Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2280

romosozumab 105mg solution for injection in pre-filled pen (Evenity®)

UCB Pharma Ltd

9 October 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

romosozumab (Evenity®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

SMC restriction: to use in patients who have experienced a fragility fracture and are at imminent risk of another fragility fracture (within 24 months).

In a phase III study in post-menopausal women with osteoporosis who were at high risk of fracture, romosozumab for 12 months followed by an oral bisphosphonate reduced the risk of fractures compared with an oral bisphosphonate alone.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

Vice Chairman
Scottish Medicines Consortium

Indication

Romosozumab is indicated in the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.[1]

Dosing Information

The recommended dose is 210mg romosozumab (administered as two subcutaneous injections of 105mg each) once monthly for 12 months. To administer the 210mg dose, 2 subcutaneous injections of romosozumab should be given into the abdomen, thigh, or upper arm. The second injection should be given immediately after the first one but at a different injection site. If the romosozumab dose is missed, administer as soon as it can be feasible. Thereafter, the next romosozumab dose should not be given earlier than one month after the last dose. Patients should be adequately supplemented with calcium and vitamin D before and during treatment.

Patients treated with romosozumab should be given the package leaflet and the patient alert card. Following completion of romosozumab therapy, transition to antiresorptive therapy is recommended in order to extend the benefit achieved with romosozumab beyond 12 months. Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis.

Refer to the Summary of product characteristics (SPC) for further details.[1]

Product availability date

18 March 2020

Summary of evidence on comparative efficacy

Romosozumab is a monoclonal antibody that increases bone formation and decreases bone resorption by binding to and inhibiting sclerostin. This leads to increases in trabecular and cortical bone mass and improvements in bone structure and strength.

The submitting company has requested that SMC considers romosozumab when positioned for use in patients who have experienced a fragility fracture and are at imminent risk of another fragility fracture (within 24 months).

Key evidence for this indication is from ARCH, an international, multicentre, randomised, double-blind, phase III study. ARCH recruited ambulatory postmenopausal women aged 55 to 90 years who met at least one of the following criteria:

- a bone mineral density (BMD) T-score of -2.5 or less at the total hip or femoral neck and either one or more moderate or severe vertebral fractures or two or more mild vertebral fractures

or

- a BMD T-score of -2.0 or less at the total hip or femoral neck and either two or more moderate or severe vertebral fractures or a fracture of the proximal femur sustained 3 to 24 months before randomisation.[2]

Patients were randomised equally to receive subcutaneous romosozumab 210mg monthly (n=2,046) or oral alendronic acid 70mg weekly (n=2,047) for 12 months. Randomisation was stratified according to age (<75 versus ≥75 years). After completion of the double-blind period, all the patients received open-label oral alendronic acid 70mg weekly until the end of the study, with blinding to the initial treatment assignment maintained. All patients received calcium 500mg to 1000mg daily and ergocalciferol (vitamin D_2) or colecalciferol (vitamin D_3) 600IU to 800IU daily.[2]

The study had two primary outcomes, the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of clinical fracture (non-vertebral and symptomatic vertebral fracture) at the time of the primary analysis.[2, 3] The primary analysis was performed when clinical fracture events had been confirmed in at least 330 patients and all the patients had completed the month 24 visit. The data cut-off was 27 February 2017 after median follow-up of approximately 33 months. The study met both primary outcomes, demonstrating superiority of romosozumab followed by alendronic acid (romosozumab / alendronic acid) over alendronic acid alone.[2, 3] A hierarchical testing strategy was used for the key secondary outcomes. These included BMD at the lumbar spine, total hip, and femoral neck at 12 and 24 months and the incidence of non-vertebral fracture at the time of the primary analysis. Other fracture outcomes including hip fracture were evaluated as additional secondary outcomes. Gains in BMD from baseline at all measured sites and at all time points were greater in patients who received romosozumab / alendronic acid than those who received alendronic acid alone. Primary and selected secondary fracture outcome results are included in Table 1. Fracture outcomes at 12 months (double-blind period) generally favoured romosozumab over alendronic acid. These included new vertebral fracture, clinical fracture, and hip fracture.[2, 3]

