EVENITY®

(romosozumab 105 mg)

Prescriber Guide

Important information on minimising risk to ensure safe and effective use.

This Prescriber guide format and content were approved by the Ministry of Health in September 2020

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1. ABOUT THIS GUIDE

- EVENITY® (romosozumab) is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture; defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- This guide contains important safety information for healthcare professionals to aid with minimizing key risks when prescribing romosozumab.
- The patient or, if appropriate, their caregiver should be educated about treatment risks and provided with a Patient Alert Card.
- Refer to the Israel Prescribing Information (PI) for more details.

2. ABOUT ROMOSOZUMAB

Romosozumab inhibits the action of sclerostin, a regulatory factor in bone metabolism. Romosozumab increases bone formation and, to a lesser extent, decreases bone resorption.

Limitations of Use

The anabolic effect of EVENITY wanes after 12 monthly doses of therapy. Therefore, the duration of EVENITY use should be limited to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered.

The first dose of EVENITY should be administered by a healthcare provider only. Starting from the second dose, the injection can be performed by an individual who has been properly trained by a healthcare provider only.

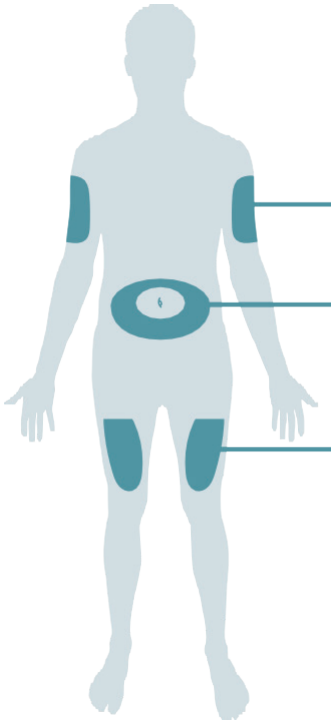
To administer the 210 mg dose, 2 subcutaneous injections of romosozumab should be given into the abdomen, thigh, or upper arm. The second injection should be given immediately after the first one but at a different injection site.

Further, detailed information on the correct procedure to inject a full dose of romosozumab is provided in the “How should you use the medicine” and “Instructions for Use” sections of the Israel package leaflet.

Each dose comprises two injections at different sites

Two pre-filled syringes
= 1 dose

Inject at different sites



3. KEY RISKS

This guide covers the risks of hypocalcaemia and myocardial infarction (MI) and stroke, and the potential risk of osteonecrosis of the jaw (ONJ), associated with romosozumab use. For detailed information about these and other risks, please refer to the romosozumab Israel Prescribing Information.

- **Romosozumab is contraindicated in patients with hypocalcaemia. Patients should have their serum calcium levels measured before initiating romosozumab therapy and should be monitored for signs and symptoms of hypocalcaemia throughout treatment.**
- **Patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients.**
- **Romosozumab is contraindicated in patients with history of MI or stroke within the preceding year.**
- **In patients without history of MI or stroke, the individual benefit-risk balance of using romosozumab treatment should be carefully evaluated prior to prescribing.**
- **Risk factors for the development of osteonecrosis of the jaw should be considered and preventative measures encouraged prior to prescribing romosozumab.**

PATIENTS SHOULD BE EDUCATED ABOUT EACH OF THESE RISKS. THE NEXT SECTION PROVIDES FURTHER INFORMATION.

4. MANAGING KEY RISKS

4.1 HYPOCALCAEMIA

Hypocalcaemia has occurred in patients receiving romosozumab in clinical trials.

Management

Hypocalcaemia is a contraindication. Correct hypocalcaemia prior to initiating therapy with romosozumab.

Patients should be adequately supplemented with calcium and vitamin D during treatment with romosozumab.

Monitor patients for signs and symptoms of hypocalcaemia throughout treatment. The predominant features of hypocalcaemia are effects on the nerves and muscles and may include:

- Muscle cramps and/or spasms.
- Paraesthesia of the extremities or periorally.
- Facial twitches.
- Seizures.
- Neuropsychiatric effects, ranging from confusion and disorientation to overt psychosis.

If any patient presents with suspected signs and/or symptoms of hypocalcaemia during treatment, serum calcium levels should be measured.

PATIENTS WITH SEVERE RENAL IMPAIRMENT OR UNDERGOING DIALYSIS

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. Monitor serum calcium and adequately supplement patients who have severe renal impairment or are receiving dialysis with calcium and vitamin D. Instruct patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

4.2 MYOCARDIAL INFARCTION AND STROKE

In a randomized controlled trial in postmenopausal women, there was a higher rate of major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal MI and nonfatal stroke, in patients treated with EVENITY compared to those treated with alendronate. The imbalance was observed only in 1 of the 2 large pivotal studies, as the incidence of positively adjudicated CV SAEs was balanced between the romosozumab and placebo arms in the placebo-controlled Study 20070337.

Management

Patients with history of MI or stroke within the preceding year: Romosozumab is contraindicated and should not be initiated.

