicity

Genotoxicity studies have not been conducted with romosozumab.

Reproductive and Developmental Toxicology

Reproductive and developmental effects of romosozumab were assessed in the rat in a preliminary and definitive embryo-fetal development study, a combined fertility and embryo-development study, and a pre-and postnatal development study.

Weekly administration of romosozumab to pregnant rats during the period of organogenesis at exposures greater than 32 times the clinical exposure produced skeletal abnormalities in the offspring. Administration of romosozumab to rats prior to mating and through to the end of lactation produced minimal to slight decreases in femoral bone mineral density and/or cortical circumferences in the offspring at 1.5 to 56 times the expected exposure in humans.

Skeletal malformations including syndactyly and polydactyly occurred in 1 out of 75 litters across all rat reproductive toxicity studies, in the litter of a dam given weekly subcutaneous romosozumab doses of 300 mg/kg (equivalent to at least 32 times the clinical exposure observed in humans following a monthly subcutaneous dose of 210 mg, based on AUC comparison).

In the offspring of female rats given weekly romosozumab doses from 6 weeks before cohabitation through mating and lactation, femoral periosteal and endocortical circumferences

were slightly decreased at 10, 60, and 300 mg/kg (equivalent to 1.5, 19, and 56 times the clinical exposure following a monthly subcutaneous dose of 210 mg, based on AUC comparison). Cortical thickness was increased at 300 mg/kg (equivalent to 56 times expected clinical exposure). Femoral metaphyseal bone mineral density was slightly decreased at 60 and 300 mg/kg (equivalent to 19 and 56 times expected clinical exposure).

No effects on fertility were observed in male and female rats given subcutaneous romosozumab doses up to 300 mg/kg (up to 56 times the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg EVENITY, based on AUC comparison). No effects were noted in reproductive organs in rats and cynomolgus monkeys dosed subcutaneously for 6 months with weekly doses up to 100 mg/kg (exposures up to 38 and 93 times, respectively, the systemic exposure observed in humans administered monthly subcutaneous doses of 210 mg based on AUC comparison).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrEVENITY™

(pronounced Ē-ven-î-tēē)

romosozumab injection

Single-Use Prefilled Syringe

Read this carefully before you start taking **EVENITY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your health care professional about your medical condition and treatment and ask if there is any new information about **EVENITY**.

Serious Warnings and Precautions

Potential risk of heart attack and stroke and death from heart or blood vessel problems

- EVENITY may increase the risk of a heart attack (myocardial infarction), stroke, and death from heart or blood vessel problems. The risk is increased in patients who had a heart attack or stroke or other types of heart or blood vessel problems. It is not recommended you take EVENITY should you have had a heart attack or stroke. Contact your health care provider if you have any heart or blood vessel problems; discuss the benefits and risks of using EVENITY with them.
- During EVENITY treatment, if you have signs or symptoms of heart attack, such as chest pain or pressure, shortness of breath, light-headedness or dizziness, contact your health care provider or get medical help right away.
- During EVENITY treatment, if you have signs or symptoms of stroke such as headache, numbness or weakness in the face, arms or legs, difficulty talking, or changes in vision or loss of balance, contact your health care provider or get medical help right away.

What is EVENITY used for?

EVENITY contains romosozumab, a medicine that helps build bone, which makes bone stronger and less likely to break. EVENITY is used to treat osteoporosis in women after menopause who are at high risk of fracture (broken bone).

Osteoporosis is a disease that makes your bones thin and fragile. Osteoporosis is most common in women following menopause. Many patients with osteoporosis have no symptoms, but they are still at risk of breaking bones because osteoporosis has made their bones weak.

How does EVENITY work?

EVENITY works differently than other osteoporosis medications. EVENITY inhibits a protein called sclerostin. By binding and preventing the activity of sclerostin, EVENITY promotes bone building and also decreases the breakdown of bone. EVENITY's dual effect of both building new bone and also decreasing breakdown of existing bone will strengthen your bones, improve your bone mass, and lower your chance of breaking bones.