Table 1: Primary and selected secondary outcomes of the ARCH study.[2, 3]

	Romosozumab / alendronic acid	Alendronic acid alone
Primary outcomes		
	n=1825	n=1834
New vertebral fractures at 24 months	6.2%	12%
Risk ratio	0.52 (95% CI: 0.40 to 0.66, p<0.001)	
	n=2046	n=2047
Incidence of clinical fracture at the time of the primary analysis	9.7%	13%

Hazard ratio	0.73 (95% CI: 0.61 to 0.88, p<0.001)	
Key secondary outcome		
Incidence of non-vertebral fractures at the time of the primary analysis	8.7%	10.6%
Hazard ratio	0.81 (95% CI: 0.66 to 0.99, p=0.04)	
Additional secondary outcome		
Incidence of hip fractures at the time of the primary analysis	2%	3.2%
Hazard ratio	0.62 (95% CI: 0.42 to 0.92, nominal p=0.02)	

CI: confidence interval

A post-hoc analysis of fracture events including new radiological vertebral, clinical vertebral and non-vertebral, non-vertebral, and hip fractures was carried out in a subpopulation of postmenopausal women with severe osteoporosis at high risk of fracture. Results at 12 months numerically favoured romosozumab over alendronic acid.[3]

STRUCTURE was a randomised, open-label, active-controlled, phase III study that recruited postmenopausal women with osteoporosis who had taken an oral bisphosphonate for at least 3 years before screening and alendronic acid the year before screening, BMD T-score of ≤–2.5 and a history of fracture (n=436). Patients were randomised equally to receive subcutaneous injections of 210mg romosozumab once monthly or 20micrograms teriparatide once daily. The primary outcome was the percentage change from baseline in areal BMD (mineral mass of bone per unit area) by dual-energy x-ray absorptiometry at the total hip to month 12 (mean of months 6 and 12). The mean percentage change from baseline in total hip areal BMD was significantly greater in the romosozumab group compared with the teriparatide group, 2.6% versus -0.6%, difference 3.2% (95% CI 2.7 to 3.8%, p<0.0001).[4, 5]

Twelve Bayesian network meta-analyses (NMA)/mixed treatment comparisons (MTC) were presented by the company comparing romosozumab against alendronic acid, risedronate, zoledronic acid, denosumab, raloxifene, and teriparatide in postmenopausal women with osteoporosis at increased risk of fracture. Twenty-nine studies were identified as being eligible for inclusion in the NMA. The reported outcomes of the analyses were vertebral fractures, non-vertebral fractures, clinical fractures, and hip fractures with networks being formed for 12, 24, and 36 months for each outcome. The results of the NMA were used to inform economic scenario analyses. There was variation in the results of the NMA for the different outcomes assessed. In summary, the results from the models estimate that romosozumab reduced the risk of fracture compared with some comparators; however more frequently no difference in fracture risk was identified as the credible intervals crossed one.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

An increased risk of cardiovascular events has been noted in the study programme for romosozumab, including an increase in adjudicated major adverse cardiovascular events in the key ARCH study.[2, 3] This was not seen in the large FRAME study. FRAME was a randomised, double-blind, placebo-controlled, phase III study of romosozumab in post-menopausal women with osteoporosis.[6] The European Medicines Agency (EMA) considered that serious cardiac events were the most important risk and other than that romosozumab had a risk profile that is expected for biological medicinal products. Romosozumab is therefore contra-indicated in patients with a history of myocardial infarction or stroke.[3]

