Evenity™ Inj. Pre-filled Syringe

[Prescription only]

(Romosozumab)

[COMPOSITION]

[Drug Product] 1 pre-filled syringe contains (1.17 mL)

Active Ingredient: Romosozumab (In-house)·····105mg

Excipients: Calcium acetate, Acetate acid, glacial, Sucrose, Polysorbate 20, Sodium hydroxide, Water for injection, Sterilized injection needle

[APPEARANCE]

A colorless and transparent plastic pre-filled syringe with integrated needle filled with liquid of colorless to light yellow, and practically free from particles.

[INDICATIONS]

1) Treatment of osteoporosis in postmenopausal women at high risk of fracture.
2) Osteoporosis in men at high risk of fracture to increase bone mass.

[DOSAGE AND ADMINISTRATION]

This drug should be administered by a healthcare provider.

The recommended dose of this drug is 210 mg (2 consecutive injection of 105 mg to the different administration site) by subcutaneous injection once every month for 12 doses.

All patients should be supplemented with calcium and vitamin D supplements.

If this drug dose is missed on the settled administration day, administer as soon as it can be rescheduled. Thereafter, this drug can be scheduled every month from the date of the last dose.

After completing this drug therapy, transition to an antiresorptive osteoporosis therapy is required.

For detailed instructions on storage, handling, and administration of this drug, follow the directions provided in the precautions for use, '13. Precautions in Administration'.

[PRECAUTIONS FOR USE]

1. Contraindications

1) Patients who have had a myocardial infarction or stroke within the preceding one year
   This drug may increase the risk of myocardial infarction and stroke during treatment (see '4. General Cautions').
2) Patients with Hypocalcemia
   This drug could lead to worsen hypocalcemia, therefore it should be treated before administration of this drug in patients with hypocalcemia (see '4. General Cautions').
3) Patients with a history of hypersensitivity to this active ingredient or to any component of the product

2. Careful Administration

1) Patients with increased risk of myocardial infarction and stroke
   Cardiovascular events of MI and stroke were observed during treatment with this drug (see '4. General Cautions').

2) Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] is lower than 30 mL/min/1.73 m^2) or receiving dialysis
The risk of developing hypocalcemia is greater (see '10. Renal impairment').

3. Drug Adverse Reactions

1) Adverse Reactions Reported in Clinical Trial
The adverse reactions described in the table below are based on 12-month pooled data from 3,695 postmenopausal women with osteoporosis or 163 men with osteoporosis treated with this drug in 2 placebo-controlled Phase II and 2 placebo-controlled Phase III clinical trials. In placebo-controlled studies, adverse reactions were occurred in 78.4% (3,025/3,858 patients) who received this drug and 80.0% (3,016/3,770 patients) who received placebo. The most common adverse reactions (≥ 10%) in this drug group were nasopharyngitis, arthralgia and back pain.
The adverse reactions in a double-blind, Phase III active-controlled study of 2,040 patients treated with this drug were similar in profile to those seen in the placebo-controlled trials.

The adverse reactions occurring in ≥2% of this drug treated and more frequently than placebo group were described in the table 1.

Adverse reactions are displayed by system organ class and frequency below using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Table 1. Adverse Reactions Occurring in ≥2% of this drug treated and more frequently than in placebo in osteoporosis patients

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Nasopharyngitis	Very Common
Nervous system disorders	Headache	Common
Respiratory, thoracic, and mediastinal disorders	Cough	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very Common
	Neck pain	Common
	Muscle spasms	Common
General disorders and administration site conditions	Peripheral edema	Common

Specific Adverse Reactions

- Hypocalcemia: It was reported in 0.4% in this drug group.
- Injection site reactions: It was reported in 5.2% in this drug group. Most frequently reported adverse reactions were injection site pain and erythema.
- Hypersensitivity: It was reported in 6.7% in this drug group. Clinically significant reactions were rash, dermatitis, urticaria, angioedema, erythema multiforme etc.

2) Immunogenicity
As with other therapeutic proteins, there is potential for immunogenicity.
In postmenopausal women dosed with 210 mg monthly this drug, the incidence of anti-

romosozumab antibodies was 18.1% (1,072/5,914 patients) for binding antibodies and 0.8% (50/5,914 patients) for neutralizing antibodies. In men with osteoporosis dosed with 210 mg monthly this drug, the incidence of anti-romosozumab antibodies was consistent [17.3% (28/162 patients) for binding antibodies and 0.6% (1/162 patients) for neutralizing antibodies] with that observed in postmenopausal women with osteoporosis.

4. General Cautions

1) Cardiovascular Adverse Events

- This drug may increase the risk of myocardial infarction and stroke during treatment.
  This drug should not be initiated in patients who have had a myocardial infarction(MI) or stroke within the preceding one year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors.
  Patients should be instructed to watch for symptoms of MI, including chest pain or pressure, shortness of breath, lightheadedness or dizziness and symptoms of stroke, including headache, numbness or weakness in face, arm, or legs, difficulty talking, changes in vision, or loss of balance. Patients should be instructed and to seek prompt medical attention if symptoms occur.
  If a patient experiences a MI or stroke during therapy, this drug should be discontinued.
- In the alendronate-controlled Phase III trial (N = 4,054) during the 12-month double-blind this drug treatment phase, there was a higher rate of major adverse cardiac events (MACE; composite of cardiovascular death, MI or stroke) in patients treated with this drug compared to those treated with alendronate. A post hoc evaluation of positively adjudicated MACE resulted in incidences of 2.0%(41/2,040) in this drug arm and 1.1%(22/2,014) in the alendronate arm. The incidence of MI events was 16 women (0.8%) in this drug arm and 5 (0.2%) in the alendronate arm; stroke occurred in 13 women (0.6%) in this drug arm and 7 (0.3%) in the alendronate arm. These events occurred in patient with and without a history of MI or stroke. The incidence of cardiovascular (CV) death was 17 women (0.8%) in this drug arm and 12 (0.6%) in the alendronate arm.
  In the placebo-controlled Phase III trial (N = 7,157) during the 12-month double-blind this drug treatment phase, the incidence of major adverse cardiac events (MACE) was comparable between placebo arm and this drug arm. A post hoc evaluation of positively adjudicated MACE resulted in incidences of 1.3%(46/3,581) in this drug arm and 1.3%(46/3,576) in the placebo arm. The incidence of MI occurred in 9 women (0.3%) in this drug arm and 8 (0.2%) in the placebo arm; stroke occurred in 8 women (0.2%) in this drug arm and 10 (0.3%) in the placebo arm. These events occurred in patient with and without a history of MI or stroke. CV death occurred in 17 women (0.5%) in this drug arm and 15 (0.4%) in the placebo arm.

