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Romosozumab-aqqg

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions, or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Romosozumab-aqqg (Evenity™) **may be considered medically necessary**, up to 12 monthly doses, for the following indication:

- Treatment of postmenopausal women with osteoporosis when the individual meets the following criteria:
  - A history of osteoporotic fracture; **OR**
  - A pre-treatment bone mineral density (BMD) T-score of ≤ -2.5; AND meets any of the following criteria:
    - Multiple risk factors for fracture; or
    - Failure or intolerance to other available osteoporosis therapy.

Romosozumab-aqqg (Evenity™) **is considered experimental, investigational and/or unproven** for non- Food and Drug Administration approved indications, including but not limited to:

- When total duration of therapy exceeds 12 monthly doses;
- When used in women who have had a prior myocardial infarction (MI) or stroke within the preceding year (12 months).

Policy Guidelines

Romosozumab-aqqg (Evenity™) should be administered subcutaneously by a healthcare provider.

Description

Osteoporosis
Osteoporosis is a bone disease that develops when bone mineral density (BMD) and bone mass decreases, or when the quality or structure of bone changes. This can lead to a decrease in bone strength that can increase the risk of fractures.

Osteoporosis can affect women and men of all races and ethnic groups; it can occur at any age, although the risk for development increases as one ages. For many women, the disease can begin to develop a year or two before menopause. It is most common in non-Hispanic White women and Asian women. African American and Hispanic women have a lower, but still significant risk, of developing osteoporosis. For men, it is more common in non-Hispanic Whites. (2)

Postmenopausal Osteoporosis

Most postmenopausal women with osteoporosis have bone loss related to estrogen deficiency and/or age. A diagnosis can be made in the presence of a fragility fracture (occurring spontaneously or from minor trauma), particularly in the spine, hip, wrist, humerus, rib, and pelvis; or with a T-score of ≤-2.5 standard deviations (SDs) at any site based upon bone mineral density measurements by dual-energy x-ray absorptiometry (DXA). The National Bone Health Alliance suggests a clinical diagnosis may be made if there is a clear elevated risk for fracture, such as when the fracture risk assessment tool (FRAX) 10-year probability of major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) is ≥20 percent or the 10-year probability of hip fracture is ≥3 percent. (3)

T-score

The World Health Organization (WHO) established a classification of BMD by DXA according to the standard deviation difference between a patient's BMD and that of a young adult reference population (T-score); see Table 1.

Table 1. Diagnostic categories for osteoporosis and low bone mass based on BMD measurement by DXA

Category	Bone Mass
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to -1.0 SD)
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD)
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5 SD)
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.
Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007. (3)

The WHO thresholds were chosen based upon fracture risk in postmenopausal White women. Similar diagnostic threshold values for men are less well defined, although for any given BMD, the age-adjusted fracture risk is similar in men and women. The International Society for Clinical Densitometry (ISCD) recommends the application of the WHO classification for men aged 50 years and older. (3)

Regulatory Status

Romosozumab-aqqg (Evenity™) is a humanized monoclonal antibody (IgG2) produced by recombinant deoxyribonucleic acid (DNA) technology that binds to and inhibits sclerostin, a regulatory factor in bone metabolism. It increases bone formation and to a lesser extent, decreases bone resorption. Evenity is given subcutaneously by a healthcare provider. Evenity was approved by the U.S. Food and Drug Administration (FDA) in 2019 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. (1)

Rationale

This medical policy is based on the U.S. Food and Drug Administration labeled indications for Evenity (romosozumab-aqqg).

Treatment of Osteoporosis in Postmenopausal Women

Study 1 (NCT01575834) (1)

Study 1 (NCT01575834) was a randomized, double-blind, placebo-controlled study of postmenopausal women aged 55 to 90 years (mean age of 71 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) for 12 months. At baseline, 18% of women had a vertebral fracture. 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. Women received 500 to 1000 mg calcium and 600 to 800 international units vitamin D supplementation daily. The coprimary efficacy endpoints were new vertebral fracture at month 12 and month 24.