What are the ingredients in EVENITY?

Medicinal ingredients: romosozumab.

Non-medicinal ingredients: acetate, calcium, polysorbate 20, sodium hydroxide, sucrose, and water for injection.

EVENITY comes in the following dosage forms:

- Each 1.17 mL prefilled syringe contains 105 mg of romosozumab (90 mg/mL). Each carton contains two single-use prefilled syringes.

Do not use EVENITY:

- If you have low calcium levels in your blood (hypocalcemia). Your health care provider can tell you if your levels are too low.
- If you are allergic to EVENITY or any of the other ingredients of this medicine (listed in **What are the ingredients in EVENITY?** section).

To help avoid side effects and ensure proper use, talk to your health care professional before you take EVENITY. Talk about any health conditions or problems you may have including, if you:

- Have a history of heart attack, stroke or other heart or blood vessel problems
- Have low calcium levels in your blood (hypocalcemia)
- Have kidney problems or are on dialysis
- Have problems with your teeth or gums and/or have plans for dental work or dental surgery

Other warnings you should know about:

EVENITY may cause low levels of calcium in your blood (hypocalcemia). Your health care provider may prescribe calcium and vitamin D supplements to help prevent low calcium levels in your blood while you take EVENITY. Take calcium and vitamin D as your health care provider tells you to. Contact your health care provider if you notice any of these symptoms:

- Spasms, twitches, or muscle cramps and numbness or tingling in your fingers, toes, or around the mouth.

Serious allergic reactions can happen with use of EVENITY. Call your health care provider or get emergency medical help right away if you have any symptoms of an allergic reaction:

- Rash, hives, and swelling usually of the face, lips, mouth, tongue, or throat which may cause difficulty in swallowing or breathing.

Serious jaw bone problems (osteonecrosis) can occur during treatment with EVENITY. Your health care provider may tell you to see a dentist before you start EVENITY. Take good care of your teeth and gums while you are taking EVENITY. Contact your health care provider and dentist right away:

- If you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge.

Unusual fractures in the thigh bone can occur during treatment with EVENITY. Contact your doctor if you notice any of these symptoms:

- New or unusual pain in your hip, groin, or thigh

Children and adolescents

The use of EVENITY in children and adolescents has not been studied.

Pregnancy and breast-feeding

EVENITY is not intended for use if you are pregnant. EVENITY has not been tested in pregnant women. It is not known if EVENITY may harm your unborn baby; however EVENITY use in pregnant animals caused harm to their offspring. Tell your health care provider if you are pregnant; think you may be pregnant; or plan to get pregnant.

It is not known if EVENITY is present in breast milk. Tell your health care provider if you are breast-feeding or plan to do so.

Tell your health care provider about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take EVENITY:

EVENITY is administered once every month. EVENITY is injected under your skin (subcutaneous) by a trained individual.

During treatment with EVENITY, you should take calcium and vitamin D as directed by your health care provider.

Ask your health care provider if you have any further questions on the use of EVENITY.

Usual dose:

The usual dose of EVENITY is 210 mg once a month.

EVENITY is administered subcutaneously as 2 injections once every month for one year.

Overdose:

There is no experience with overdosage with EVENITY.

