09-J3000-33

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Reviewed: 01/10/24

Revised: 02/15/24

Subject: Romosozumab-aqqg (Evenity®)

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DESCRIPTION:

Romosozumab-aqqg (Evenity®) is a humanized monoclonal antibody that binds to and inhibits sclerostin, a regulatory factory in bone metabolism. Bone formation is stimulated on trabecular and cortical bone surfaces by stimulating osteoblastic activity. Bone resorption is decreased to a lesser extent.

The Food and Drug Administration (FDA) approved romosozumab-aqqg (Evenity®) in April 2019 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. High fracture risk is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. Romosozumab use is limited to 12 months since the anabolic effect wanes after this period. An antiresportive agent is recommended if continued treatment of postmenopausal osteoporosis is needed.

Romosozumab was evaluated in postmenopausal women with osteoporosis in 2 large randomized studies In study 1, romosozumab was compared with placebo in postmenopausal women with a bone mineral density (BMD) T-score less than or equal to -2.5 at the total hip or femoral neck(n=7180). There were 18% and 22% of subjects with a vertebral or non vertebral fracture at baseline. Blinded treatment with romosozumab or placebo was given once monthly for 12 months followed by open-label denosumab for 12 months. Subjects also received at least 500 mg calcium and 600 international units of vitamin D supplementation daily and a loading dose of vitamin D within one week of randomization if 40 ng/mL or less. The coprimary endpoints were new vertebral fracture at month 12 and 24. Romosozumab significantly decreased the risk of new vertebral fracture at month 12 and 24 compared with placebo (Month 12, 0.5% vs 1.8%, $p<0.001$ and Month 24, 0.6% vs 2.5%, $p<0.001$) in postmenopausal women who were at high risk of fracture. A composite endpoint of symptomatic vertebral fracture and nonvertebral fracture was also significantly reduced as compared to placebo at 12 months; however, the incidence of nonvertebral fractures was not significantly different at month 12 or 24. The most common

adverse reactions were injection site reactions, arthralgia, and headache. The incidence of myocardial infarction (0.3 vs 0.2%), stroke (0.2% vs 0.3%), cardiovascular death (0.5% vs 0.4%), and positively adjudicated major adverse cardiac events (MACE) was similar with romosozumab as compared to placebo in study 1 (0.8% vs 0.8%, HR 1.03 [95% CI 0.62,1.72]). Osteonecrosis of the jaw and atypical femoral fracture was reported in the romosozumab treatment group (<0.1%).

In study 2, romosozumab was compared to alendronate in postmenopausal women with a BMD T-score of 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 (n=4093). There were 96% and 38% of subjects with a vertebral or non vertebral fracture at baseline. Women received either monthly subcutaneous injections of romosozumab or alendronate 70 mg weekly for 12 months followed by open label alendronate weekly. Subjects also received at least 500 mg calcium and 600 intenational units of vitamin D supplementation daily and a loading dose of vitamin D within one week of randomization if 40 ng/mL or less. The coprimary endpoints were the incidence of morphometric vertebral fracture at 24 months and time to the first clinical fracture through the primary analysis period (ending when all subjects had completed the 24 month visit and at least 330 subjects had a clinical fracture). Clinical fracture was a composite endpoint of nonvertebral fracture and symptomatic vertebral fracture. Romosozumab followed by alendronate significantly decreased the incidence of new vertebral fracture at 24 months as compared to alendronate alone (4.1% vs 8.0%, p<0.001). Romosozumab followed by alendronate also significantly reduced the risk of clinical fracture through the end of the primary analysis period as compared to alendronate (9.7% vs 13%, p<0.001) ; the risk of nonvertebral fracture was also significantly reduced through the primary analysis period (HR 0.081, p=0.04). The median duration of subject follow-up for the primary analysis period was 33 months and 99% of subjects had a prior fracture. The most common adverse reactions were injection site reactions, arthralgia, and headache. There was a higher incidence of myocardial infarction (0.8 vs 0.2%), stroke (0.6% vs 0.3%), cardiovascular death (0.8% vs 0.6%), and positively adjudicated major adverse cardiac events (MACE) with romosozumab as compared to alendronate in study 2 (2% vs 1.1%, HR 1.87 [95% CI 1.11,3.14]) . Osteonecrosis of the jaw and atypical femoral fracture was reported in the romosozumab followed by alendronate treatment group (each <0.1%) and in the alendronate only group (<0.1% and 0.2%).

According to evidence based guidelines (e.g., American Academy of Clinical Endocrinologists/American College of Endocrinology guidelines for treatment of postmenopausal women with osteoporosis), abaloparatide, denosumab, romosozumab, teriparatide, and zoledronic acid are appropriate initial therapy for patients at very high risk of fracture. The 2020 Endocrine Society guideline recommends initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, ibandronate) to reduce fracture risk in postmenopausal women at high risk of fractures and denosumab is an alternative initial treatment. Romosozumab is recommended in postmenopausal women at very high risk of fracture, such as those with severe osteoporosis (i.e., low T-score < -2.5 and fractures) or multiple vertebral fractures for up to one year for the reduction of vertebral, hip, and nonvertebral fractures. The guideline further states that women at high risk of cardiovascular disease (e.g., prior myocardial infarction) and stroke should not be considered for romosozumab pending further studies on cardiovascular risk associated with treatment.

POSITION STATEMENT:

I. Initiation of Romosozumab-aqqg (Evenity™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Postmenopausal Osteoporosis

a. Member meets **ONE** of the following:

i. Member has a pre-treatment bone mineral density (BMD) T-score of -2.5 or lower[a]

ii. Member has a history of osteoporotic hip or spine fracture

iii. Member has a BMD T-score between -1.0 and -2.5[a] and **ONE** of the following:

1. FRAX[b] 10-year probability major osteoporotic fracture ≥ 20%

2. FRAX[b] 10-year probability of hip fracture ≥ 3%

3. Fragility fracture of the proximal humerus, pelvis, or distal forearm

b. The cumulative duration of romosozumab-aqqg has not exceeded a total of 1 year in the member's lifetime

c. Romosozumab-aqqg will not be used in combination with other anabolic or antiresorptive agents (e.g., bisphosphonates, denosumab, parathyroid hormone analogs)

d. Member has not had a stroke or myocardial infarction in the past year

e. **ONE** of the following – documentation must be submitted:

i. Member has an inadequate response[c] to injectable antiresorptive therapy [zoledronic acid (Reclast®) or denosumab (Prolia®)][d]

ii. Member has a contraindication to **BOTH** zoledronic acid and denosumab[d]

iii. Member has a BMD T-score of -2.5 or lower[a] **AND** a history of osteoporotic fracture

iv. Member has a history of multiple osteoporotic vertebral fractures

v. Member had osteoporotic fractures while receiving a FDA approved treatment for osteoporosis

vi. Member had osteoporotic fractures while on long-term therapy with a medication known to cause skeletal harm (e.g., glucocorticoids)

vii. Member has a history of osteoporotic fracture in the past 12 months

viii. Member is at high risk of falls or has a history of falls

ix. Member has a BMD T-score of -3.0 or lower[a]

x. FRAX[b] 10-year probability of major osteoporotic fracture ≥ 30%

xi. FRAX[b] 10-year probability of hip fracture ≥ 4.5%

f. Dose does not exceed 210 mg monthly

Approval duration: 1 year (maximum lifetime duration is 1 year)

[a] Measured at the femoral neck, total hip, lumbar spine, or 33% radius

[b] FRAX® Fracture Risk Assessment Tool. https://www.sheffield.ac.uk/FRAX/index.aspx

[c] Inadequate response is defined as a new fracture in a compliant member or significant loss of bone mineral density on follow-up scans.

[d] Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Romosozumab-aqqg is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Treatment is limited to 12 monthly doses followed by continued therapy with an anti-resorptive agent if warranted. Adequately supplement calcium and vitamin D during treatment.
- Two separate subcutaneous injections (two 105 mg prefilled syringes) should be administered by a healthcare provider once every month for 12 doses in the abdomen, thigh, or upper arm. The total dose is 210 mg.

Dose Adjustments

- None

Drug Availability

- 105 mg/1.17 mL solution in a single-use prefilled syringe. A full dose requires 2 single-use prefilled syringes.

PRECAUTIONS:

Boxed Warning

- Romosozumab-aqqg may increase the risk of myocardial infarction, stroke and cardiovascular death. It should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Confer whether the benefits outweigh the risks in patients with other cardiovascular risk factors. If a patient experiences a myocardial infarction or stroke during therapy it should be discontinued.

Contraindications

- Hypocalcemia must be corrected prior to initiation of therapy
- Known hypersensitivity to romosozumab-aqqg

Precautions/Warnings

- Major Adverse Cardiac Events (MACE): Monitor for symptoms of MI and stroke and seek prompt medical attention if symptoms occur.
- Hypersensitivity reactions including angioedema, erythema multiforme, dermatitis, rash and urticaria may occur and treatment should be discontinued if a clinically significant allergic reaction occurs.
- Hypocalcemia: Supplement calcium and vitamin D during treatment. Patients with severe renal impairment or are receiving dialysis are at greater risk and should be monitored.
- Osteonecrosis of the jaw: Monitor for symptoms and consider discontinuation of therapy based on benefit-risk assessment.
- Atypical femoral fracture: Evaluate new or unusual thigh, hip, or groin pain to rule out an incomplete femur fracture.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3111	Injection, romosozumab-aqqg, 1 mg

ICD-10 Diagnoses Codes That Support Medical Necessity

E28.310	Symptomatic premature menopause
E28.319	Asymptomatic premature menopause
E28.39	Other primary ovarian failure
M80.00XA – M80.00XS M80.011A – M80.011S M80.012A – M80.012S M80.019A – M80.019S M80.021A – M80.021S M80.022A – M80.022S M80.029A – M80.029S M80.031A – M80.031S M80.032A – M80.032S M80.039A – M80.039S M80.041A – M80.041S M80.042A – M80.042S M80.049A – M80.049S M80.051A – M80.051S M80.052A – M80.052S M80.059A – M80.059S M80.061A – M80.061S M80.062A – M80.062S M80.069A – M80.069S M80.071A – M80.071S M80.072A – M80.072S	Age-related osteoporosis with current pathological fracture

M80.079A – M80.079S M80.08XA – M80.08XS M80.0AXA – M80.0AXS M80.0B1A – M80.0B1S M80.0B2A – M80.0B2S M80.0B9A – M80.0B9S	
M80.80XA – M80.80XS M80.811A – M80.811S M80.812A – M80.812S M80.819A – M80.819S M80.821A – M80.821S M80.822A – M80.822S M80.829A – M80.829S M80.831A – M80.831S M80.832A – M80.832S M80.839A – M80.839S M80.841A – M80.841S M80.842A – M80.842S M80.849A – M80.849S M80.851A – M80.851S M80.852A – M80.852S M80.859A – M80.859S M80.861A – M80.861S M80.862A – M80.862S M80.869A – M80.869S M80.871A – M80.871S M80.872A – M80.872S M80.879A – M80.879S M80.88XA – M80.88XS M80.8AXA – M80.8AXS M80.8B1A – M80.8B1S M80.8B2A – M80.8B2S M80.8B9A – M80.8B9S	Other osteoporosis with current pathological fracture
M81.0	Age-related osteoporosis without current pathological fracture
M81.8	Other osteoporosis without current pathological fracture
N95.1	Menopausal and female climacteric states
Z78.0	Asymptomatic menopausal state

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.DEFINITIONS:

Osteoporosis: reduction in the amount of bone mass, leading to fractures after minimal trauma. Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density (BMD) value for the hip, spine, or wrist of 2.5 standard deviations (SD) or more below the mean for healthy young white women, or a T-score of less than or equal to –2.5. The disease is characterized by an increased risk of fractures, which can result in pain, diminished quality of life, decreased physical mobility and independence, inability to work, and increased burden on caregivers.

Postmenopausal: occurring after menopause.

Risk Factors for Osteoporosis: For osteoporotic fractures, includes low BMD, parental history of hip fracture, low body weight, previous fracture, smoking, excess alcohol intake, glucocorticoid use, secondary osteoporosis (e.g., rheumatoid arthritis) and history of falls. These readily accessible and commonplace factors are associated with the risk of hip fracture and, in most cases, with that of vertebral and other types of fracture as well.

RELATED GUIDELINES:

Abaloparatide (Tymlos), 09-J2000-85
Bone Mineral Density Studies, 04-70000-21
Denosumab (Prolia™, Xgeva™) Injection, 09-J1000-25
Teriparatide (Forteo, Teriparatide injection), 09-J0000-47

OTHER:

None Applicable

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11. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 2022-12-30]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
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13. Shoback D, Rosen CJ, Black DM et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. *J Clin Endocrinol Metab.* 2020; 105 (3): 1-8.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/10/24.

GUIDELINE UPDATE INFORMATION:

06/15/19	New Medical Coverage Guideline.
10/01/19	Revision: Added HCPCS J3111 and removed C9399 and J3490.
01/01/20	Revision to guideline consisting of updating the position statement.
04/15/20	Review and revision to guideline; consisting of updating the description, position statement and references.
10/01/20	Revision to ICD-10 coding.
02/15/21	Review and revision to guideline; consisting of updating the description, position statement and references.
02/15/22	Review and revision to guideline; consisting of updating references.
02/15/23	Review and revision to guideline; consisting of updating the references.
10/01/23	ICD-10 additions.
02/15/24	Review and revision to guideline; consisting of updating the references.