

Corporate Medical Policy

Romozosumab-aqqg (Evenity™)

File Name:	romozosumab_eventy
Origination:	7/2019
Last CAP Review:	9/2020
Next CAP Review:	6/2021
Last Review:	9/2020

Description of Procedure or Service

Romozosumab-aqqg (Evenity) is a sclerostin inhibitor 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; or patients who have failed or are intolerant to other available osteoporosis therapy.

Osteoporosis is a bone disorder marked by low bone mass, microarchitectural disruption of the bones, and skeletal fragility, which leads to decreased bone strength and increased fracture risk. The World Health Organization (WHO) diagnostic classification defines osteoporosis by a bone mineral density (BMD) at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young-adult reference population (T-score). The most common sites of fragility fractures in osteoporosis are the spine (vertebral compression fractures), hip, and wrist. Osteoporotic fractures and their associated complications contribute to increased mortality and a substantial health burden. Postmenopausal women are commonly diagnosed with osteoporosis due to bone loss caused by estrogen deficiency and/or age.

Pharmacotherapy is recommended in postmenopausal women with a history of fragility fracture(s) or with osteoporosis based on measurement of BMD (T-score ≤ -2.5). The choice of treatment agent is often individualized based on efficacy, cost, safety, convenience, and other patient-specific circumstances, as quality clinical trials providing direct drug comparisons are lacking. First-line therapy is typically reserved for oral bisphosphonates if tolerated; however, other anti-resorptive agents include denosumab, selective estrogen receptor modulators (SERMs), and estrogen/progestin therapy. Anabolic agents (i.e. teriparatide, abaloparatide, romozosumab) stimulate bone formation and remodeling, and may be used as short-term therapy (1-2 years) in postmenopausal women with severe osteoporosis at high risk for fracture, with osteoporosis and an intolerance/contraindication to bisphosphonates, or whom have failed other osteoporosis therapies (fracture and/or loss of BMD despite therapy compliance). Anti-resorptive therapy is often restarted following anabolic treatment, in order to preserve or increase BMD gains achieved with the anabolic agent.

Romozosumab-aqqg (Evenity) is a humanized monoclonal antibody (IgG2) that was approved by the U.S. Food and Drug Administration (FDA) in April 2019 for the treatment of postmenopausal osteoporosis. It works by increasing bone formation and, to a lesser extent, decreases bone resorption by binding to and inhibiting sclerostin.

Related Medical Policies:

Denosumab (Prolia™, XGEVA™)

Romozosumab-aqqg (Evenity™)

Related Pharmacy Policies:

Forteo® - Tymlos®

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for romozosumab-aqqg (Evenity™) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Romozosumab (Evenity) is covered

Romozosumab-aqqg (Evenity) is considered medically necessary for the treatment of osteoporosis in postmenopausal women when **ALL** of the following criteria are met:

1. The patient has a confirmed diagnosis of osteoporosis and is at high risk for fracture as defined by one of the following:
 - a. A history of previous osteoporosis related fracture, or
 - b. A pre-treatment bone mineral density (BMD) T-score of ≤ -3 at the total hip or femoral neck, or
 - c. A pre-treatment bone mineral density (BMD) T-score of ≤ -2.5 at the total hip or femoral neck, and one of the following:
 - i. The patient has tried and failed or has an intolerance or contraindication to bisphosphonates, or
 - ii. The patient has tried and failed* other injectable osteoporosis therapies (i.e. denosumab, abaloparatide, teriparatide); AND
2. Romozosumab will not be used in combination with other pharmacological agents used to treat osteoporosis; AND
3. The patient does not have hypocalcemia or hypocalcemia has been corrected prior to initiating romozosumab; AND
4. The patient has not had a myocardial infarction or stroke within the preceding year; AND
5. The total duration of romozosumab therapy will not exceed 12 months.

*Treatment failure is defined as having a fracture with loss of BMD despite compliance with osteoporosis therapy

Authorization: Total duration 12 months

When Romozosumab (Evenity) is not covered

Romosozumab-aqgg (Evenity™)

Romosozumab-aqgg (Evenity) is considered **investigational** and therefore not covered when the above criteria are not met, and for all other indications not listed above.