In the 12 month double-blind treatment period, adverse events occurred in 76% (1544/2040) of the romosozumab group and 79% (1584/2014) of the alendronic acid group. In the romosozumab and alendronic acid groups respectively serious adverse events were reported in 13% and 14% of patients and adverse events leading to discontinuation of study treatment in 3.4% and 3.2%.[2] In the double-blind period, adjudicated major cardiovascular AEs were reported more frequently in the romosozumab group than the alendronic acid group, 2.5% versus 1.9% of patients in the respective groups. Cardiac ischaemic events were reported in 0.8% and 0.3% and cerebrovascular events were also reported in 0.8% and 0.3% of the groups.[2]

At the time of the primary analysis, after median 33 months of treatment (including both the double blind and open-label period where both groups received alendronic acid), adverse events had occurred in 87% of the romosozumab / alendronic acid group and 89% of the alendronic acid alone group. In the romosozumab / alendronic acid and alendronic acid alone groups respectively serious adverse events were reported in 29% and 30% of patients and adverse events leading to discontinuation of study treatment in 6.5% and 7.2%.[2] The most frequently reported treatment-emergent AEs in the romosozumab / alendronic acid group versus the alendronic acid group were: nasopharyngitis (12% versus 12%), headache (5.6% versus 5.9%), cough (3.9% versus 2.9%), and dyspepsia (2.8% versus 2.6%).[3]

In the 12 month double-blind period 1.5% (n=30) of patients died in the romosozumab group and 1% (n=21) in the alendronic acid group. The EMA noted that the overall numerical imbalance in deaths was mainly due to fatal cardiac disorders and neoplasms in the romosozumab group. At the time of the primary analysis, 4.4% of the romosozumab / alendronic acid group and 4.5% of the alendronic acid alone group had died (90 deaths in both groups).[3]

Summary of clinical effectiveness issues

Osteoporosis is characterised by low BMD and severe osteoporosis is defined as a T-score ≤-2.50 in lumbar spine or total hip with one or more fractures.[3] Alendronic acid, risedronate and zoledronic acid are recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or dual-energy X-ray absorptiometry (DXA)-proven osteoporosis. Zoledronic acid, ibandronic acid, denosumab,

hormone replacement therapy, tibolone, strontium ranelate, and raloxifene are alternative treatment options that may be considered. Teriparatide (parathyroid hormone 1-34) is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. In postmenopausal women with at least two moderate or one severe low-trauma vertebral fractures, teriparatide is recommended over oral bisphosphonates to prevent vertebral fracture.[5] The mechanism of action of romosozumab is novel and differs from teriparatide, currently the only other licensed bone-forming therapy available in the UK.

Clinical experts consulted by SMC considered that romosozumab fills an unmet need in this therapeutic area, namely prevention of further fractures in patients with severe postmenopausal osteoporosis. The submitting company has requested that SMC considers romosozumab when positioned for use in patients who have experienced a fragility fracture and are at imminent risk of another fragility fracture (within 24 months). Patients with a history of osteoporotic fracture are at increased risk of subsequent fracture, which is highest during the first 24 months following a fracture[7] and there is unmet need in this patient group.

The key ARCH study demonstrated superiority of romosozumab / alendronic acid over alendronic acid alone for the co-primary outcomes, incidence of new radiological vertebral fractures at 24 months and clinical fractures during the primary analysis period. Secondary outcomes were generally supportive including incidence of non-vertebral fractures and hip fractures at the time of the primary analysis. Fracture outcomes at 12 months (double-blind period) generally favoured romosozumab over alendronic acid. These included new vertebral fracture, clinical fracture, and hip fracture. Romosozumab increased BMD compared with alendronic acid at 12 and 24 months, measured at lumbar spine, total hip and femoral neck. Overall, the EMA considered that the efficacy of romosozumab seemed to be clinically relevant in the proposed target population of postmenopausal women with severe osteoporosis.

Hip fractures can be considered as the most serious consequence of osteoporosis, since these are associated with serious risks, potentially permanent disability and increased mortality. The incidence of hip fracture was an additional secondary outcome and not included in the statistical analysis plan. The reduction in non-vertebral fractures was small and not statistically significant at 12 or 24 months. However, at the time point of the primary analysis, romosozumab / alendronic acid had reduced non-vertebral fractures compared with alendronic acid alone. The low number of non-vertebral fractures may have impaired the detection of an effect of romosozumab on these fractures.