If you think you have taken too much EVENITY, contact your health care professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

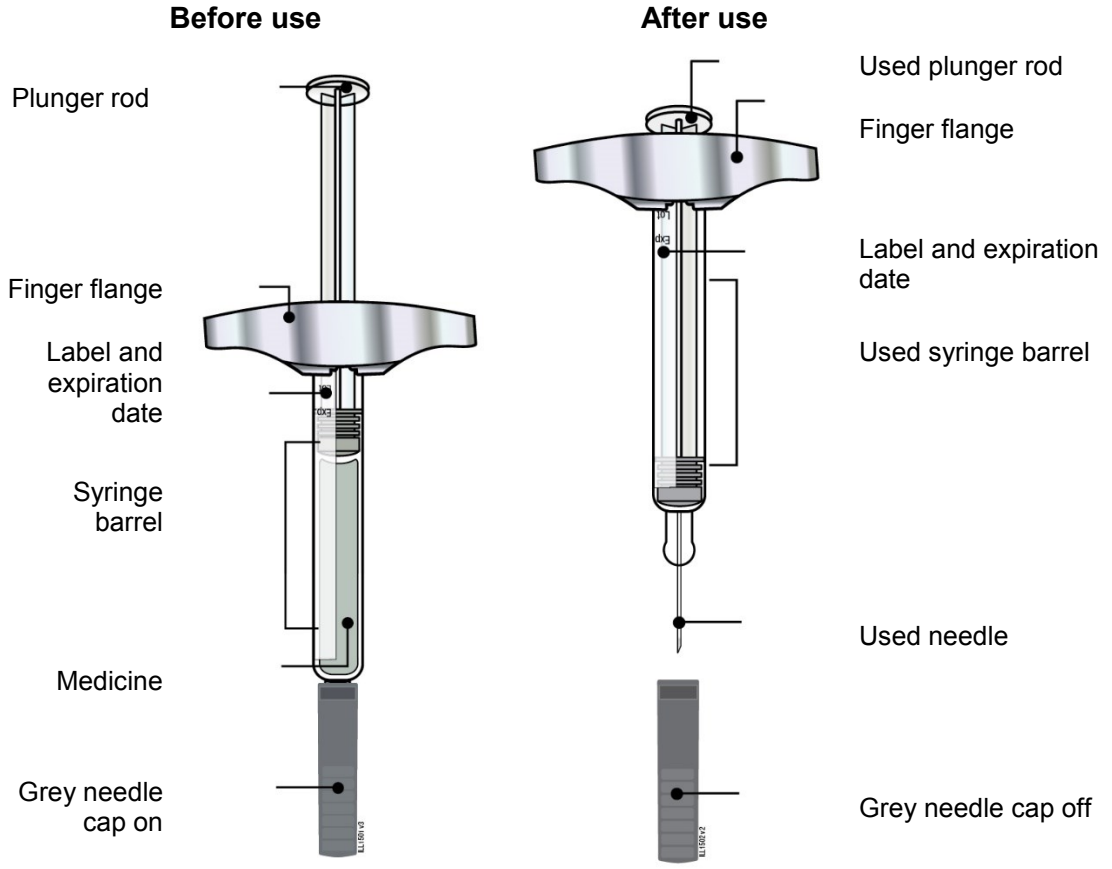
Missed Dose:

If you miss a dose of EVENITY, contact your health care provider as soon as possible to schedule your next dose. After that injections should be scheduled every month from the date of the last injection.

EVENITY Single-Use Prefilled Syringe:

The following instructions are for preparing and giving an injection of EVENITY using a single-use prefilled syringe.

Guide to Parts



Important: Needle is inside

Important:

Before you use an EVENITY prefilled syringe, read this important information:

Use both syringes in this carton for one full dose.

Storing the EVENITY prefilled syringe

- Keep the syringe out of the reach of children.
- Keep the syringe in the original carton to protect from light or physical damage.
- The syringe should be kept in the refrigerator at 2° C to 8° C.
- If needed, you may store the syringe at room temperature (up to 25° C) in the original carton for up to 30 days. Throw away EVENITY that has been stored at room temperature after 30 days in appropriate sharps container.

- **Do not** store the syringe in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.
- **Do not** freeze.