2) Hypocalcemia and mineral metabolism
   Transient hypocalcemia has been observed in patients receiving this drug. Correct hypocalcemia and the other abnormal mineral metabolism prior to initiating therapy with this drug. Monitor patients for signs and symptoms of hypocalcemia during treatment, monitoring of serum calcium and mineral levels are recommended in patients predisposed to hypocalcemia and abnormal mineral metabolism. Patients should be adequately supplemented with calcium and vitamin D.

3) Hypersensitivity
   Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria occurred in this drug group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of this drug.

4) 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 rarely in patients receiving this drug in the clinical trials.

A routine oral exam should be performed prior to initiation of this drug treatment, and it is required to evaluate risk factors for ONJ. A dental examination with appropriate preventive dentistry is recommended prior to treatment with this drug in patients with risk factors for ONJ such as invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and comorbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with this drug. Invasive dental procedures should be avoided while administrating this drug.

Patients who are suspected of having or who develop ONJ while on this drug should receive care by a dentist or an oral surgeon. Discontinuation of this drug therapy should be considered based on individual benefit-risk assessment.

5) Atypical Femoral Fracture

Atypical low-energy or low-trauma fracture of the femoral shaft, which can occur spontaneously, has occurred rarely in patients receiving this drug in the clinical trials. 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 during treatment of this drug. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of this drug therapy should be considered based on individual benefit-risk assessment.

5. Drug-Drug Interactions

No drug interaction studies have been conducted with this drug.

6. Use in Pregnancy and Nursing Mothers

1) Pregnancy

- There are no studies of this drug in pregnant women. Therefore, it is not known whether this drug can cause fetal harm when administered to a pregnant woman. This drug is not indicated for use in women of reproductive potential.
- In reproductive and developmental studies performed in rats, in fetuses from maternal rats administered this drug at exposures over 30-fold higher than the systemic exposure observed in humans(AUC in humans following a monthly subcutaneous dose of 210 mg this drug), an increase in the incidence of reduced ventral processes on the sixth cervical vertebra, a skeletal process not found in humans was seen, which resolved in pups examined postnatally. Skeletal abnormalities including syndactyly and polydactyly, occurred in 1 out of 75 litters across all studies. There were no adverse effects observed on postnatal growth and development.

2) Nursing Mothers

It is not known whether this drug is excreted in human milk. This drug is not indicated for use in women of reproductive potential.

3) Fertility

No data are available on the effect of this drug on human fertility. In fertility and embryo-fetal development study in the rats, it did not show any effects on fertility endpoints at doses up to 300

mg/kg (up to 54-fold higher than the systemic exposure observed in human based on comparison of AUC after administration of clinical dose).

7. Pediatrics
The safety and efficacy of this drug have not been established in pediatric patients.

8. Geriatrics
Of the 6,525 postmenopausal women with osteoporosis treated with this drug in clinical studies, 5,222 (80%) were ≥ 65 years old and 2,385 (36.6%) were ≥ 75 years old. Of the 163 men with osteoporosis treated with this drug in clinical studies, 132 (80.9%) were ≥ 65 years old and 70 (42.9%) were ≥ 75 years old. No overall differences in safety or efficacy were observed among these patients and younger patients.

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

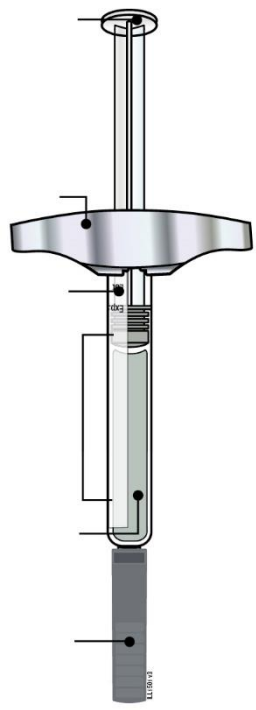
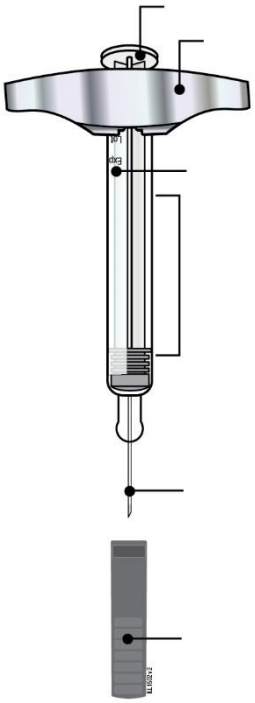
10. Renal Impairment
No dose adjustment is required in patients with renal impairment.
In clinical study, patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease patients receiving dialysis are at greater decrease of serum calcium levels compare to the subjects with normal renal function. Monitoring of serum calcium levels is highly recommended for the patients with severe renal impairment or patients receiving dialysis. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

11. Overdose
There is no experience with overdosage in clinical trials with this drug.

12. Effects on Ability to Drive and Use Machines
No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving this drug.

13. Precautions in Administration
1) Prior to subcutaneous administration, allow this drug to sit at room temperature for at least 30 minutes before injecting. Do not warm in any other way.
2) Visually inspect this drug for particles and discoloration prior to administration. This drug is a clear to opalescent, colorless to light yellow solution. Do not use if the solution is cloudy or discolored or contains particles.
3) Administer this drug 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.
4) The method of administration of this drug is as follow. Refer to the 'Instructions for Use' in insert paper for the comprehensive instructions for the administration of this drug.

Guide to parts

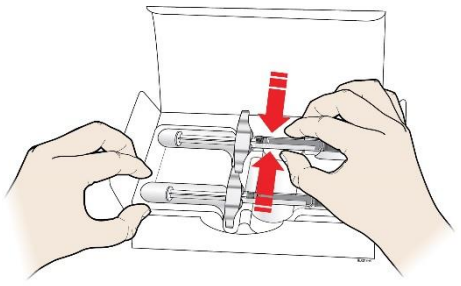
Before use	After use
	
Important: Needle is inside	

Important information
To deliver a full dose, use both syringes in this carton for one full dose.

