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CADTH Reimbursement Recommendation

Romosozumab (Evenity)

Indication: 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

Sponsor: Amgen Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Evenity?

CADTH recommends that Evenity should be reimbursed by public drug plans for the treatment of osteoporosis in postmenopausal women if certain conditions are met.

Which Patients Are Eligible for Coverage?

Evenity should only be covered to treat postmenopausal women with a history of osteoporosis-related fracture and who are likely to have such a fracture in the future and who have never received previous medications for osteoporosis.

What Are the Conditions for Reimbursement?

Evenity should only be reimbursed if the cost is reduced and if it is not prescribed concurrently with other osteoporosis medications, except for calcium and/or vitamin D.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that 12 months of Evenity therapy followed by 12 months of alendronate therapy reduced the risk of fractures better than alendronate alone.
- Evenity may address some of the needs that are important to patients, including reducing the risk of osteoporosis-related fractures.
- Based on public list prices, Evenity is not considered cost-effective relative to treatments that are already reimbursed by public drug plans at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year in postmenopausal women with a history of osteoporotic fracture and who are at very high risk for future fracture. Economic evidence suggests that the price of Evenity needs to be reduced by at least 53% price for it to be considered cost-effective in this patient population.
- Based on public list prices, Evenity is expected to cost the public drug plans $51,154,841 over 3 years.

Additional Information

What Is Osteoporosis?

Osteoporosis is a bone disease characterized by low bone mass, weakened bone strength, and decreased bone quality, which results in an increased risk of fracture. Osteoporosis affects 2 million Canadians, primarily postmenopausal women.

Unmet Needs in Osteoporosis

Most patients with osteoporosis are currently treated with oral bisphosphonates. These treatments are inconvenient to take and may cause treatment-related gastrointestinal tract discomfort, such as abdominal pain, dyspepsia, nausea, and vomiting. There is a need for an effective treatment that prevents osteoporosis-related fractures that can be easily administered and is well-tolerated by patients.

How Much Does Evenity Cost?

Treatment with Evenity is expected to cost approximately $7,881 per patient for 12 months.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that romosozumab be reimbursed for the treatment of osteoporosis in postmenopausal women, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In a phase III, double-blind, randomized controlled trial (RCT) (ARCH, N = 4,093) in postmenopausal women with osteoporosis who were at high risk of fracture, romosozumab 210 mg subcutaneous monthly for 12 months followed by an oral bisphosphonate reduced the risk of fractures compared with an oral bisphosphonate alone. Fewer patients treated with romosozumab for 12 months followed by alendronate for 12 months (4.1%) had a new vertebral fracture compared with alendronate alone at 24 months (8.0%; relative risk = 0.50; 95% CI, 0.38 to 0.66). Treatment with romosozumab followed by alendronate was also associated with a lower incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) compared with alendronate alone (9.7% versus 13.0%, respectively; hazard ratio = 0.73; 95% CI, 0.61 to 0.88). Analyses of key secondary outcomes, such as the incidence of nonvertebral fractures (including hip), favoured romosozumab followed by alendronate versus alendronate alone. In their input to CADTH, patients expressed a desire for treatments that prevent osteoporosis-related fractures because of the substantial impact that fractures, and the fear of fractures, have on patients' lives.

The sponsor's request for reimbursement specified a narrower patient population from the indication: women with postmenopausal osteoporosis with a history of osteoporotic fracture and who are at very high risk for future fracture. In this population, using the sponsor-submitted price for romosozumab and publicly listed prices for all other drug costs, CADTH estimated the sequential incremental cost-effectiveness ratio (ICER) to be $219,799 per quality-adjusted life-year (QALY) relative to currently reimbursed options. A reduction in price of at least 53% is required for romosozumab to be considered cost-effective at a $50,000 per QALY threshold in this population. These conclusions rely on results from an indirect treatment comparison (ITC), which was deemed to have substantial uncertainty associated with it. Therefore, further price reductions may be required to ensure cost-effectiveness given that romosozumab is substantially more expensive than alternatives for which there is no direct evidence.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients with a history of osteoporotic fracture and who are at high risk for future fracture, defined as a 10-year fracture risk ≥ 20% as defined by the FRAX tool.	The ARCH trial included patients who had a history of fracture (> 99%) or a prevalent fracture (96%). Patients had a mean 10-year probability of a major osteoporotic fracture of 20% at baseline based on FRAX.