The inclusion criteria of the ARCH study varied slightly from the WHO definition of severe osteoporosis. The ARCH study did not include pre-specified subgroup analyses in patients who had experienced their prior fracture within 24 months, in line with the proposed positioning.

The comparator in the ARCH study was alendronic acid, a recommended treatment option for this indication. In addition, the STRUCTURE open-label study compared romosozumab with teriparatide in postmenopausal women with osteoporosis who had been receiving oral

bisphosphonates. The submitting company presented indirect treatment comparisons versus other potential comparators. The population included in the analyses was wider than the requested positioning of patients who have experienced a fragility fracture and are at imminent risk of another fragility fracture (within 24 months). There was variation in the baseline characteristics of patients and methodology of the studies included in the networks, and heterogeneity in the reporting of fracture outcomes across the studies included in the NMA. These limitations lead to uncertainty in the interpretation of the results.

Clinical experts consulted by SMC considered that romosozumab is a therapeutic advancement due to the novel mechanism of action and efficacy. They considered that the introduction of this medicine may impact on the patient and service delivery as it is administered as a monthly subcutaneous injection. Patients would need to be taught how to administer the injection themselves or it would require to be given by a healthcare professional.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing romosozumab followed by alendronic acid to alendronic acid alone for treatment of severe osteoporosis in postmenopausal women at high risk of fracture, with the company proposing romosozumab for use in patients who have experienced a fragility fracture and are at imminent risk of another fragility fracture (within 24 months). SMC clinical experts indicated that oral bisphosphonates would be the preferred treatment and alendronic acid is a relevant comparator, though teriparatide would likely be used for severe osteoporosis and is the treatment most likely to be displaced by romosozumab.

The economic analysis used an individual patient-level micro-simulation model with five health states (at risk, hip fracture, vertebral fracture, non-hip/non-vertebral fracture, and death). The model used a six month cycle and adopted a lifetime horizon of 26 years (up to 100 years of age), with patients entering the model at a mean age of 74 years. The patients included in the base case analysis were postmenopausal women with severe osteoporosis and a fragility fracture, who had a recent major osteoporotic fracture (MOF) within 24 months, and a 10-year MOF probability of 30%.

The clinical data for romosozumab/ alendronic acid were taken from the double-blind, randomised, phase III ARCH study, which informed the key parameters in the economic model, including patient baseline characteristics (age, body mass index (BMI), femoral neck T-score), and adverse events. Baseline risk fracture and incidence was based on a published study, general population fracture risk, and an increased risk due to osteoporosis and age. A fracture risk reduction for each treatment was based on efficacy estimates from the ARCH study or NMA. Bayesian NMAs, as described above, were conducted to enable comparisons with bisphosphonates risedronate and zoledronic acid, as well as raloxifene, teriparatide and denosumab. The company stated that there were limitations with the NMAs hence the results for the comparisons between romosozumab/ alendronic acid and the additional comparators were

presented as scenario analyses. Hazard ratios from the ARCH study, or from a NMA, were estimated for each fracture type to estimate the fracture risk for treatments.

The company apply an 'offset time' to estimate efficacy for each treatment beyond treatment duration, assuming anti-fracture efficacy persists for the same time beyond treatment discontinuation as the treatment duration received as a linear decline until it reaches no effect over the offset time. Beyond efficacy modelled over the offset period, no further efficacy from treatment is assumed and patients follow disease natural history.

Duration of treatment for romosozumab was based on the SPC, which states a duration of 12 months treatment followed by anti-resorptive therapies. The duration of treatment for alendronic acid was up to 3 years following romosozumab or up to 4 years in the comparator arm. The proportion of patients on treatment for the specified maximum treatment durations was modified using persistence rates from the ARCH trial or real world data.