① **Step 1: Prepare**

a. Remove two syringes from the carton. Grab the syringe barrel to remove the syringe from the tray.

Grab Here



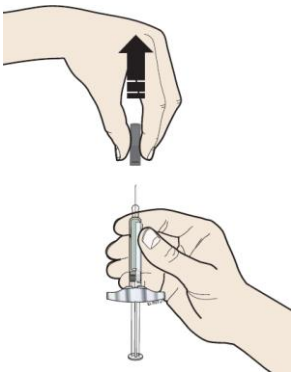
b. Make sure the medicine in the syringe is clear and colorless to light yellow.

c. Wash your hands thoroughly, and place the materials needed for injection on a clean, well-lit work surface.

d. Prepare two injection sites, one for each of the two injections, and clean the injection sites with alcohol wipes. Let the skin dry.

② **Step 2: Get Ready**

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



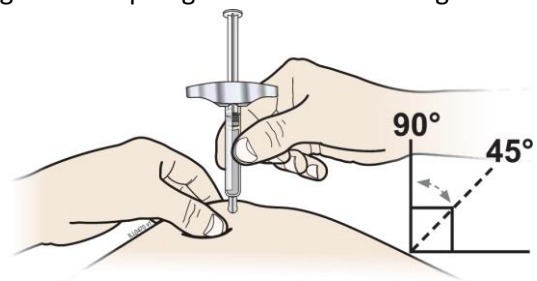
- It is normal to see a drop of liquid at the end of the needle.
- Do not twist or bend the gray needle cap.
- Do not put the gray needle cap back onto the syringe.
- Do not remove the gray needle cap from the syringe until you are ready to inject.

b. Pinch skin firmly to create an injection site surface.

③ **Step 3: Inject**

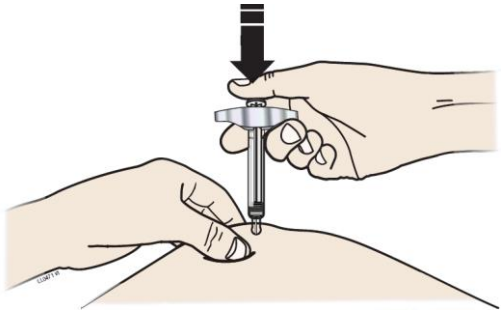
a. Hold the pinch, and insert the syringe into the skin at 45 to 90 degrees.

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



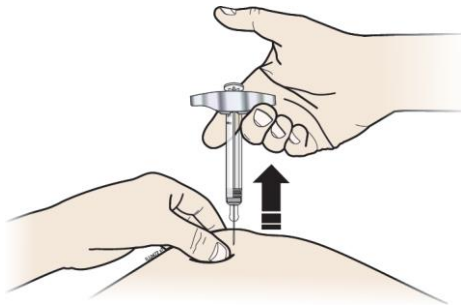
b. Using slow and constant pressure push the plunger rod all the way down until it stops moving.

- Important: Keep skin pinched while injecting.



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

- After you remove the syringe from the 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.



④ Finish

a. Discard the used syringe and the gray needle cap.
   - Do not reuse the syringe.

b. 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.

⑤ Repeat all steps with the second syringe to inject the full dose.

14. Precautions for Storage and Handling

1) Keep the syringe out of the reach of children.
2) Refrigerate (at 2 to 8°C) in the original carton to protect from light or physical damage.
3) If removed from the refrigerator, this drug should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days. Throw away this drug that has been stored at room temperature after 30 days.
4) Protect this drug from direct light and do not expose to temperatures above 25°C.
5) Do not freeze, and do not use the syringe if it has been frozen.
6) Do not store this drug in extreme heat or cold (ex. vehicle's glove box or trunk etc.).
7) Do not shake.
8) In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.
9) 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.

15. Information for Health Care Providers

1) Pharmacological Properties

Mechanism of Action

Romosozumab is a humanized monoclonal antibody (IgG2) that binds and inhibits sclerostin. Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption.

Pharmacodynamic Effects

This drug has a dual effect on bone, increasing bone formation and decreasing bone resorption. In postmenopausal women with osteoporosis, this drug increased the bone formation marker procollagen type 1 N-terminal propeptide (P1NP) early in treatment, with a peak increase of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to placebo levels at month 9 and a decline to approximately 15% below placebo at month 12. This drug decreased the bone resorption marker type 1 collagen C-telopeptide (CTX) with a maximal reduction of approximately 55% relative to placebo 2 weeks after initiating treatment. CTX levels remained below

placebo and were approximately 25% below placebo at month 12.
In men with osteoporosis, similar patterns in bone turnover marker changes were observed.
After discontinuation of this drug therapy in postmenopausal women with osteoporosis, P1NP levels returned to baseline within 12 months; CTX increased above baseline levels within 3 months and returned toward baseline levels by month 12, reflecting reversibility of effect. Upon retreatment with this drug after 12 months off treatment, the level of increase in P1NP and decrease in CTX by this drug was similar to that observed during the initial treatment.
In women transitioning from oral alendronate, this drug also increased bone formation and decreased bone resorption.

2) Pharmacokinetic information
Following 0.1~10 mg/kg SC administration, romosozumab exhibits nonlinear pharmacokinetics.
Administration of a single dose of 210mg romosozumab in healthy male and female subjects (N = 90, age range: 21 to 65 years) resulted in a mean (standard deviation [SD]) maximum serum concentration (Cmax) of 22.2 (5.8) μg/mL and a mean area under the concentration-time curve (AUC) of 389 (127) μg/day/mL. The median time to maximum romosozumab concentration (Tmax) was 5 days (range: 2 to 7 days).
Following a 210 mg subcutaneous dose, bioavailability was 81%. After Cmax, serum levels declined with a mean effective half-life of 12.8 days. Steady state was generally reached by month 3 with minimal accumulation (less than 2-fold) following monthly dosing.
The presence of anti-romosozumab binding antibodies decreased romosozumab exposure up to 22%, which was not considered clinically meaningful.
Based on a population pharmacokinetic analysis, age (20–89 years), gender, race, 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 (< 15% change) based on exposure-response analyses and was not considered clinically meaningful. Thus, no dose adjustment is necessary based on age, gender race, disease state, or body weight.
The pharmacokinetics of romosozumab were similar in patients transitioning from bisphosphonate therapy.
Drug Interactions
No drug-drug interaction studies have been conducted with romosozumab.
Special Populations
Pediatrics: The pharmacokinetics of romosozumab in pediatric patients have not been assessed.
Gender: The pharmacokinetics of romosozumab were similar in postmenopausal women and in men with osteoporosis.
Geriatrics: The pharmacokinetics of romosozumab were not affected by age from 20 to 89 years.
Renal Impairment: Following a single 210 mg dose of romosozumab in a clinical study of 16 patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring hemodialysis, mean Cmax 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.
A population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. However, based on both the renal impairment study and population PK analysis, this increase is not clinically meaningful and no dose adjustment is necessary

in these patients.

