Drug Monograph

Drug/Drug Class:	**Evenity™ (romosozumab-aqqg) subcutaneous injection / Sclerostin inhibitor**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Evenity is available in a single-use prefilled syringe for injection containing 105 mg romosozumab per 1.17 ml solution. A full dose of Evenity requires two single-use prefilled syringes. Amgen Inc., Thousand Oaks, California 91320-1799
Summary of Findings:	Evenity's approval was based on results from two clinical trials involving more than 11,000 women with postmenopausal osteoporosis. In a randomized, double-blind, placebo-controlled study, Evenity demonstrated a reduction in the incidence of clinical fractures, which was a composite endpoint of symptomatic vertebral and nonvertebral fractures, but 88% of these fractures were nonvertebral and the incidence of nonvertebral fractures was not statistically significant at 12 or 24 months. In a randomized, double-blind, alendronate-controlled study, Evenity significantly reduced the risk of clinical fracture through the end of the primary analysis. In the Evenity followed by alendronate group, the risk of nonvertebral fracture was also reduced.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3,4]

An estimated 30% of postmenopausal women in the United States have osteoporosis and the majority have bone loss due to estrogen deficiency and/ or age. Osteoporosis results in a decrease in bone strength and increase risk of fracture. Assessment of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) is the gold standard in diagnosing osteoporosis. After ruling out other causes, a T-score of -2.5 or less qualifies for a diagnosis of osteoporosis. Due to therapies available that can slow or reverse the progression of osteoporosis, early diagnosis is important.

Dosage Form [1]

Evenity is available in a single-use prefilled syringe for injection containing 105 mg romosozumab per 1.17 ml solution. A full dose of Evenity requires two single-use prefilled syringes.

Manufacturer [1]

Amgen Inc., Thousand Oaks, California 91320-1799

Indication(s) [1]

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. Limitations of Use: Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Evenity inhibits the action of sclerostin, a regulatory factor in bone metabolism. Evenity increases bone formation and, to a lesser extent, decreases bone resorption. Animal studies showed that romosozumab-aqqg stimulates new bone formation on trabecular and cortical bone surfaces by stimulating osteoblastic activity resulting in increases in trabecular and cortical bone mass and improvements in bone structure and strength

Pharmacokinetics:

	Evenity
Absorption	Median time to maximum concentration is 5 days. (range: 2 to 7 days)
Distribution	3.92 L
Metabolism	Not yet been characterized but expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Elimination	Nonlinear pharmacokinetics with the clearance of romosozumab-aqqg decreasing as the dose increased
Half-life	12.8 days after 3 doses of 3 mg/kg every 4 weeks

Efficacy of Evenity (Study 1)

STUDY DESIGN	Randomized, double-blind, placebo-controlled clinical trial (N = 7,180)
INCLUSION CRITERIA	Postmenopausal women aged 55 to 90 years with bone mineral density (BMD) T-score less than or equal to −2.5 at the total hip or femoral neck
EXCLUSION CRITERIA	Patients not meeting the inclusion criteria.
TREATMENT REGIMEN	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.
RESULTS	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. Evenity significantly reduced the incidence of clinical fracture (a composite endpoint of symptomatic vertebral fracture and nonvertebral fracture) at 12 months. 88% of these clinical fractures were nonvertebral fractures and the incidence of nonvertebral fractures was not statistically significantly different. At month 12, Evenity significantly increased BMD with the treatment differences in

	BMD being 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. In patients not transitioned to denosumab, BMD returned to approximately baseline within 12 months after discontinuation of Evenity.
SAFETY	Not specified.

Efficacy of Evenity (Study 2)

STUDY DESIGN	Randomized, double-blind, alendronate-controlled clinical trial (N = 4,093)
INCLUSION CRITERIA	Postmenopausal women aged 55 to 90 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
EXCLUSION CRITERIA	Patients not meeting the inclusion criteria.
TREATMENT REGIMEN	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 coprimary 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.
RESULTS	Evenity significantly reduced the incidence of new vertebral fracture at 24 months. Evenity significantly reduced the risk of clinical fracture through the end of the primary analysis period. 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). Evenity significantly increased BMD by 8.7% at the lumbar spine, 3.3% at the total hip, and 3.2% at the femoral neck. 12 months of Evenity followed by 12 months of alendronate treatment significantly increased BMD compared with alendronate alone with the BMD increase at month 12 being 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.
SAFETY	Not specified.

Contraindications [(1)]

- Hypocalcemia
- Known hypersensitivity to any component of Evenity

Warnings and Precautions [(1)]

- **Black Box Warning**: WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH. Evenity may increase the risk of myocardial infarction, stroke, and cardiovascular death. Evenity should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. If a patient experiences a myocardial infarction or stroke during therapy, Evenity should be discontinued.
- Major Adverse Cardiac Events (MACE): Monitor for symptoms of MI and stroke and seek prompt medical attention if symptoms occur.
- Hypersensitivity: Hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Discontinue Evenity if a clinically significant allergic reaction occurs.
- Hypocalcemia: Adequately supplement calcium and vitamin D during treatment with Evenity.

- Osteonecrosis of the Jaw: Monitor for symptoms. 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.

Adverse Effects [(1)]

Adverse Reactions ≥2%	Evenity 210mg (N=3581) %	Placebo (N=3,576) %
Arthralgia	13.1	12.1
Headache	6.6	5.8
Muscle spasms	4.6	3.9
Edema peripheral	2.4	1.9
Asthenia	2.3	2.2
Neck Pain	2.2	1.5
Insomnia	2.0	1.9
Paresthesia	2.0	1.7

Drug Interactions [(1)]

- Not Specified

Dosage and Administration [(1)]

The recommended dose of Evenity is 210 mg administered subcutaneously in the abdomen, thigh or upper arm by a healthcare provider. Two separate syringes (and two separate subcutaneous injections) are needed to administer the total dose of 210 mg of Evenity. Inject two 105 mg/1.17 mL prefilled syringes, one after the other, once every month for 12 doses. Patients should be adequately supplemented with calcium and vitamin D during treatment.

Missed dose: Administer as soon as it can be rescheduled. Thereafter, injection can be scheduled every month from the date of the last dose.

Storage and handling: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake. If removed from the refrigerator, can be kept at room temperature up to 25°C (77°F) in the original carton and must be used within 30 days. Do not expose to temperatures above 25°C (77°F). Allow to sit at room temperature for at least 30 minutes before injecting.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost/Month
Romosozumab-aqqg	Evenity	Amgen Inc.	210 mg subq once monthly	$1,817.68**
Teriparatide	Forteo	Eli Lilly	20 mcg subq once daily	$3,306.12*
Abalopratide	Tymlos	Radius	80 mcg subq once daily	$1,770.60*

* NADAC

** Maximum Allowable Cost

Conclusion [1,2]

Evenity (romosozumab-aqqg) was approved by the FDA for the treatment of osteoporosis in postmenopausal women at high risk for fracture. Evenity is the first anabolic agent that has the effect of increasing bone formation and reducing bone resorption, to a lesser extent. Other anabolic agents currently available are Lilly's Forteo and Radius Health's Tymlos. Evenity has a black box warning that it may increase the risk of myocardial infarction, stroke, and cardiovascular death.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Product Information: Evenity™ (romosozumab-aqqg) Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320-1799 4/2019.
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3) Rosen, Harold; Schmader, Kenneth. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on July 24, 2019.)
4) Lewiecki, E Michael. Prevention of osteoporosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on July 26, 2019.)

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