Using the EVENITY prefilled syringe

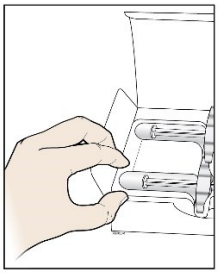
- Administration should be performed by an individual who has been trained to administer EVENITY.
- **Do not** use a syringe after the expiration date on the label.
- **Do not** shake the syringe.
- **Do not** remove the grey needle cap from the syringe until you are ready to inject.
- **Do not** freeze or use the syringe if it has been frozen.
- **Do not** use a syringe if it has been dropped on a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new syringe.
- The syringe is not made with natural rubber latex.

Step 1: Prepare

Read this before you inject.

- To deliver a full dose, inject **two** 105 mg syringes, one after the other.

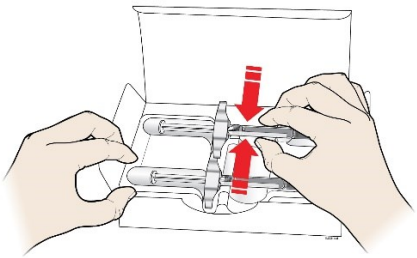
A. Remove two syringes from the carton.



Place finger or thumb on edge of tray to secure it while you remove syringe.

Grab the syringe barrel to remove the syringe from the tray.

Grab Here



For safety reasons:

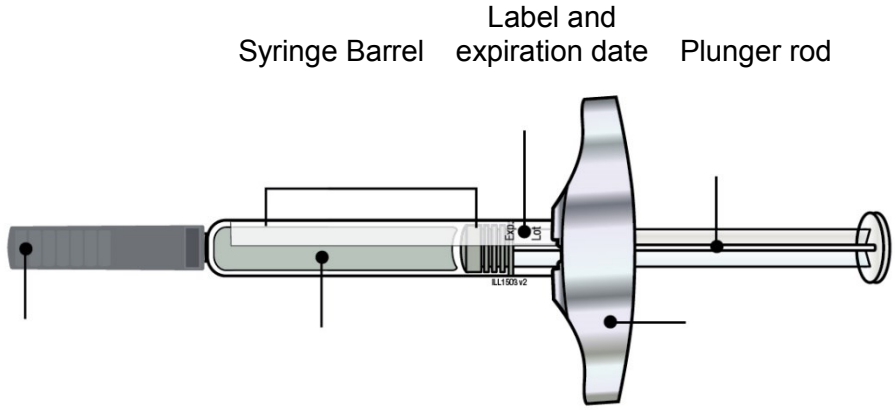
- **Do not** grasp the plunger rod.
- **Do not** grasp the grey needle cap.
- **Do not** remove the grey needle cap until you are ready to inject.
- **Do not** remove the finger flange. This is part of the syringe.

Leave the syringes at room temperature for at least 30 minutes before injecting for patient's comfort.

- **Do not** put the syringes back in the refrigerator once they have reached room temperature.
- **Do not** try to warm the syringe by using a heat source such as hot water or microwave.
- **Do not** leave the syringes in direct sunlight.
- **Do not** shake the syringes.

Important: Always hold the prefilled syringe by the syringe barrel.

B. Inspect the syringe.



Always hold the syringe by the syringe barrel.

Make sure the medicine in the syringe is clear and colourless to light yellow.

- **Do not** use the syringe if the medicine is cloudy or discoloured or contains particles.
- **Do not** use the syringe if any part appears cracked or broken.
- **Do not** use the syringe if the grey needle cap is missing or not securely attached.
- **Do not** use the syringe if the expiration date printed on the label has passed.

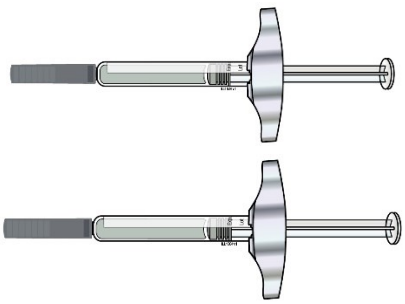
In all cases, use a new syringe and call Amgen Medical Information at 1-866-502-6436.