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

3) Clinical Data

Treatment of Osteoporosis in Postmenopausal Women

Study 20110142 (ARCH, alendronate-controlled) was a randomized, double-blind, alendronate-controlled, study of 4,093 postmenopausal women aged 55 to 90 years (mean age of 74.3 years), with a median follow-up of 33 months.

The enrolled women met one of the following.

- BMD T-score at the total hip or femoral neck of ≤ -2.50 and either:
  - at least 1 moderate or severe vertebral fracture or
  - at least 2 mild vertebral fractures;

or

- BMD T-score at the total hip or femoral neck of ≤ -2.00 and either:
  - at least 2 moderate or severe vertebral fractures or
  - a fracture of the proximal femur that occurred within 3 to 24 months prior to randomization.

The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.96, -2.80, and -2.90, respectively, 96.1% of women had a vertebral fracture at baseline, and 99.8% of women had a previous fracture. Women were randomized (1:1) to receive either monthly subcutaneous injections of this drug (N = 2,046) or oral weekly alendronate (N = 2,047) for 12 months, with daily supplementation of calcium and 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 analysis was performed when all women had completed the month 24 study visit and clinical fracture events were confirmed for at least 330 women which occurred after a median of 33 months on study. The primary efficacy endpoints were the incidence of new vertebral fracture through month 24 and the incidence of clinical fracture (defined as the composite of nonvertebral fracture and clinical vertebral fracture) at primary analysis. Secondary efficacy endpoints included the incidence of nonvertebral fractures, hip fractures, and major nonvertebral fractures at the primary analysis, and percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at month 12 and month 24.

Effect on New* Vertebral *and Clinical Fractures

This drug reduced the incidence of new vertebral fracture at 24 months and clinical fracture after a median of 33 months (see Table2).

Table 2. The Effect of this drug on the Incidence of New Vertebral and Clinical Fractures

	Incidence of Fracture (%)		Absolute Risk Reduction (%) (95% CI)[a]	Relative Risk Reduction (%) (95% CI)[b]	Adjusted p-value[c]
	alendronate/ alendronate	romosozumab/ alendronate			
Month 12					
New vertebral fracture	5.0 [85/1,703]	3.2 [55/1,696]	1.8 (0.51, 3.17)	36 (11, 54)	NA[d]
Clinical fracture	5.4 [110/2,047]	3.9 [79/2,046]	1.8 (0.5, 3.1)	28 (4, 46)	NA[d]
Month 24					

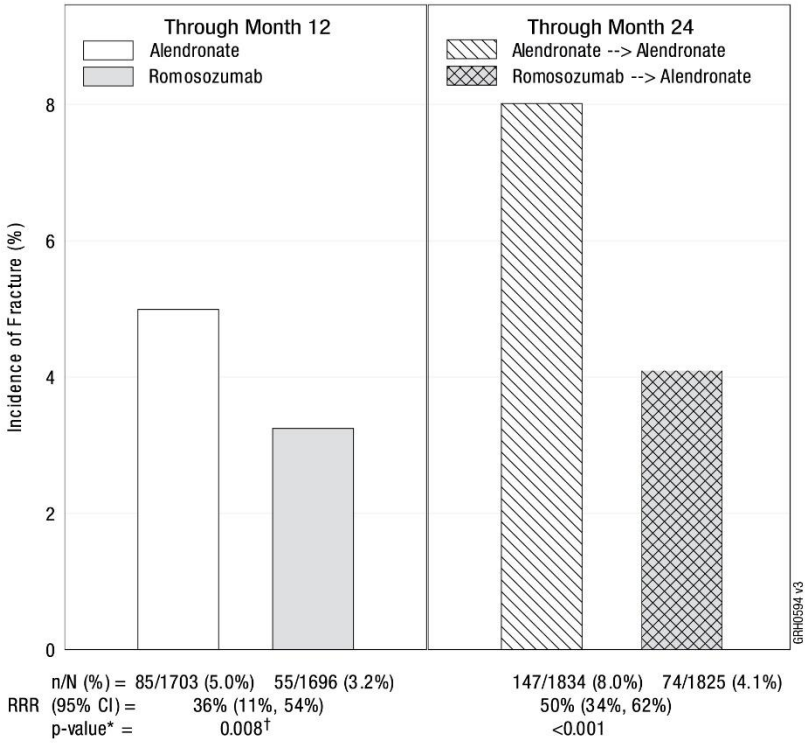
New vertebral fracture	8.0 [147/1,834]	4.1 [74/1,825]	4.0 (2.50, 5.57)	50 (34, 62)	< 0.001
Clinical fracture	9.6 [197/2,047]	7.1 [146/2,046]	2.7 (0.8, 4.5)	26 (9, 41)	NA[d]
At a median of 33 months					
Clinical fracture	13.0 [266/2,047]	9.7 [198/2,046]	NA	27 (12, 39)	< 0.001

Incidence of Fracture (%) = [Number of subjects who occurred fracture/Number of subjects of analysis]

a. Absolute risk reduction is 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. Relative risk reduction is 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 (new vertebral fracture) or Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline (clinical fracture).
c. Adjusted p-values are based on Hochberg procedure and are to be compared to a significance level of 0.05.
d. NA: Endpoint was not part of sequential testing strategy; therefore, p-value adjustment is not applicable.

This drug for 12 months followed by alendronate for 12 months demonstrated a persistent effect in reducing the incidence of new vertebral fractures (see Figure 1).

Figure 1. Effect of this drug on Incidence of New Vertebral Fractures through Month 12 and Month 24



N = Number of subjects in the primary analysis set for vertebral fractures
n = Number of subjects experiencing a fracture
Relative risk reduction (RRR) is based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
*p-values are based on separate logistic regression models adjusted for age strata, baseline total hip BMD T-score and presence of severe vertebral fracture at baseline.
† P-value does not meet multiplicity adjusted statistical significance.

Effect on Bone Mineral Density (BMD)

This drug significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with alendronate at month 12. At month 24, 12-month treatment with this drug followed by 12-month treatment with alendronate significantly increased BMD compared with alendronate alone for 24 months at the lumbar spine, total hip, and femoral neck. The BMD increase with this drug over alendronate observed at month 12 was maintained at month 24 (see Table 3).

Table 3. Mean Percent Change in BMD from Baseline through Month 12 and Month 24

	alendronate/alendronate Mean (95% CI) N = 2,047	romosozumab/alendronate Mean (95% CI) N = 2,046	Treatment Difference from alendronate/alendronate (95% CI)
At Month 12			
Lumbar spine	5.0 (4.73, 5.21)	13.7 (13.36, 13.99)	8.7 [a] (8.31, 9.09)
Total hip	2.8 (2.67, 3.02)	6.2 (5.94, 6.39)	3.3 [a] (3.03, 3.60)
Femoral neck	1.7 (1.46, 1.98)	4.9 (4.65, 5.23)	3.2 [a] (2.90, 3.54)
At Month 24			
Lumbar spine	7.2 (6.90, 7.53)	15.3 (14.89, 15.69)	8.1 [a] (7.58, 8.57)
Total hip	3.5 (3.23, 3.68)	7.2 (6.95, 7.48)	3.8 [a] (3.42, 4.10)
Femoral neck	2.3 (1.96, 2.57)	6.0 (5.69, 6.37)	3.8 [a] (3.40, 4.14)

N: Number of subjects randomized

a. P-value < 0.001 based on an ANCOVA model, adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction

Study 20070337 (FRAME, placebo-controlled) was a randomized, double-blind, placebo-controlled study of 7,180 postmenopausal women aged 55 to 90 years (mean age of 70.9 years). Women with BMD T-score at the total hip or femoral neck of -2.50 or less, -3.50 or more were enrolled. The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.72, -2.47, and -2.75, respectively, and 18.3% of women had a vertebral fracture at baseline.

Women were randomized to receive subcutaneous injections of either this drug (N= 3,589) or placebo (N = 3,591) once every month for 12 months with daily supplementation of calcium and vitamin D. After the 12-month treatment, women in both arms transitioned to open-label denosumab (denosumab 60mg subcutaneous every 6 months for 12 months) while remaining blinded to initial treatment.

The co-primary efficacy endpoints were the incidence of new vertebral fractures through month 12 and through month 24. Secondary efficacy endpoints included the incidence of clinical fractures (all symptomatic fractures including nonvertebral and painful vertebral fractures), nonvertebral fractures, new or worsening vertebral fractures, major nonvertebral fractures, hip fractures, and percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck, and were evaluated though 24 months.

Effect on New Vertebral and Clinical Fractures

This drug significantly reduced the incidence of new vertebral fractures through month 12 ($p < 0.001$), as shown in Table 4. The reduction in new vertebral fracture risk persisted through the second year in women who received this drug during the first year and transitioned to denosumab compared to those who transitioned from placebo to denosumab (month 24; $p < 0.001$).

Table 4. The Effect of this drug on the Incidence Rate of New Vertebral and Clinical Fractures through Month 12 and Month 24

	Incidence Rate of Fracture (%)		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)	Adjusted p-value[a]
	placebo/ denosumab	romosozumab/ denosumab			
Month 12					
New vertebral Fracture[b]	1.8 (59/3,322)	0.5 (16/3,321)	1.3 (0.79, 1.80)	73 (53, 84)	< 0.001
Clinical Fracture[c]	2.5 (90/3,591)	1.6 (58/3,589)	1.2 (0.4, 1.9)	36 (11, 54)	0.008
Month 24					
New vertebral Fracture[b]	2.5 (84/3,327)	0.6 (21/3,325)	1.9 (1.30, 2.49)	75 (60, 84)	< 0.001
Clinical Fracture[c]	4.1 (147/3,591)	2.8 (99/3,589)	1.4 (0.5, 2.4)	33 (13, 48)	0.096

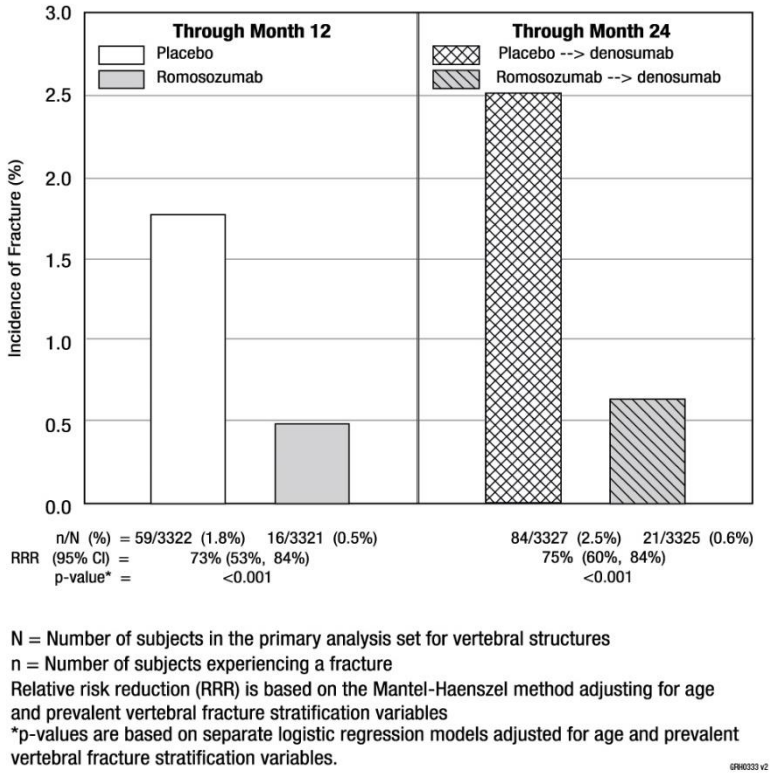
Incidence of Fracture (%) = Number of subjects who occurred fracture/Number of subjects of analysis

[a] Adjusted p-values are to be compared to a significance level of 0.05.

[b] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age and prevalent vertebral fracture stratification factors. Treatment comparisons are based on logistic regression model adjusted for stratification factors.