Effect on Fractures

Evenity significantly reduced the incidence of new vertebral fractures through month 12 compared to placebo. In addition, the significant 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 (see Table 2).

Table 2. Effective Evenity on the Incidence and Risk of Fractures in Study 1

	Proportion of Women with Fractures		**Absolute Risk Reduction (%) (95% CI)[a]**	**Relative Risk Reduction (%) (95% CI)[a]**	**p-value[b]**
At Month 12	**Placebo (N=3591)**	**Evenity (N=3589)**			
New vertebral fracture	1.8%	0.5%	1.3 (0.8, 1.8)	73 (53, 84)	<0.001
At Month 14	**Placebo Followed by Denosumab (N=3591)**	**Evenity Followed by Denosumab (N=3589)**			

New vertebral fracture	2.5%	0.6%	1.9 (1.3, 2.5)	75 (60, 84)	<0.001

CI: confidence interval.

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

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

Evenity significantly reduced the incidence of clinical fracture (a composite endpoint of symptomatic vertebral fracture and nonvertebral fracture) at 12 months. However, 88% of these clinical fractures were nonvertebral fractures and the incidence of nonvertebral fractures was not statistically significantly different when comparing Evenity-treated women to placebo-treated women at month 12 or month 24.

Effect on Bone Mineral Density (BMD)

Evenity significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with placebo at month 12. The treatment differences in BMD were 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck.

Following the transition from Evenity to denosumab at month 12, BMD continued to increase through month 24. In patients who transitioned from placebo to denosumab, BMD also increased with denosumab use. The differences in BMD achieved at month 12 between Evenity and placebo patients were overall maintained at month 24, when comparing patients who transitioned from Evenity to denosumab to those who transitioned from placebo to denosumab. There was no evidence of differences in effects on BMD at the lumbar spine or total hip across subgroups defined by baseline age, baseline BMD, or geographic region.

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

Bone Histology and Histomorphometry

A total of 154 transiliac crest bone biopsy specimens were obtained from 139 postmenopausal women with osteoporosis at month 2, month 12, and/or month 24. All of these biopsies were adequate for qualitative histology and 138 (90%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments from women 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). At month 2 in women treated with Evenity, histomorphometric indices of bone formation at trabecular and endocortical surfaces were increased. These effects on bone formation were accompanied by a decrease in indices of bone resorption. At month 12, both bone formation and resorption

indices were decreased with Evenity, while bone volume, and trabecular and cortical thickness were increased.

Study 2 (NCT01631214) (1)

Study 2 (NCT01631214) was a randomized, double-blind, alendronate-controlled study of postmenopausal women aged 55 to 90 years (mean age of 74 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 history of a proximal femur fracture. Women were randomized (1:1) to receive either monthly subcutaneous injections of Evenity (N = 2046) or oral alendronate 70 mg weekly (N = 2047) for 12 months, with 500 to 1000 mg calcium and 600 to 800 international units vitamin D supplementation daily. After the 12-month treatment period, women in both arms transitioned to open-label alendronate 70 mg weekly while remaining blinded to their initial treatment.

This was an event driven trial. The two 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, which ended when at least 330 subjects had a clinical fracture and all subjects had completed the 24-month visit. Clinical fracture was a composite endpoint of nonvertebral fracture and symptomatic vertebral fracture.

Effect on Fractures

Evenity significantly reduced the incidence of new vertebral fractures at 24 months (see Table 3).

Table 3. Effect of Evenity on the Incidence of New Vertebral Fractures in Study 2

	Proportion of Women with Fracture (%)		**Risk Reduction**		**p-value[b]**
	Alendronate Alone (N=2047)	**Evenity Followed by Alendronate (N=2046)**	**Absolute Risk Reduction (%) (95% CI)[a]**	**Relative Risk Reduction (%) (95% CI)[a]**	
New vertebral facture through month 24	8.0%	4.1%	4.0 (2.5, 5.6)	50 (34, 62)	<0.001

CI: confidence interval.