C. Gather all materials needed for the injection.

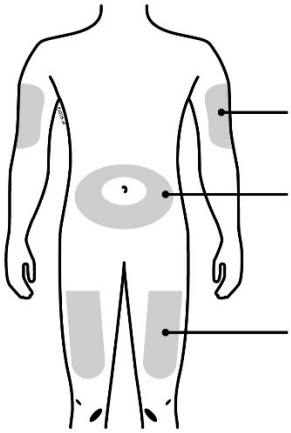
Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- Two syringes
- Two alcohol wipes
- Two cotton balls or two gauze pads
- Two adhesive bandages
- Sharps disposal container

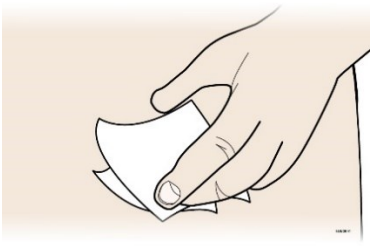


D. Prepare and clean two injection sites, one for each of the two injections.



You can use:

- The thigh
- Stomach area (abdomen), except for a two-inch (five centimeters) area right around the navel
- Outer area of upper arm



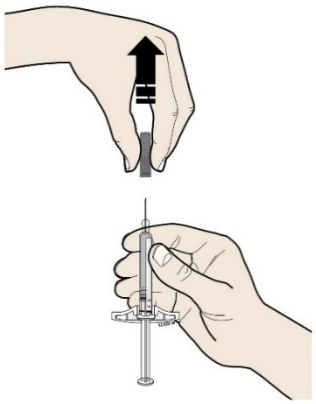
Clean the injection sites with alcohol wipes.

Let the skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give an injection. If you want to use the same injection site, make sure it is not the same spot on the injection site you used for the previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard.
- Avoid injecting directly into raised, thick, red, or scaly skin patch or lesion, or areas with scars or stretch marks.

Step 2: Get ready

E. Choose the first syringe. Pull the grey needle cap straight off and away from the body when you are ready to inject.

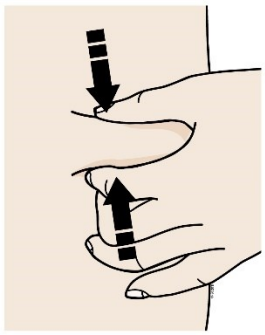


It is normal to see a drop of liquid at the end of the needle.

- **Do not** twist or bend the grey needle cap.
- **Do not** put the grey needle cap back onto the syringe.
- **Do not** remove the grey needle cap from the syringe until you are ready to inject.

Important: Throw the needle cap into a sharps disposal container.

F. Pinch the injection site to create a firm surface.

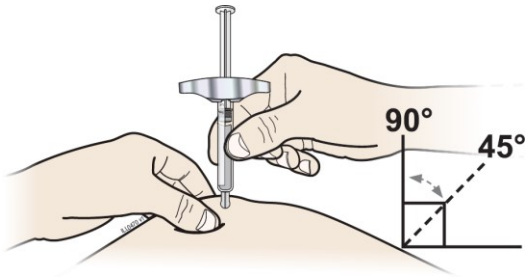


Pinch skin firmly between your thumb and fingers, creating an area about two inches wide (five centimeters).

Important: Keep skin pinched while injecting.