[c] Clinical fractures include all symptomatic fractures including nonvertebral and painful vertebral fractures. Treatment comparisons are based on Cox proportional hazards model adjusted for age and prevalent vertebral fracture stratification factors.

Figure 2. Effect of this drug on Incidence of New Vertebral Fractures through Month 12 and Month 24



N = Number of subjects in the primary analysis set for vertebral structures
n = Number of subjects experiencing a fracture
Relative risk reduction (RRR) is based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture stratification variables
*p-values are based on separate logistic regression models adjusted for age and prevalent vertebral fracture stratification variables.

GRH0333 v2

Effect on Bone Mineral Density (BMD)

This drug significantly increased BMD at the lumbar spine, total hip, and femoral neck compared to placebo at month 12. Following 12 months of treatment, this drug increased BMD at the lumbar spine from baseline in 99% of postmenopausal women. Ninety-two percent of women treated with this drug achieved at least a 5% increase from baseline in BMD at lumbar spine by month 12 and 68% gained 10% or more. These effects were sustained with transition to another osteoporosis treatment; women who received this drug for 12 months followed by denosumab for 12 months had greater increases in BMD at the lumbar spine, total hip, and femoral neck at month 24 compared to women who received placebo for 12 months followed by denosumab for 12 months (Table 5).

Table 5. Mean Percent Change in BMD from Baseline through Month 12 and Month 24

	placebo/denosumab Mean (95% CI) N = 3,591[a]	**romosozumab/denosumab Mean (95% CI) N = 3,589 [a]**	**Treatment Difference from Placebo/denosumab Mean (95% CI)**
At Month 12			
Lumbar spine	0.4 (0.2, 0.5)	13.1 (12.8, 13.3)	12.7[b] (12.4, 12.9)
Total hip	0.3 (0.1, 0.4)	6.0 (5.9, 6.2)	5.8[b] (5.6, 6.0)
Femoral neck	0.3 (0.1, 0.5)	5.5 (5.2, 5.7)	5.2[b] (4.9, 5.4)
At Month 24			
Lumbar spine	5.5 (5.3, 5.7)	16.6 (16.3, 16.8)	11.1[b] (10.8, 11.4)
Total hip	3.2 (3.1, 3.3)	8.5 (8.3, 8.7)	5.3[b] (5.1, 5.5)
Femoral neck	2.3 (2.1, 2.6)	7.3 (7.0, 7.5)	4.9[b] (4.7, 5.2)

[a] Number of women randomized

[b] Based on an ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction, p-value < 0.001 without adjustment for multiplicity

Study 20150242 was a randomized, double-blind, placebo-controlled study of 67 postmenopausal South Korean women aged 56 to 88 years (mean age of 67.5 years) with osteoporosis. Women with BMD T-score -2.50 or less, and more than -4.0 at the lumbar spine, total hip, or femoral neck were enrolled. The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.66, -2.17, and -2.49, respectively; mean BMD T-scores were balanced between treatment groups at baseline. Women were randomized 1:1 to receive subcutaneous injections of either this drug (N = 34) or placebo (N = 33) once every month with daily supplementation of calcium and vitamin D during 6 months.

Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline at month 6. Secondary efficacy variables included percent change in total hip and femoral neck BMD from baseline to month 6.

The treatment differences in BMD at 6 months were 9.6% at the lumbar spine, 2.6% at the total hip, and 2.2% at femoral neck (Table 6).

Table 6. The Effect of this drug on BMD at Lumbar Spine, Total Hip, and Femoral Neck At Month 6

At Month 6	Mean Percent Change in BMD from Baseline		Difference from Placebo Mean (95% CI)
	Placebo Mean (95% CI) N = 33 [a]	Romosozumab Mean (95% CI) N = 34 [a]	
Lumbar spine	-0.1 (-1.6, 1.5)	9.5 (7.8, 11.2)	9.6 [b] (7.6, 11.5)
Total hip	0.3 (-0.5, 1.2)	2.9 (2.0, 3.8)	2.6 [b] (1.4, 3.7)
Femoral neck	0.8 (-0.7, 2.2)	3.0 (1.7, 4.2)	2.2 [c] (0.7, 3.6)

[a] Number of subjects randomized

[b] p-value < 0.001 based on an ANCOVA

[c] p = 0.004 based on an ANCOVA

Treatment of Osteoporosis in Men

Study 20110174 (BRIDGE) was a randomized, double-blind, placebo-controlled study of 245 men aged 55 to 89 years (mean age of 72.1 years) with osteoporosis. Men with a BMD T-score at the lumbar spine, total hip of femoral neck of -2.50 or less, or BMD T- score at the lumbar spine, total hip of femoral neck of -1.50 or less and a history of fragility fracture were enrolled. Men were excluded if they had a BMD T-score of -3.50 or less at the total hip or femoral neck. The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.26, -1.92, and -2.33, respectively. Men were randomized 2:1 to receive subcutaneous injections of either this drug (N = 163) or placebo (N = 82) once every month with daily supplementation of calcium and vitamin D.

Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline at month 12. Secondary efficacy variables included percent change in total hip and femoral neck BMD from baseline to month 12 and percent change in lumbar spine, total hip, and femoral neck BMD from baseline to month 6.

Treatment with this drug significantly increased BMD at month 12. The treatment differences in BMD at 6 months were 8.7% at the lumbar spine, 1.4% at the total hip, and 1.3% at femoral neck. At 12 months, the treatment differences were 10.9% at the lumbar spine, 3% at the total hip, and 2.4% at the femoral neck (Table 7).