The continued use of romosozumab-aqgg (Evenity) beyond 12 monthly doses is considered **investigational**.

Policy Guidelines

The recommended dosage for Evenity is a total of 210 mg administered subcutaneously (as two separate syringes) once every month for 12 months in the abdomen, thigh, or upper arm. Administration should be completed by a healthcare provider. The patient should also receive adequate supplementation with calcium and vitamin D during Evenity treatment.

The anabolic effect of Evenity wanes after 12 monthly doses of treatment. Therefore, the duration of Evenity use should be limited to 12 monthly doses. If osteoporosis treatment is still warranted, continued therapy with an anti-resorptive agent (i.e. bisphosphonates, estrogens, SERMs, calcitonin, denosumab) should be considered.

Use of Evenity is contraindicated in patients with hypocalcemia. Patients with pre-existing hypocalcemia must be corrected before starting treatment with Evenity.

The FDA has issued black box warnings for potential increased risk of myocardial infarction (MI), stroke, and cardiovascular death in patients receiving Evenity. Treatment with Evenity should not be initiated in patients who have had a MI or stroke within the preceding year, and consideration of benefit versus risk should be taken in patients with other cardiovascular risk factors. Evenity should be discontinued if the patient experiences a MI or stroke while receiving treatment. Other warnings and/or precautions include risk of developing osteonecrosis of the jaw, as well as atypical low-energy or low trauma femoral fractures.

Clinical Trial Evidence

The efficacy and safety of romosozumab (Evenity) for the treatment of osteoporosis in postmenopausal women was evaluated in two pivotal phase 3 clinical trials (Study 1 and Study 2).

The FRAME study (Study 1; NCT01575834) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial assessing postmenopausal women aged 55 to 90 years (mean age of 70.9 years) with a BMD T-score of ≤ -2.5 at the total hip or femoral neck. Women were excluded from the trial who had a history of hip fracture, any severe or more than 2 moderate vertebral fractures, recent use of agents affecting bone metabolism, a history of metabolic bone disease, osteonecrosis of the jaw, current hypercalcemia or hypocalcemia, or vitamin D insufficiency. At baseline, a total of 1317 patients (18.3%) had a prevalent vertebral fracture. Women in the trial were randomized (1:1) to receive subcutaneous injections of either romosozumab at a dose of 210 mg (n=3589) or placebo (n=3591) once monthly for 12 months, followed by open-label anti-resorptive therapy (denosumab) at a dose of 60 mg administered subcutaneously every 6 months for an additional 12 months. All patients received daily calcium and vitamin D supplementation. The coprimary efficacy endpoints were the cumulative incidences of new vertebral fractures at 12 months and 24 months. At 12 months, new vertebral fractures had occurred in 16/3321 patients (0.5%) in the romosozumab group versus 59/3322 (1.8%) in the placebo group (representing a 73% lower risk with romosozumab; $p < 0.001$). At 24 months, the rates of vertebral fractures were significantly lower in the romosozumab group compared to the placebo group following transition to denosumab (0.6% in the romosozumab group vs. 2.5% in the placebo group, a 75% lower risk with romosozumab; $p < 0.001$). The study authors concluded that romosozumab significantly lowered the incidence of new vertebral

Romosozumab-aqqg (Evenity™)

fractures compared to placebo in postmenopausal women with osteoporosis at 12 months, and also following the transition to denosumab at 24 months.

The ARCH study (Study 2; NCT01631214) was a randomized, double-blind, alendronate-controlled clinical trial evaluating postmenopausal women aged 55 to 90 years (mean age of 74 years) with a BMD T-score of ≤ -2.5 at the total hip or femoral neck and either one moderate or severe vertebral fracture or two mild vertebral fractures, or a BMD T-score ≤ -2.0 at the total hip or femoral neck and either two moderate or severe vertebral fractures or a history of a proximal femur fracture. Women were excluded from the trial as previously described in Study 1 and for intolerance or contraindication to oral alendronate. Women were randomized (1:1) to receive either monthly subcutaneous romosozumab at a dose of 210 mg (n=2046) or weekly oral alendronate at a dose of 70 mg (n=2047) for 12 months. All patients received daily calcium and vitamin D supplementation. After the 12-month double-blind treatment period, both groups transitioned to open-label weekly oral alendronate 70 mg until the end of the trial, while remaining blinded to the initial treatment assignment. The coprimary efficacy endpoints were the cumulative incidence of new vertebral fracture at 24 months and time to the first clinical fracture (non-vertebral and symptomatic vertebral fracture) through the primary analysis period, which ended when ≥ 330 patients had a clinical fracture and all patients had completed the 24-month visit. Over a 24-month period, a 48% lower risk of new vertebral fractures was observed in the romosozumab-to-alendronate group (6.2% [127/2046 patients]) than in the alendronate-to-alendronate group (11.9% [243/2047 patients]) ($p < 0.001$). Clinical fractures occurred in 198/2046 patients (9.7%) in the romosozumab-to-alendronate group versus 266/2047 patients (13.0%) in the alendronate-to-alendronate group, representing a 27% lower risk with romosozumab ($p < 0.001$). During the first 12 months, serious cardiovascular adverse events were observed more frequently in the romosozumab group than with alendronate (2.5% vs. 1.9%). The study authors concluded that, in postmenopausal women with osteoporosis at high risk for fracture, 12 months of romosozumab treatment followed by alendronate significantly lowered fracture risk compared to alendronate alone.

The efficacy and safety of romosozumab-aqqg was evaluated for the treatment of osteoporosis in men in a randomized, double-blind, placebo-controlled phase 3 trial of 245 men with osteoporosis or osteopenia and a history of fragility fracture (BRIDGE study; NCT02186171). Results showed that romosozumab increased BMD at the lumbar spine and total hip compared to placebo over 12 months; however, the incidence of serious cardiovascular adverse events in study participants receiving romosozumab was greater than the placebo group (4.9 versus 2.5 percent). Romosozumab has not been approved by the FDA for the treatment of osteoporosis in men.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbssc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J3111

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Romosozumab-aqqg (Evenity™)

Scientific Background and Reference Sources

Amgen Inc. Evenity (romosozumab-aqqg) injection for subcutaneous use. Highlights of prescribing information. April 2019. Available at: https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi.ashx. Last accessed June 2019.

U.S Food and Drug Administration. FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-osteoporosis-postmenopausal-women-high-risk-fracture>. Last accessed June 2019.

Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-43.

Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417-27.

Cosman F, de Beur SJ, LeBoff MS, et al. National Osteoporosis Foundation (NOF). Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359-81.

Barrionuevo P, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab*. 2019;104(5):1623-30.

Medical Director review 6/2019

Specialty Matched Consultant Advisory Panel 9/2019

Specialty Matched Consultant Advisory Panel 9/2020

Medical Director review 10/2020

Policy Implementation/Update Information

- | | |
|----------|--|
| 7/1/19 | New policy developed. Evenity is considered medically necessary for the treatment of osteoporosis in postmenopausal women. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 6/2019. (krc) |
| 10/1/19 | Specialty Matched Consultant Advisory Panel review 9/18/2019. No change to policy intent. Added HCPCS code J3111 to Billing/Coding section and deleted codes C9399, J3490, and J3590 effective 10/1/19. (krc) |
| 10/13/20 | Updated "When Covered" section to include the following criteria: "A pre-treatment bone mineral density (BMD) T-score of ≤ -3 at the total hip or femoral neck," and requirement of trial and failure or contraindication to bisphosphonates or other injectable osteoporosis therapies for T-score of ≤ -2.5 with no history of osteoporosis related fracture. Edit made to statement in "When Not Covered" section to clarify intent. Updated clinical evidence summary in Policy Guidelines. Specialty Matched Consultant Advisory Panel review 9/16/2020. Medical Director review 10/2020. (krc) |

Romozosumab-aqqg (Evenity™)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.