Reimbursement condition	Reason
2. The patient must be treatment naive to osteoporosis medications, except for calcium and/or vitamin D.	Only 9% of patients enrolled in the ARCH trial had prior use of osteoporosis medications, such as oral bisphosphonates. The currently available evidence demonstrating reduced risk of fracture with romosozumab compared with alendronate in predominantly treatment-naive patients, the lack of evidence on initiating treatment with romosozumab in treatment-experienced patients, and the bone-forming mechanism of action of the drug support the use of romosozumab in patients who have not been previously treated with osteoporosis medications.
3. Maximum duration of reimbursement is 12 months.	The maximum duration of treatment with romosozumab in the ARCH trial was 12 months. The approved duration of treatment by Health Canada for romosozumab is limited to 12 months.
Prescribing	
1. Romosozumab should not be prescribed concurrently with other osteoporosis medications, except for calcium and/or vitamin D.	The is no evidence supporting concurrent treatment with romosozumab and other osteoporosis medications. Concurrent therapy was not permitted in the ARCH trial, except with calcium and vitamin D.
Pricing	
1. Price reduction needed.	In the CADTH base case, a sequential ICER was derived for romosozumab of $219,799 per QALY when compared to currently funded alternatives in patients covered under the requested reimbursement population. A price reduction of 53% would be required for romosozumab to achieve an ICER of $50,000 per QALY in this population. These price reductions are based on an ITC which was deemed to have substantial uncertainty associated with it. Therefore, a higher price reduction may be required to ensure cost-effectiveness, given that romosozumab is substantially more expensive than alternatives for which there is no direct evidence.

FRAX = Fracture Risk Assessment; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; QALY = quality-adjusted life-year.

Discussion Points

- CDEC discussed the place in therapy for romosozumab. Almost all patients enrolled in the ARCH trial had a history of fracture (including nonvertebral fractures and vertebral fractures), and the 10-year probability of a major osteoporotic fracture calculated by the Fracture Risk Assessment tool (FRAX) was 20%. More than 90% of patients enrolled in the ARCH trial (and the FRAME trial) were treatment naive to osteoporosis medications. The ARCH trial was not designed to inform the effects of romosozumab in those who were intolerant or not responsive to other osteoporosis medications, such as bisphosphonates. Thus, the currently available evidence in addition to the bone-forming mechanism of action of romosozumab supports its use before an antiresorptive medication in patients who have had a fracture, are at high risk for future fracture, and have not previously received medications for osteoporosis.

- CDEC noted a potentially increased risk of cardiovascular events with romosozumab treatment, including an increase in myocardial infarction and stroke in the ARCH trial. Health Canada and other regulatory agencies considered that serious cardiac and cerebrovascular events were the primary events of concern. The product monograph for romosozumab has a boxed warning regarding the potentially increased risk of myocardial infarction, stroke, and cardiovascular death with romosozumab treatment and that romosozumab is not recommended in patients with a history of myocardial infarction or stroke. It also indicates that treatment should be discontinued in patients who experience a myocardial infarction or stroke. During the 12-month double-blind treatment period of the ARCH study, adjudicated serious cardiovascular adverse events were reported more frequently in the romosozumab group than the alendronate group (2.5% versus 1.9% of patients, respectively). Cardiac ischemic events were reported in 0.8% and 0.3% of patients in the romosozumab group and alendronate group, respectively; cerebrovascular events were reported in 0.8% and 0.3% of patients in these groups.
- CDEC discussed the results of another phase III RCT, the FRAME study, which compared romosozumab 210 mg subcutaneous monthly for 12 months with placebo in postmenopausal women with osteoporosis who were at moderate risk of fracture. Both treatment groups received denosumab for 12 months after the initial double-blind period. The study achieved the first primary outcome, demonstrating the incidence of new vertebral fractures through 12 months of treatment was lower with romosozumab (0.5%) than with placebo (1.8%). However, given the key limitations of the study (i.e., it did not include the target patient population and it used a placebo comparator), CDEC only considered the results of the FRAME study as supportive of the efficacy of romosozumab and not sufficient evidence to inform the comparative clinical effects of romosozumab.
- In the sponsor-provided ITC, romosozumab followed by an antiresorptive medication was favoured in reducing the risk of new nonvertebral fractures compared with currently available treatments. However, the results of the ITC are associated with a high degree of uncertainty because key assumptions related to homogeneity and transitivity were not met.

Background

Romosozumab has a Health Canada indication 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. Romosozumab is a humanized monoclonal antibody that inhibits the action of sclerostin, a regulatory factor in bone metabolism. It is available as a solution for subcutaneous injection in a prefilled syringe, 105 mg/1.17 mL, and the Health Canada–approved dose is 210 mg administered once every month. Treatment duration of romosozumab is limited to 12 monthly doses.

The sponsor's reimbursement request was for the treatment of osteoporosis in postmenopausal women with a history of osteoporotic fracture who are at very high risk for future fracture.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a review of 2 RCTs in postmenopausal women with osteoporosis
- patients' perspectives gathered by 1 patient group: Osteoporosis Canada
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with osteoporosis
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group, Osteoporosis Canada, submitted input of patients' perspectives obtained from in-person interviews and surveys that they conducted.

The patient group indicated that the most important and feared consequence of osteoporosis is the risk of fracture. From the patient perspective, the impact of a fracture can be substantial: fractures in the older population are associated with acute and often chronic pain, changes in levels of or loss of independence, decreased mobility, social isolation resulting in depression, or institutionalization as a result of a fragility fracture. Hip fracture in particular is associated with significant decline in the patient's ability to live independently and higher death rates resulting from complications. For younger seniors, this may result in time away from work, possibly with a financial impact.

It was expressed that patients value a new treatment option that works differently from conventional options, especially if it is easier to administer and has fewer side effects. Respondents to the Osteoporosis Canada survey reported the outcomes that were of most importance to them were the following: preserving health-related quality of life (HRQoL), preventing fracture-related deaths, preventing admission to long-term care homes, preserving their ability to perform daily physical and social activities, preventing osteoporotic fractures, and avoiding serious side effects.

Clinician Input

The clinical expert indicated that even though oral bisphosphonates are most commonly prescribed for the treatment of osteoporosis in postmenopausal women, they are associated with limitations such as inconvenient administration, gastrointestinal toxicities, and low absorption rates. Use of parenteral bisphosphonates is relatively limited because they are perceived as drugs to be prescribed by a specialist and some patients are reluctant to receive IV infusion or subcutaneous injection. Treatment options for certain patient groups, such as those with renal insufficiency and renal failure, are limited.

In the clinical expert's opinion, romosozumab can be used as a first-line treatment for patients with the lowest bone mineral density (BMD) and greatest risk of fracture.

The expert stated that treatment response is assessed using change in BMD after the treatment and suggested that measurement of BMD be conducted at 12 months when the patient transitions to antiresorptive therapy, and again 12 months to 18 months later after a treatment change.

The expert indicated that romosozumab treatment should be discontinued if the patient experiences intolerable adverse events. If a cardiovascular event occurs, the clinician should consider stopping the treatment.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
The product monograph advises no dosage adjustment may be required in patients with severe renal impairment (eGFR 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2) or end-stage renal disease requiring hemodialysis; however, romosozumab should be used with caution. How will clinicians consider use of romosozumab in patients with renal impairment?	Clinical expert input agreed that use of romosozumab in patients with kidney impairment or end-stage kidney disease should be considered with caution. For a patient with kidney impairment or failure and low bone formation, it is reasonable to use romosozumab. However, the clinical expert suggested that the use of romosozumab is inappropriate for patients who have high bone turnover and high bone resorption due to secondary hyperparathyroidism and treatment with glucocorticoids. CDEC noted that most patients with an eGFR < 30 mL/min/1.73 m^2 are followed by a nephrologist who can help determine if romosozumab is appropriate to prescribe. Patients with an eGFR of < 35 mL/min/1.73 m^2 were excluded from the ARCH and FRAME trials.
The trial data are in women aged 55 years to 90 years. Would postmenopausal women younger than 55 years of age be considered for romosozumab in practice?	Clinical expert input indicated that bone mass declines in postmenopausal women, which increases the risk of fracture. Therefore, postmenopausal women who are younger than 55 years of age would be considered for romosozumab therapy in practice. Postmenopausal women should include those with premature ovarian failure and those who have had a surgical menopause (e.g., after ovariectomy, which can occur at any premenopausal age). CDEC concluded that reimbursement of romosozumab should be based on clinical factors and not on age.
Would patients who are currently receiving active treatment for osteoporosis (e.g., bisphosphonates) be switched to romosozumab in practice?	CDEC discussed clinical expert input that in practice settings if patients are receiving active treatment for osteoporosis and not achieving treatment goals and are still at high risk of facture, clinicians would likely switch to romosozumab. However, CDEC noted that the ARCH and FRAME trials were designed to include patients who had not been treated with osteoporosis medications. Although the ARCH trial included patients who had previously been treated with an osteoporosis medication (9%, mostly oral bisphosphonates) despite the eligibility criteria, the trial was not designed to evaluate the effects of switching to romosozumab. Therefore, there is no evidence for the effects of switching from osteoporosis medications to romosozumab.

Implementation issues	Response
Would patients who have tried teriparatide and not achieved treatment goals be prescribed romosozumab?	Similar to the previous response, there is no evidence to inform switching from treatment with teriparatide to romosozumab. Only 1% of patients included in the ARCH trial had previously been treated with PTH or a PTH derivative. However, the study was not designed to evaluate switching from previous treatments to romosozumab.
Would the drug be initiated in the hospital setting after a fracture, and then maintained in the community setting?	CDEC determined that patients could be started on romosozumab in the hospital setting, depending on hospital formulary availability, and continued in the community setting.
Considerations for continuation or renewal of therapy	
Are there any issues with access to BMD testing within jurisdictions, especially in the COVID-19 context? Is testing difficult to access in rural areas?	Access to BMD testing varies across the country. During the lockdown phases of the COVID-19 pandemic, it was not possible to have BMD testing. The clinical expert consulted indicated that, at present, BMD testing has returned to normal in most areas of the country. Rural areas have reduced access to BMD among other radiological procedures.
The trial data and the product monograph support use of romosozumab as a 12-month treatment course. However, neither provide clear guidance on re-treatment with romosozumab. How would this be considered in clinical practice? Especially if there is evidence after the initial treatment that treatment goals were not achieved? What factors would lead you to think re-treatment with romosozumab would not benefit the patient?	The clinical expert noted that if a patient had no discernible benefit from a first treatment course of romosozumab, it is unlikely that a second course would be beneficial, although this remains an evidence gap. The clinical expert indicated that, in clinical practice settings, if a patient had obvious gains in BMD with romosozumab and then after an interval showed a marked decline in BMD and/or new fragility fractures, re-treatment with romosozumab would be considered. No evidence was available for CDEC to deliberate on regarding re-treatment with romosozumab.
If a dose of romosozumab is missed or treatment needs to be temporarily stopped (e.g., a patient undergoes a procedure that requires its discontinuation), how would this be handled in clinical practice? Is the regimen restarted or does the patient transition to another form of therapy or does the patient receive the rest of the medication for a total of 12 months?	Clinical expert input indicated that patients should receive a full 12 months of treatment with romosozumab, even if the treatment is interrupted. If the treatment interruption is expected to last several months, the patient should be treated with an antiresorptive until romosozumab can be resumed. CDEC noted that there was no evidence that addressed this issue.
Considerations for discontinuation of therapy	
Aside from serious adverse events (e.g., major cardiovascular events), are there any reasons that treatment with romosozumab would be discontinued before completing the recommended 12-month regimen?	The clinical expert noted that, in practice settings, the main reason for treatment discontinuation would be serious adverse effects of the medication. CDEC noted the following: • A higher percentage of patients treated with romosozumab than with alendronate had a cardiovascular event (2.5% vs. 1.9%) during the first 12 months of treatment in the ARCH trial. • The product monograph for romosozumab describes the potentially increased risk of myocardial infarction, stroke, and cardiovascular death with romosozumab treatment. It recommends discontinuing treatment if the patient experiences a myocardial infarction or stroke.

Implementation issues	Response
Considerations for prescribing of therapy	
Will romosozumab be prescribed initially by a clinical specialist (e.g., endocrinologist)? There may be limited access to specialists within some regions.	Primary care prescribers as well as specialists should be able to prescribe romosozumab.
Romosozumab is recommended for use as monotherapy, but are there scenarios in which physicians may want to prescribe it in concurrent combination (instead of sequential) with other treatments for osteoporosis such as oral bisphosphonates?	Evidence on any potential benefit from combination therapy with romosozumab is lacking. However, patients should receive optimized calcium and vitamin D intake in combination with romosozumab. All patients in the ARCH and FRAME trials received calcium and vitamin D.

BMD = bone mineral density; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; vs. = versus.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Two phase III studies (ARCH, N = 4,093; FRAME, N = 7,180;) were included in the CADTH systematic review. The trials enrolled postmenopausal women (aged 55 years to 90 years) with osteoporosis.

The ARCH study was a double-blind RCT that assessed the efficacy and safety of romosozumab 210 mg subcutaneous monthly followed by alendronate 70 mg weekly versus alendronate 70 mg weekly alone for the treatment of osteoporosis in postmenopausal women at high risk of fracture. The initial double-blind treatment phase was 12 months, followed by a 12-month open-label alendronate treatment phase. The primary efficacy end points in the ARCH study were incidence of new vertebral fracture at month 24 and incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) during the primary analysis period, which refers to randomization to the time point that clinical fractures were confirmed for at least 330 patients, and all patients completed the month 24 study visit. Secondary efficacy end points included the incidence of various types of fracture and change from baseline in BMD T-score. In this study, the mean age of patients at baseline was 74 years and almost all patients had a history of osteoporotic fracture or a prevalent fracture at baseline. The mean 10-year probability of a major osteoporotic fracture in this patient population at baseline was 20%, reflecting a high-risk population.

The FRAME study was a double-blind RCT that assessed the efficacy and safety of romosozumab versus placebo for the treatment of osteoporosis in postmenopausal women. Eligible patients were randomized to receive romosozumab 210 mg subcutaneous or placebo once a month for 12 months. After the 12-month double-blind treatment period, both groups received open-label denosumab 60 mg every 6 months for an additional 12 months. After the first 24-month treatment (12 months with romosozumab or placebo followed by 12 months with denosumab), patients entered a 12-month open-label extension period, in which they continued to receive denosumab 60 mg every 6 months. The co-primary efficacy end points were incidence of new vertebral fracture at month 12 and month 24. Secondary efficacy end

points included the incidence of various types of fracture and change from baseline in BMD T-score. In this study, the mean age of the patients at baseline was 71 years and 41% of the patients had a history of fracture. The mean 10-year probability of a major osteoporotic fracture in this patient population at baseline was 13%, reflecting a moderate-risk population.

Efficacy Results

In the ARCH study, treatment with romosozumab for 12 months followed by alendronate therapy for another 12 months was associated with a reduced risk of new vertebral fracture (relative risk = 0.50; 95% CI, 0.38 to 0.66) compared with treatment with alendronate for 2 years. Romosozumab followed by alendronate was also associated with a lower incidence of new clinical fracture versus alendronate alone (hazard ratio = 0.73; 95% CI, 0.61 to 0.88). Results on other fracture-related outcomes in this study (nonvertebral fracture, new vertebral fracture, clinical fracture, hip fracture, major nonvertebral fracture, major osteoporotic fracture, and all osteoporotic fracture) also favoured romosozumab followed by alendronate over alendronate alone. The estimated difference in rates of nonvertebral fractures was found to be statistically significant for patients on romosozumab compared with alendronate. Firm conclusions cannot be drawn for other fracture end points because they were not adjusted for multiple statistical testing.

In the FRAME study, treatment with romosozumab was associated with a reduction in new vertebral fractures through 12 months of treatment versus placebo (relative risk = 0.73; 95% CI, 0.53 to 0.84). Results on a number of fracture-related outcomes (nonvertebral fracture, major nonvertebral fracture, new or worsening vertebral fracture, hip fracture, major osteoporotic fracture, and multiple new or worsening vertebral fracture) favoured romosozumab because fewer patients in the romosozumab group developed these fractures compared with those in the placebo group. Estimated differences in risk of fracture between the romosozumab and placebo groups was statistically significant for clinical fractures but failed to reach statistical significance for nonvertebral fractures. Firm conclusions for all other secondary end points cannot be made because the testing procedure was stopped after the failed test for nonvertebral fractures.

HRQoL assessment was an exploratory outcome in both the ARCH and FRAME studies. It was evaluated using the generic quality of life assessment tool EuroQol 5-Dimensions (EQ-5D) Health Survey and a disease-specific questionnaire, Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV). Results of the 2 studies did not show consistent or clinically meaningful changes on either of these tools between romosozumab and the comparators.

Change in BMD from baseline was measured at the lumbar spine, total hip, and femoral neck in the ARCH and FRAME studies. In the ARCH study, treatment with romosozumab was associated with increased BMD from baseline at all 3 sites compared with alendronate. Similar results were observed in the FRAME study when comparing romosozumab to placebo; however, BMD end points were not adjusted for multiple comparisons in this study.

Harms Results

At month 12 in the ARCH trial, the percentage of patients who had an adverse event (75.7% versus 78.6%), had a serious adverse event (12.8% versus 13.8%), or discontinued study treatment due to an adverse event (3.4% versus 3.2%) was similar for both the patients who received romosozumab and those who received alendronate, respectively. Thirty patients (1.5%) and 21 patients (1.0%) in the romosozumab and alendronate groups, respectively, died during this phase of the study. The differences between the treatment groups for

adverse events remained similar by month 24. Death occurred in 60 patients (2.9%) in the romosozumab followed by alendronate group and 69 patients (3.5%) patients in the alendronate alone group during the open-label alendronate treatment period. Therefore, there was a cumulative total of 90 deaths (4.4%) in the romosozumab followed by alendronate group and 90 deaths (4.5%) in the alendronate alone group.

In the FRAME trial, adverse events occurred at similar frequencies in both the romosozumab group and placebo group (78.4% versus 79.7%, respectively) during the 12 months of treatment. At month 12, the percentage of patients who experienced serious adverse events (9.6% versus 8.7%) or withdrew due to adverse events (2.9% versus 2.6%) was also similar in both the romosozumab group and placebo group, respectively. The percentage of adverse events in the romosozumab followed by denosumab group and the placebo followed by denosumab groups was the same at month 24 of the study. Twenty-nine patients (0.8%) in the romosozumab group and 23 patients (0.6%) in the placebo group died during double-blind treatment. A cumulative total of 52 (1.5%) deaths occurred in the romosozumab followed by denosumab group by month 24, while 47 (1.3%) deaths occurred in the placebo followed by denosumab group.

At month 12 in the ARCH study, hypersensitivity occurred in 6.0% of patients in the romosozumab group and 5.9% of patients in the alendronate group. Serious cardiovascular events were reported in 2.5% of patients treated with romosozumab and 1.9% of patients treated with alendronate. Of the major adverse cardiac events, ischemic cardiac events (0.8% versus 0.3%) and cerebrovascular events (0.8% versus 0.3%) were more frequent in the romosozumab group versus the alendronate group, respectively. At month 24, hypersensitivity occurred in 10.0% of patients in the romosozumab followed by alendronate group and 9.2% of patients in the alendronate alone group. Serious cardiovascular events were reported in 6.5% of patients treated with romosozumab followed by alendronate and 6.1% of patients treated with alendronate alone. One case of osteonecrosis of the jaw occurred in each treatment group by month 24.

In the FRAME trial, hypersensitivity occurred in 6.8% of patients in the romosozumab group and 6.9% of patients in the placebo group. Serious cardiovascular events were reported in 1.2% of patients treated with romosozumab and 1.1% of patients treated with placebo. At month 24, hypersensitivity occurred in 8.8% of patients in the romosozumab followed by denosumab group and 9.3% of patients in the placebo followed by denosumab group. Serious cardiovascular events were reported in 2.3% of patients treated with romosozumab followed by denosumab and 2.2% of patients treated with placebo followed by denosumab. Two cases of osteonecrosis of the jaw occurred in the romosozumab followed by denosumab treatment group by month 24, while no cases occurred in the placebo followed by denosumab group.

Critical Appraisal

The completion rate after 1 year of treatment was greater than 80% in the FRAME trial and 77% in the ARCH trial after 2 years of treatment. The reasons for dropout were similar between the treatment groups. The dropout rates were consistent with other clinical trials of medications for osteoporosis. Nonetheless, the dropout rates were still high, which may impact the validity of the study results because of the proportion of data that needed to be imputed for analyses. In both studies, a last observation carried forward method was used to account for missing data for most efficacy end points. Sensitivity analyses that did not assume that missing data were missing at random were conducted. These sensitivity

analyses confirmed that the trial results were generally robust to the handling of missing data in the primary and secondary analyses.

In the FRAME and ARCH studies, multiplicity was controlled for based on a step-down procedure, with the primary and selected secondary outcome measures included. Outcomes outside of the testing hierarchy, such as HRQoL (an exploratory outcome in both studies), should be interpreted with consideration for the possible inflated type I error.

It is difficult to determine the magnitude of the treatment effect with romosozumab from the FRAME study. The comparator was placebo during the first 12-month treatment period. At month 24, patients treated with romosozumab followed by denosumab had 2 years of active treatment while those in the placebo followed by denosumab group had only 1 year of active treatment. Therefore, the groups had different risks of fracture and were likely not comparable.

There is limited direct evidence between romosozumab and relevant comparators with only a comparison with alendronate in the ARCH study to inform the comparative efficacy and safety of romosozumab versus other osteoporosis medications (see ITC limitations).

Indirect Comparisons

Description

The sponsor-submitted ITC aimed to evaluate the relative clinical efficacy of romosozumab to several treatments for osteoporosis, including denosumab, raloxifene, zoledronate, risedronate, and alendronate. Included studies enrolled postmenopausal women with primary osteoporosis or osteopenia who were at risk for developing fragility fractures. The outcomes analyzed were vertebral, hip, or nonvertebral fragility fractures.

Efficacy Results

The sponsor-submitted ITC used a frequentist network meta-analysis. The analysis found that romosozumab resulted in a reduction in risk of sustaining hip, nonvertebral, or vertebral fragility fractures compared with raloxifene, and a reduction in sustaining vertebral fractures compared with alendronate and risedronate. There were no differences between romosozumab and zoledronate or denosumab for any of the fracture outcomes.

Harms Results

Adverse events were not evaluated.

Critical Appraisal

Overall, 55 of 107 included RCTs had a high risk of bias. The risk of bias was high in most of the RCTs involving calcitonin, calcium, and vitamin D, as well as some older bisphosphonate trials. No RCTs were excluded based on the assessment of bias.

Clinical heterogeneity was present in the analysis due to varying study duration, blinding, dosage, fracture risk assessment, publication date, patient demographic and clinical characteristics, and clinical effect modifiers (e.g., calcium and vitamin D intake). The potential impact of these were not evaluated and adjusted for (where appropriate) in the ITC. Also, the FRAME and ARCH trials were pooled despite different patient populations and treatment regimens.

Some studies in the evidence network reported fractures by location without the "nonvertebral" label. In these cases, all the fractures, including hip and/or pelvis fractures, were considered nonvertebral. Therefore, incidences of the same hip fracture were used in the calculations of 2 different outcomes: the risk of sustaining hip fractures and the risk of sustaining nonvertebral fractures. This double counting reduced the comparability of the results for different outcomes and the overall internal validity of the ITC.

It was not explicitly stated in the ITC whether vertebral fractures were defined and assessed in the studies as symptomatic or non-symptomatic, which limits the generalizability of the synthesized results for vertebral fractures and the overall external validity of the ITC.

The definition of "placebo" was not provided; hence, it was not possible to know whether the definition for this intervention was consistent across studies.

Other Relevant Evidence

Description of Studies

The FRAME Extension Study enrolled patients after the 24-month primary analysis of the FRAME study. The study was designed as a 12-month open-label extension period in which patients continuing from the FRAME study remained on denosumab 60 mg every 6 months.

Efficacy Results

By month 36, all fracture locations (i.e., new vertebral, clinical, nonvertebral, major nonvertebral, new or worsening vertebral, hip, major osteoporotic, and multiple new or worsening vertebral) showed a decreased relative risk in fracture among patients treated initially with romosozumab followed by denosumab compared with patients treated initially with placebo followed by denosumab. The percent change in BMD at the lumbar spine, hip, and femoral neck from baseline to month 36 was also improved among patients in the romosozumab followed by denosumab group compared with patients in the placebo followed by denosumab group.