Table 7. The Effect of this drug on BMD at Lumbar Spine, Total Hip, and Femoral Neck At Month 6 and Month12

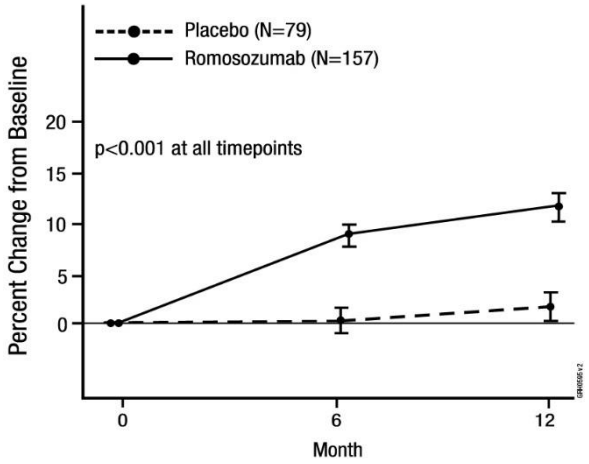
	Mean Percent Change in BMD From Baseline		Treatment Difference from placebo Mean (95% CI)
	placebo Mean (95% CI) N = 82[a]	romosozumab Mean (95% CI) N = 163 [a]	
At Month 6			
Lumbar spine	0.3 (-0.6, 1.2)	9 (8.2, 9.7)	8.7[b] (7.6, 9.7)
Total hip	0.2 (-0.2, 0.7)	1.6 (1.2, 2.0)	1.4[b] (0.8, 2.0)
Femoral neck	0.0 (-0.7, 0.7)	1.2 (0.6, 1.8)	1.3[c] (0.4, 2.1)
At Month 12			
Lumbar spine	1.2 (0.2, 2.2)	12.1 (11.2, 13.0)	10.9[b] (9.6, 12.2)
Total hip	-0.5 (-1.1, 0.1)	2.5 (2.1, 2.9)	3.0[b] (2.3, 3.7)
Femoral neck	-0.2 (-1.0, 0.6)	2.2 (1.5, 2.9)	2.4[b] (1.5, 3.3)

[a] Number of men randomized

[b] p-value < 0.001 based on an ANCOVA model

[c] p-value 0.0033 based on an ANCOVA model

Figure 3. Percent Change in Lumbar Spine BMD From Baseline Over 1 year



- N = Number of subjects in the primary efficacy analysis set for the lumbar spine, total hip or femoral neck BMD
- Point estimates and 95% confidence intervals are based on ANCOVA model adjusting for treatment, baseline DXA BMD value, machine type, machine type-by-baseline DXA BMD value, baseline testosterone level, geographic region (stratification factor), and using a variance structure allowing for heterogeneity between treatment groups.
- Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the study period.

4) Toxicology Data

① 104 weeks carcinogenicity study was conducted with doses of 3, 10 and 50 mg/kg/week administered by subcutaneous injection to Sprague-Dawley male and female rats 50 mg/kg/week dose resulted in systemic exposures that were up to 19 times higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with macroscopic bone thickening at all doses. There were no effects of romosozumab on mortality or tumor incidence in male or female rats.

② Mutagenesis study has not been conducted, as monoclonal antibodies are not expected to alter DNA or chromosomes.

③ In repeat-dose toxicity, no adverse effects were noted in SD rats and cynomolgus monkeys after 26 once-weekly subcutaneous injections at doses 3, 10 and 100 mg/kg. 100 mg/kg/week dose resulted in systemic exposures 37 and 90 times higher, respectively, than the systemic exposure observed in humans (based on AUC comparison).

[STORAGE CONDITION]

hermetic container, Store in refrigerator (2 ~ 8°C), Protect from direct light

[PACKAGING UNIT]

2 pre-filled syringe/Box (1.17 mL/pre-filled syringe)

[EXPIRY DATE]

Refer to the outer package (YY/MM/DD)

[MARKETING AUTHORIZATION HOLDER]

Amgen Inc., One Amgen Center Drive, 38-5-A, Thousand Oaks, CA 91320, USA

[MANUFACTURER]
Drug substance: Immunex Rhode Island Corporation,
40 Technology Way, West Greenwich, Rhode Island, 02817, USA
Drug product: Patheon Italia S.p.A.,
Viale G.B. Stucchi 110-20900 MONZA (MB) Italy
Packaging and labeling: Amgen Manufacturing Ltd.,
State Road 31, Km 24.6, Juncos, Puerto Rico 00777-4060, USA

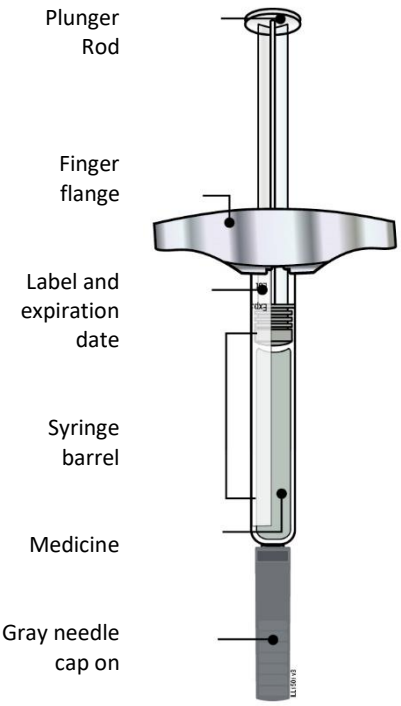
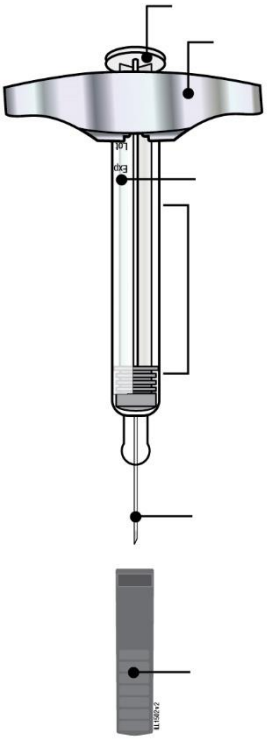
[IMPORTER]
Amgen Korea Limited,
20 floor, 19, Eulji-ro 5-gil, Jung-gu, Seoul, Korea

- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule.
- Relief of injury from adverse drug reaction: Korea Institute of Drug Safety & Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS medicines integrated information system (http://nedrug.mfds.go.kr) or the importer website (www.amgen.co.kr).
- Importer contact phone: 00798 611 3554(toll free)/ 02-3434-4899 / medinfo.JAPAC@amgen.com

Revision date: 2020. 02. 28
Version number: KREVEPI02

Instructions for use

Evenity® Inj. pre-filled syringe (Romosozumab)

Guide to parts	
Before use	**After use**
	
Important: Needle is inside	

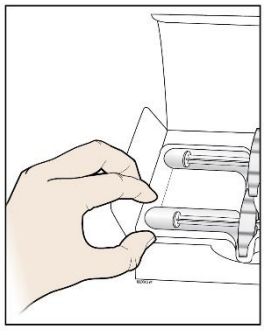
Important
Before you use this drug prefilled syringe, read this important information: **Use both syringes in this carton for one full dose.** **Storing the Evenity prefilled syringe** • Keep the syringe out of the reach of children. • Keep the syringe in the original carton to protect from light or 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 at 20° C to 25° C for up to 30 days. Throw away this drug that has been stored at room temperature after 30 days. • 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 this drug prefilled syringe** • Administration should be performed by an individual who has been trained to administer this drug. • Do not use a syringe after the expiration date on the label. • Do not shake the syringe. • Do not remove the gray 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.