EQ-5D data were collected in ARCH but were not used in the economic analysis due to treatment-specific quality of life data being collected at predetermined, discrete time points irrespective of fracture occurrence during the trial and was not considered sensitive to a decrease in quality of life after a fracture and may underestimate the potential quality of life gain with treatment. Instead, HRQoL was included in the economic analysis by applying utility multipliers to UK general population utility values. Utility multipliers were included for hip, vertebral and non-hip/ non-vertebral fractures, sourced from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS). Disutilities for adverse events were included as a one-off decrement only, applied at the start of treatment with bisphosphonate medication.

Costs included medicine acquisition, medicine administration, concomitant medication/ treatment initiation, disease management, health state monitoring associated with fractures and nursing home stays, and treatment of adverse events. Resource use relating to monitoring whilst on therapies and disease management, such as nursing home care following a hip fracture, were included and based on published estimates from Denmark and Sweden.

All-cause, age-specific mortality was included in the model for the Scottish general population and accounted for excess mortality due to fractures and co-morbidities.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

In the base case for romosozumab/ alendronic acid versus alendronic acid the incremental cost-effectiveness ratio (ICER) is estimated at £35,284 per quality adjusted life year (QALY) using the list price for romosozumab. Romosozumab/ alendronic acid was estimated to increase survival

compared to alendronic acid alone. The main driver of increased costs was additional medicine acquisition costs for romosozumab.

Deterministic sensitivity analysis showed that the ICER was most sensitive to variation in the starting age, time horizon, treatment offset periods, risk of fracture, and utility multipliers for year 2+. The key sensitivity analyses are presented in table 2. All parameters in the model were not varied in one-way sensitivity analysis but it did identify key uncertainties in the model.

Table 2: Selected sensitivity analysis results (romosozumab/ alendronic acid vs alendronic acid)

	Scenario Analysis	**ICER (list price)**
	Base case	£35,284
1	10 year time horizon	£48,186
2	Starting patient age of 65 years	£64,532
3	Starting patient age of 70 years	£32,030
4	Offset time of 5 years	£51,586
5	Offset time of 3 years	£50,479
6	Offset time of 1 year	£48,014
7	RR romosozumab hip fracture – upper 95% CI	£130,577
8	RR alendronate hip fracture – upper 95% CI	dominant
9	RR alendronate vertebrae fracture – upper 95% CI	£19,163
10	Vertebrae utility fracture utility multiplier – upper 95% CI	£53,738
CI = confidence interval, ICER = incremental cost effectiveness ratio, RR = risk ratio		

Due to limitations with the available head-to-head efficacy evidence and the NMAs, the company presented scenario analyses versus other comparators that may be relevant in Scottish clinical practice (Table 3).

Table 3: Base case results for romosozumab (followed by alendronic acid) versus alternative comparators

Comparator	**ICER (list price)**
Teriparatide (24 months)	dominant
Teriparatide (18 months)	dominant
Raloxifene (48 months)	£12,727
Denosumab (lifetime)	£89,633
Risedronate (48 months)	£45,595
Zoledronic acid (48 months)	£42,091
ICER = incremental cost effectiveness ratio, LY = life year, NR = not reported, PAS = patient access scheme, QALY = quality-adjusted life year	

The economic analysis was associated with a number of weaknesses and uncertainties:

- There is no direct clinical evidence for romosozumab/ alendronic acid versus some potentially relevant comparators. Whilst an NMA was conducted to estimate the efficacy between romosozumab/ alendronic acid and these comparators, as noted above, the NMA had some limitations and leads to uncertainty. Teriparatide was considered a potentially

relevant comparator but whilst the ICER was favourable for romosozumab/ alendronic acid the NMA results suggest there was no significant difference between these two treatment arms due to confidence intervals crossing 1 for all fractures and at all time points. A cost-minimisation approach assuming equal efficacy for the comparison with teriparatide was subsequently provided by the company.

- The efficacy estimates applied in the model from ARCH for romosozumab/ alendronic acid versus alendronic acid are for the full patient population in the study, rather than the proposed population in the economic analysis. However, additional information provided by the company suggested the cost-effectiveness results based on the proposed positioning would be similar to the overall population.
- The ICER is sensitive to variations in key efficacy parameters estimating the risk of hip or vertebrae fractures for both romosozumab/ alendronic acid and alendronic acid, and also the longer-term efficacy assumptions relating to 'offset period'. This leads to higher ICERs above usual cost-effectiveness acceptability thresholds.
- The lifetime horizon leads to increased uncertainty due to long extrapolation beyond trial data, and shorter durations of 10 years leads to an increased ICER.

Despite these issues, the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The Royal Osteoporosis Society, which is a registered charity.

- The Royal Osteoporosis Society has received 9% pharmaceutical company funding in the past two years, including from the submitting company.

- Osteoporosis is a condition where bones lose strength. The risk of fracture is significantly increased in those with osteoporosis. Spinal fractures cause pain, height loss and curvature of the spine. Hip fractures can cause decreased mobility and lack of independence. Hip and spinal fractures can severely affect quality of life and decrease life expectancy.

- The vast majority of patients with osteoporosis are treated with oral bisphosphonates. Some may be intolerant of these due to side effects, particularly gastrointestinal upset. In addition, the use of oral bisphosphonates is limited by certain co-morbidities and a proportion of patients on oral bisphosphonates will sustain further fractures despite treatment.

- Romosozumab is a subcutaneous injection administered monthly for 12 months and therefore avoids the need to take medication orally and the side effects of this. It can be self-administered which could decrease GP/hospital appointments. The reduction in the risk of vertebral and clinical fractures would improve the quality of life of patients. Romosozumab is also important to patients and carers because it offers a treatment option for those who cannot take existing options, offering hope. A disadvantage is that the treatment only lasts for

one year and then patients will be required to change onto a different treatment which may be confusing for some patients/carers.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published clinical guidance entitled Management of osteoporosis and the prevention of fragility fractures (SIGN 142) in March 2015 and published a revised edition in June 2020.[5] This guidance makes the following key recommendations:

- People with a history of fragility fractures over the age of 50 should be offered DXA scanning to evaluate the need for anti-osteoporosis therapy.
- Fracture-risk assessment should be carried out, preferably using QFracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom anti-osteoporosis treatment is being considered.
- Measurement of bone mineral density by DXA at the spine and hip should be carried out following fracture-risk assessment in patients in whom anti-osteoporosis treatment is being considered.
- Repeat BMD measurements by DXA after an interval of three years may be considered to assess response to treatment in postmenopausal women.
- Patients over the age of 50 who have experienced a fragility fracture should be managed within a formal integrated system of care that incorporates a fracture liaison service.

The SIGN guideline includes a treatment algorithm entitled "*Pathway from risk factors to pharmacological treatment selection in postmenopausal women*" which recommends the order of treatments based on the assessment of risk.[5]

Alendronic acid, risedronate and zoledronic acid are recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis. Zoledronic acid is recommended to prevent further fractures in postmenopausal women with recent hip fractures who are unable or unwilling to take oral osteoporosis treatments, without undertaking BMD measurements if these are felt to be inappropriate or impractical. Zoledronic acid may also be considered to reduce risk of clinical fractures in women over 65 years of age who have osteopenia at hip or femoral neck on DXA. Oral ibandronic acid (150mg monthly) may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis. Intravenous ibandronic acid (3mg every three months) may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis who are intolerant of oral therapy or those in whom adherence to oral therapy may be difficult.

Strontium ranelate may be considered for the treatment of severe postmenopausal osteoporosis to reduce the risk of vertebral and non-vertebral fractures in patients without established cardiovascular disease when other treatments are contraindicated.

Denosumab is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with DXA-proven osteoporosis for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions. Following discontinuation of denosumab, transition to an antiresorptive therapy should be considered, with the aim of preventing the rebound increase in bone turnover.

Teriparatide (parathyroid hormone 1-34) is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. In postmenopausal women with at least two moderate or one severe low-trauma vertebral fractures, teriparatide is recommended over oral bisphosphonates, to prevent vertebral fracture. As teriparatide discontinuation is associated with bone loss, treatment with an antiresorptive agent should be considered to maintain the increase in bone density once a course of teriparatide has been completed.

Hormone replacement therapy may be considered for the prevention of vertebral, nonvertebral and hip fractures in younger postmenopausal women.

Tibolone may be considered to prevent vertebral and non-vertebral fractures in younger postmenopausal women, particularly those with menopausal symptoms.

Raloxifene may be considered as a treatment option for the prevention of vertebral fractures in postmenopausal women when other treatments are contraindicated or unsuitable.

The guidance also notes that romosozumab has gained marketing authorisation within the UK and Europe. A decision from the SMC on its use in NHSScotland is awaited before a recommendation can be made.[5]

The UK National Osteoporosis Guideline Group (NOGG) published the UK Clinical guideline for the prevention and treatment of osteoporosis[8] in 2008. This guidance was updated in 2017 and recommends alendronic acid or risedronate as the first line treatment for the majority of women with postmenopausal osteoporosis. In patients intolerant of oral treatment of with a contraindication the guidance recommends that intravenous bisphosphonates or denosumab are the most appropriate alternatives, followed by additional alternatives raloxifene or hormone replacement therapy. The NOGG guidance states that teriparatide treatment should be restricted to patients at very high risk of fracture, especially vertebral fractures, due to its high cost. The guidance recommends that treatment should be reviewed after 3 years for patients receiving zoledronic acid and after 5 years for patients receiving oral bisphosphonate treatment. Furthermore, the guideline recommends that treatment beyond 3 to 5 years can normally be recommended in patients ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while, on treatment, and those taking oral glucocorticoids. The NOGG guidance also recommends that if "*treatment is discontinued, fracture risk should be reassessed after a new fracture, regardless of when this occurs. If no new fracture occurs, assessment of fracture risk should be performed again after 18 months to 3 years*."[8]

Additional information: comparators

Bisphosphonates (including alendronic acid, risedronate, zoledronic acid, and ibandronic acid), teriparatide and denosumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
romosozumab	210mg once monthly by subcutaneous injection for 12 months.	5,133

Costs from BNF online on 06 July 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. UCB Pharma Limited. Romosozumab solution for injection in pre-filled pen/syringe. Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 16/12/2019.
2. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T*, et al.* Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. New England Journal of Medicine. 2017;377(15):1417-27.
3. The European Medicines Agency (EMA) European Public Assessment Report. Romosozumab (Evenity®). 17.10.19, EMEA/H/C/004465/0000. www.ema.europa.eu.
4. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS*, et al.* Romosozumab (Sclerostin Monoclonal Antibody) Versus Teriparatide in Postmenopausal Women with Osteoporosis Transitioning from Oral Bisphosphonate Therapy: A Randomised, Open-Label, Phase 3 Trial. Lancet. 2017;390(10102):1585–94. Epub 2017/08/02.
5. Scottish Intercollegiate Guidelines Network (SIGN). Management of osteoporosis and the prevention of fragility fractures.(SIGN 142). 2015. Available at: https://www.sign.ac.uk/assets/sign142.pdf.
6. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S*, et al.* Romosozumab Treatment in Postmenopausal Women with Osteoporosis. The New England journal of medicine. 2016;375(16):1532–43. Epub 2016/11/01.
7. Pinedo-Villanueva R, Charokopou M, Toth E, Donnelly K, Cooper C, Prieto-Alhambra D*, et al.* Imminent Fracture Risk Assessments in the UK FLS Setting: Implications and Challenges. Archives of Osteoporosis. 2019;14(1):12.
8. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N*, et al.* UK clinical guideline for the prevention and treatment of osteoporosis. Archives of osteoporosis. 2017;12(1):43.

This assessment is based on data submitted by the applicant company up to and including 14 August 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment

process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.