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

Evenity significantly reduced the risk of clinical fracture through the end of the primary analysis period (see Table 4). 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 4. Effect of Evenity on the Risk of Clinical Fractures in Study 2

	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

CI: confidence interval.

[a] % = number of subjects who had a clinical 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 medial duration of follow-up for the primary analysis period was 33 months.

[c] Hazard ratio and P-value are based on Cox proportional hazards model adjusting for age strata, baseline total hip bone mineral density (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 8.7% at the lumbar spine, 3.3% at the total hip, and 3.2% 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 8.1% at the lumbar spine, 3.8% at the total hip, and 3.8% at the femoral neck.

There was no evidence of differences in effects on BMD at the lumbar spine or total hip across subgroups defined by baseline age, baseline BMD, or geographic region.

Summary of Evidence

Based on the review of studies provided to the U.S. Food and Drug Administration for approval, Evenity (romosozumab-acqg) may be considered medically necessary for the treatment of postmenopausal women with osteoporosis when the individual has a history of osteoporotic fracture or a pre-treatment bone mineral density (BMD) T-score of ≤ -2.5; AND has multiple risk factors for fracture or failure or intolerance to other available osteoporosis therapy.
Evenity (romosozumab-acqg) is considered experimental, investigational, and/or unproven for all other non-FDA approved indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3111

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Evenity™ (romosozumab-aqqg) (December 2019). Available at: <https://www.accessdata.fda.gov> (accessed June 9, 2025).

Other:

2. NIH. Osteoporosis Overview, Symptoms, & Causes. NIH Osteoporosis and Related Bone Diseases National Resource Center. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Available at: <https://www.niams.nih.gov> (accessed July 9, 2025).
3. Rosen HN, Drake MT. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. In: UpToDate, Rosen CJ, Schmader KE (Eds), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed July 9, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
09/01/2025	Document updated with literature review. The following changes were made to Coverage: 1) Revised coverage to be in alignment with the current FDA label for romosozumab-aqqg (Evenity™); 2) Added "non-Food and Drug Administration approved" to the existing experimental, investigational and/or unproven statement; and 3) Moved content from NOTE 1 to Policy Guidelines section. No new references added; some removed.
11/15/2024	Reviewed. The following change was made to Coverage: removed the phrase "at the total hip or femoral neck" from the statement "A pre-treatment bone mineral density (BMD) T-score of ≤ -2.5…" No other changes made. No references added.
04/01/2024	New medical document. Romosozumab-aqqg (Evenity™) may be considered medically necessary, up to 12 monthly doses, for treatment of osteoporosis in postmenopausal women with osteoporosis when the individual meets the following criteria: at high risk for fracture, defined by one of the following: a history of osteoporotic fracture, or pre-treatment bone mineral density (BMD) T-score of ≤ -2.5 at the total hip or femoral neck; or a pre-treatment bone mineral density T-score between -1.0 and -2.5 and a high pre-treatment FRAX fracture probability; and meets any of the following criteria: indicators of very high fracture risk (e.g., advanced age, frailty, glucocorticoid use, very low T-score [less than or equal to -3], or increased fall risk);or the individual has failed prior treatment with or is intolerant to other available osteoporosis therapy (e.g., zoledronic acid [Reclast], teriparatide [Forteo, Bonsity]); or individual has had an oral bisphosphonate trial of at least 1-year duration or there is a clinical reason to avoid treatment with an oral bisphosphonate; and and the individual will not receive concurrently with parathyroid hormone analogs (e.g., teriparatide, abaloparatide) or RANK ligand inhibitors (e.g., denosumab). Romosozumab-aqqg (Evenity™) is considered experimental, investigational and/or unproven for all other indications, including but not limited to when total duration of therapy exceeds 12 monthly doses; or when used in women who have had a prior myocardial infarction or stroke within the preceding year (12 months).