Harms Results

Adverse events occurred in similar frequencies across both treatment groups (88% in the romosozumab followed by denosumab group and 89% in the placebo followed by denosumab group). Serious adverse events were reported in 20% and 21% of patients in the romosozumab followed by denosumab group and placebo followed by denosumab group, respectively. Adverse events that led to treatment discontinuation were infrequently reported, occurring in 4% of patients in each treatment group. Fatal events were reported in 2% of patients in each treatment group.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	**Health Canada–approved population**: Postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture **OR** multiple risk factors for fracture **Reimbursement Request population**: Women with postmenopausal osteoporosis with a history of osteoporotic fracture **AND** who are at very high risk for future fracture **Those approved by Health Canada but not requested for reimbursement**: Women with postmenopausal osteoporosis with multiple risk factors for fracture **OR** prior fracture but who are not deemed very high risk for future fracture
Treatment	Romosozumab followed by alendronate
Comparators	Alendronate, denosumab, raloxifene, risedronate, zoledronate
Perspective	Canadian publicly funded health care payer
Outcomes	Number of fractures, QALYs, life-years
Time horizon	Lifetime (50 years)
Key data source	Effectiveness of comparators: network meta-analysis of osteoporosis randomized controlled trials Effectiveness of romosozumab came from the ARCH trial and the FRAME trial
Submitted results	• Health Canada population: Romosozumab followed by alendronate dominated all other treatments (i.e., romosozumab was less expensive and associated with more QALYs). • Requested reimbursement population: Romosozumab followed by alendronate dominated all other treatments.
Key limitations	• The sponsor assumed that the treatment benefit of romosozumab followed by alendronate, relative to all other pharmacologic treatments, lasted for 5 years after discontinuing alendronate. It is not clear that the evidence used to support this applies to the high-risk population used in the model. Additionally, there is no evidence on the long-term effect of romosozumab (one-time treatment for 1 year) and assuming a treatment effect of 9 years may be optimistic. Finally, there is no evidence on the long-term relative effect on fractures of alendronate or romosozumab compared to other treatments in the model. • The cost of long-term care after a fracture was assumed to be $184.96 daily or $67,000 annually. Because the cost of post-fracture long-term care was already included in the recurring direct medical costs related to fracture, this resulted in double counting. • The sponsor assumed excess mortality from fracture for 3 years after vertebral and hip fracture. Data from the ARCH and FRAME trials do not support a difference in mortality. The CADTH clinical expert felt there may be a mortality risk directly attributed to hip fractures. This mortality risk could last 1 year after a hip fracture due to limited mobility during this time. • The sponsor assumed a hip or vertebral fracture would always influence patients' utility with effects lasting up to 29 years. The utility values used in the model, obtained from an international study, showed a trend of improvement up to 18 months; however, the sponsor assumed no further improvement after 18 months. No evidence was found to support this assumption.

Component	Description
	• The CADTH clinical expert suggested that many physicians will administer romosozumab themselves as they currently do with denosumab and expect less than 10% of patients to self-administer romosozumab. • There is uncertainty regarding what proportion of patients that meets Health Canada indication would meet the specific requested reimbursement criteria. Values used in the cost-utility analysis lacked clinical plausibility and also did not match values used in the sponsor's BIA analysis.
CADTH reanalysis results	• To account for key limitations, several changes were made to the CADTH base case: there was no relative treatment effect after 5 years when all therapies are discontinued, the additional cost of long-term care was set to $0 because this was already included in the direct health care costs, mortality attributable to hip fracture was lowered, long-term quality-of-life consequences associated with hip fracture were decreased, cost of administration was increased, and the proportion of patients who have multiple risk factors with no prior hip or vertebral fracture history was increased. • Using the Health Canada indication, CADTH estimated that the sequential ICER associated with romosozumab followed by alendronate was $561,229 per QALY when compared with zoledronate ($6,295 in incremental costs, 0.011 incremental QALYs). The probability of romosozumab followed by alendronate being cost-effective at a $50,000 per QALY threshold was 0%. ◦ At this ICER, an 80% price reduction would be required to achieve an ICER below $50,000 per QALY. • In the reimbursement request population, CADTH estimated that the sequential ICER associated with romosozumab followed by alendronate was $219,799 per QALY when compared with zoledronate ($5,420 in incremental costs, 0.025 incremental QALYs). The probability of romosozumab followed by alendronate being cost-effective at a $50,000 per QALY threshold was 0%. ◦ At this ICER, an 53% price reduction would be required to achieve an ICER below $50,000 per QALY.

BIA = budget impact analysis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Budget Impact

The CADTH reanalysis of the sponsor BIA included updating the percentage of patients eligible for therapy and increasing the proportion of patients eligible for public drug plan coverage.

Based on the CADTH reanalyses, the budget impact of reimbursing romosozumab in the full Health Canada–indicated population is expected to be $179,247,490 in year 1, $227,606,038 in year 2, and $277,342,470 in year 3, for a 3-year total budget impact of $684,195,999. If it is only funded in the reimbursement-requested population, the budget impact decreases to $51,154,841 over 3 years.

CADTH Canadian Drug Expert Committee (CDEC) Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: September 22, 2021

Regrets: Two expert committee members did not attend.

Conflicts of interest: None