Patients without history of MI or stroke: When determining whether to use romosozumab for an individual patient, consideration should be given to her cardiovascular risk based on risk factors (eg, established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the benefit outweighs the risk.

Monitor for signs and symptoms of MI and stroke and instruct patients to seek prompt medical attention if symptoms occur. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued.

Background

In two large, controlled fracture trials of romosozumab for the treatment of osteoporosis in postmenopausal women, serious cardiovascular adverse events were prospectively adjudicated.

In an active-controlled trial, Study 20110142 (N = 4093), during the 12-month double-blind treatment phase:

- 16 women (0.8%) had myocardial infarction in the romosozumab arm versus 5 women (0.2%) in the alendronate arm.
- 13 women (0.6%) had stroke in the romosozumab arm versus 7 women (0.3%) in the alendronate arm.

In a placebo-controlled trial, Study 20070337 (N = 7180), during the 12-month double-blind treatment phase.

- 9 women (0.3%) had myocardial infarction in the romosozumab arm versus 8 women (0.2%) in the placebo arm.
- 8 women (0.2%) had stroke in the romosozumab arm versus 10 women (0.3%) in the placebo arm.

4.3 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 been reported in patients receiving EVENITY. A routine oral examination should be performed by the prescriber prior to initiation of EVENITY treatment.

Osteonecrosis of the jaw has been reported rarely (may affect up to 1 in 1000 people) in patients receiving romosozumab.

Management

All patients should be encouraged to:

- Immediately report any oral symptoms, such as dental mobility pain or swelling or non-healing of sores or discharge during treatment with romosozumab.
- Maintain good oral hygiene.
- Receive routine dental check-ups.

If appropriate, consider arranging a dental examination before a patient starts romosozumab treatment.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on benefit-risk assessment. Patients who are suspected of having or who develop ONJ while on EVENITY should receive care by a dentist or an oral surgeon. In these patients, dental surgery to treat ONJ may exacerbate the condition. Discontinuation of EVENITY should be considered based on benefit-risk assessment.

Risk factors

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, eg, tooth extractions.
- Potency of the medicinal product that inhibits bone resorption (the risk increases with the anti-resorptive potency of the compound), and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (eg, anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, bisphosphonates, denosumab, chemotherapy, angiogenesis inhibitors, radiotherapy to the head and neck.

5. GENERAL REMINDER LIST

Before prescribing romosozumab, you should ensure:

Serum calcium levels are measured prior to treatment initiation, and hypocalcaemia is corrected before administering romosozumab.

Serum calcium levels are monitored for patients with severe renal impairment or receiving dialysis, who are at increased risk of developing hypocalcaemia.

Risk factors for developing osteonecrosis of the jaw are considered, including:

- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, eg, tooth extractions.
- Potency of the medicinal product that inhibits bone resorption, and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (eg, anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to the head and neck.

The benefit of using romosozumab outweighs the risk.

Patients have been provided with the Patient Alert Card and read the Israeli package leaflet.

Patients and/or their caregivers are trained on subcutaneous injection technique, and have received the detailed Instructions for Use as available in the package leaflet, before they will administer romosozumab.

A specific checklist for risk of myocardial infarction and stroke is included in the next section.

6. CHECKLIST FOR RISK OF MYOCARDIAL INFARCTION AND STROKE

Before prescribing romosozumab, you should:

Verify that patients do not have a history of myocardial infarction or stroke within the preceding year, which is a contraindication.

Perform a careful assessment of the cardiovascular risk profile.

- Consider risk factors such as established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, and age.

Ensure that the benefit of using romosozumab outweighs the risk.

7. PATIENT ALERT CARD

Patients or, if appropriate, their caregiver should be educated to reinforce understanding of these risks and the importance of contacting a healthcare professional if they experience suggestive signs and/or symptoms.

A Patient Alert Card should be provided to each patient prescribed romosozumab. This card aids patients in remembering/recognizing signs and symptoms of key risks that are associated with romosozumab treatment. It also provides guidance to patients on what they should do should they experience signs and/or symptoms.

Patients should be advised to carry the Patient Alert Card with them at all times and to show it to any healthcare professional who may be treating them.

To obtain additional copies of the Patient Alert Card, please contact the local Distributor Medison at medison@medison.co.il

8. REPORTING ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/ or report to local Distributor Medison: pv@Medison.co.il or 03-925-0365.

Please provide as much information as possible when reporting suspected adverse reactions, including comorbidities, past medical history, concomitant medication, and relevant timings and dates.

If you require any further information about the use of romosozumab, please contact local distributor in Israel Medison at medison@medison.co.il or via telephone 03-9250250.

Until the approved Israeli Evenity packs* are available on the market, please ensure a copy of the Israeli Patient Information Leaflet, attached here, is provided to the patient with each prescription. For the Israeli Prescribing Information please visit the MOH website https://data.health.gov.il/drugs/alonim/Rishum_16_318358820.pdf

*Foreign packs are allowed to be distributed under the provisions of §29C and contain the foreign prescribing and patient information.