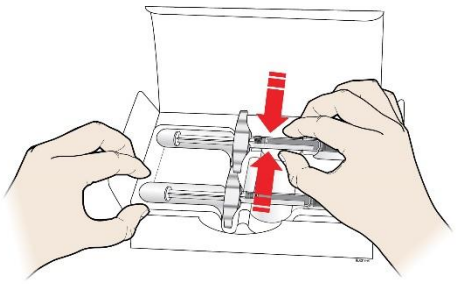
A	Remove two syringes from the carton



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 gray needle cap.
- Do not remove the gray needle cap until you are ready to inject.
- Do not remove the finger flange. This is part of the syringe.

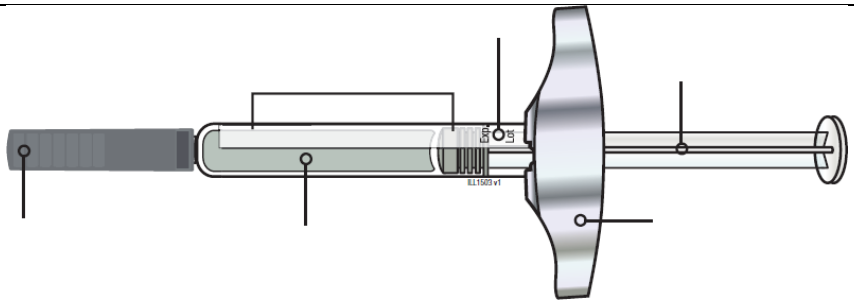
Leave the syringes at room temperature for at least 30 minutes before injecting.

- 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

Syringe barrel | Label and expiration date | Plunger rod



Gray needle cap on | Medicine | Finger flange

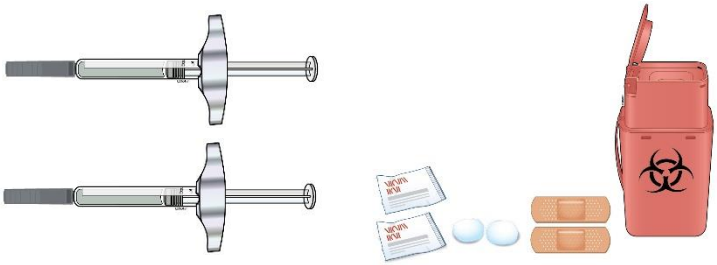
Always hold the syringe by the syringe barrel.
Make sure the medicine in the syringe is clear and colorless to light yellow.

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

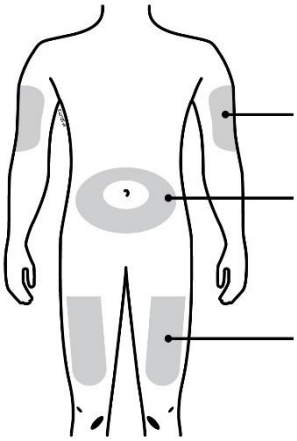
C	Gather all materials needed for the injection.

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.



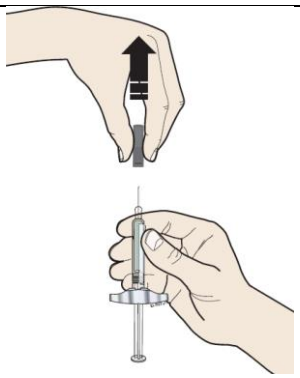
You can use:

- The thigh
- Stomach area (abdomen), except for a two-inch 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 a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard.
- Avoid injecting 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 gray needle cap straight off and away from the body when you are ready to inject.

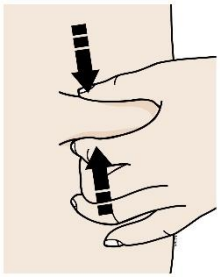


It is normal to see a drop of liquid at the end of the needle.

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

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

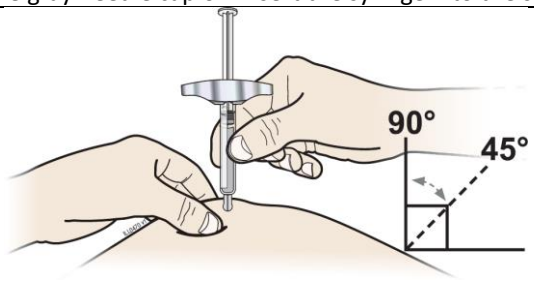
F	Pinch the injection site to create a firm surface.



Pinch skin firmly between your thumb and fingers, creating an area about two inches wide.
Important: Keep skin pinched while injecting.

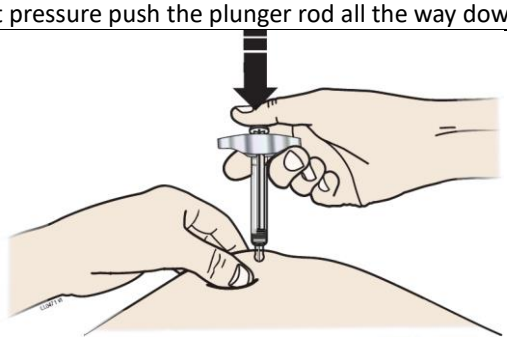
Step 3: Inject

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

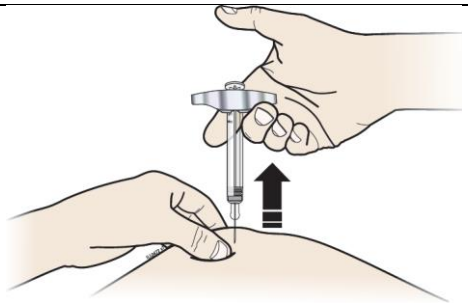


Do not place your finger on the plunger rod while inserting the needle.

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 the 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 gray needle cap.

Talk with your healthcare provider about proper disposal. There may be local guidelines for disposal.

- 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.**