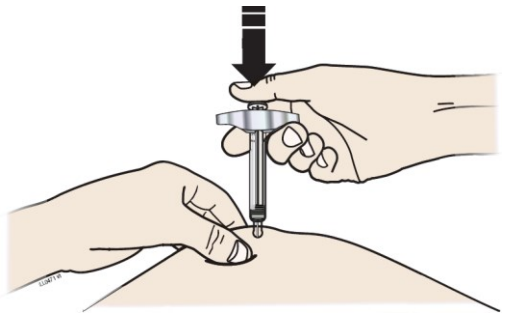
Step 3: Inject

G. Hold the pinch. With the grey needle cap off, insert the syringe into the skin at 45 to 90 degrees.

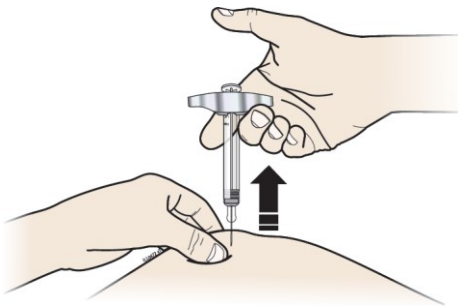


Do not place your finger on the plunger rod while inserting the needle.

H. Using slow and constant pressure, push the plunger rod all the way down until it stops moving.



I. When done, release your thumb and gently lift the syringe off of the skin.



Note: After you remove the syringe from skin, the syringe barrel should be empty.

Important: If it looks like the medicine is still in the syringe barrel, this means you have not delivered a full injection.

Step 4: Finish

J. Discard the used syringe and the grey cap.

Put the used syringe in a sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.

If you do not have a sharps disposal container, you may use a container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.

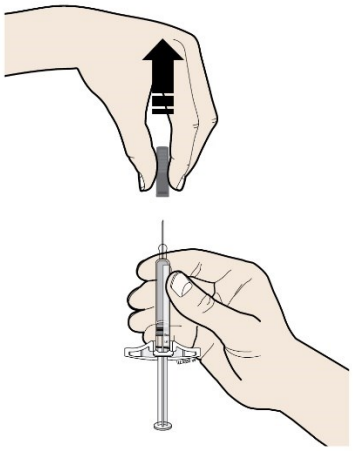
- **Do not** reuse the syringe.
- **Do not** recycle the syringe or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the reach of children.

K. Examine the injection site.

If there is blood, press a cotton ball or gauze pad on the injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

L. Repeat all steps with the second syringe to inject the full dose.



What are possible side effects from using EVENITY?

These are not all the possible side effects you may feel when taking EVENITY. If you experience any side effects including those not listed here, contact your health care professional. Please also see the warnings information above.

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

Possible side effects of EVENITY may include:

- Common cold (viral upper respiratory tract infection)
- Joint pain (arthralgia)
- Back pain
- Pain and redness at the site where EVENITY was injected

Serious side effects and what to do about them			
Symptom / effect	**Talk to your health care professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
COMMON [a] **(≥ 1%, 1 to 10% of patients)**			
Allergic reaction (hypersensitivity)		√	√
UNCOMMON [a] **(≥ 0.1%, < 1% of patients)**			
Low levels of calcium in the blood (hypocalcemia)		√	√
Heart attack (myocardial infarction)[b]		√	√
Stroke[b]		√	√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your health care professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
RARE[a] **(≥ 0.01%, < 0.1% of patients)**			
Sore in mouth involving gums or jaw bones (osteonecrosis of the jaw)[b]		√	√
Unusual thigh bone fractures (atypical femoral fracture)[b]		√	√

[a] Frequency regardless of seriousness

[b] Positively adjudicated

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your health care professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

- Refrigerate at 2˚C to 8˚C in the original carton.
- If removed from the refrigerator, EVENITY should be kept at room temperature (up to 25°C) in the original carton and must be used within 30 days.
- Protect EVENITY from direct light and do not expose to temperatures above 25°C.
- Do not freeze.
- Do not store EVENITY in extreme heat or cold.
- Do not shake.
- Keep EVENITY out of the reach of children.
- Any unused product or waste material should be disposed of in accordance with local requirements.

If you want more information about EVENITY:

- Talk to your health care professional
- Find the full product monograph that is prepared for health care professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.amgen.ca or by calling 1-866-50-AMGEN (1-866-502-6436).

This leaflet was prepared by Amgen Canada Inc.

Last Revised: