HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
10 MARCH 2021
The legally binding text is the original French opinion version

romosozumab
EVENITY 105 mg solution for injection in pre-filled pen

First assessment

Key points

Favourable opinion for reimbursement in the treatment of severe postmenopausal osteoporosis only in women aged < 75 years with a history of severe fracture and in the absence of a history of coronary heart disease.

Unfavourable opinion for reimbursement in women with postmenopausal osteoporosis aged ≥ 75 years or < 75 years with a history of coronary heart disease.

What therapeutic improvement?

No clinical added value in the therapeutic strategy on the basis of currently available data.

Role in the care pathway?

The aim of osteoporosis treatment is to prevent the occurrence of fractures by reinforcing the solidity (or resistance) of bone tissue and by preventing falls.

The treatment decision is based on the fracture risk, which depends on the existence of a history of fracture due to bone fragility and the bone mineral density (BMD), as well as other risk factors.

Before any specific treatment is prescribed, any vitamin D and/or calcium deficiency should be corrected (particularly in the oldest patients), by adjusting dietary intake and/or medicinal supplementation. In addition, physical exercise and fall prevention are part of the overall management strategy for osteoporosis patients.

Medicinal fracture-prevention treatment is indicated only in the event of a high fracture risk (a BMD with a T-score < -2.5 but greater than - 3 is not sufficient to decide to initiate treatment). Patients with a high fracture risk are defined as those having had a fracture due to bone fragility or, in the absence of a fracture, patients with a marked reduction in bone density (T score < - 3) or with a T score ≤ - 2.5 combined with other fracture risk factors, in particular age > 60 years, previous or current systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day of prednisone equivalent, a BMI < 19 kg/m², a history of femoral neck extremity fracture in a first-degree relative, an early menopause (before the age of 40 years).

The care pathway in postmenopausal osteoporosis (PMO) is described in Annex 2.

In women with severe postmenopausal osteoporosis with a history of severe fracture, the recommended treatments are:

- bisphosphonates (zoledronate, alendronate, risedronate),
- denosumab, only during second-line therapy as follow-on treatment after bisphosphonates,
- and teriparatide, only in women having had at least two vertebral fractures.

In women aged under 70 years, with no venous thromboembolism risk factors, with spinal osteoporosis, at low risk of femoral neck fracture (absence of the following risk factors: femoral T-score < - 3, high fall risk, history of non-vertebral fracture), raloxifen may also be used to reduce the vertebral fracture risk.

Role of the medicinal product in the care pathway

Considering:

- demonstration of the superiority of EVENITY (romosozumab) treatment, administered for 12 months followed by alendronate compared to alendronate alone, on the fracture risk (vertebral fractures, clinical fractures and non-vertebral fractures) in women with severe osteoporosis and a history of severe fracture during first-line treatment (ARCH study),

- demonstration of the superiority of EVENITY (romosozumab) compared to teriparatide, only in terms of BMD (interim endpoint), in women previously treated with bisphosphonates, i.e. from the second line of treatment (STRUCTURE study),

- uncertainties concerning the safety due to higher risks of death and serious cardiovascular events (myocardial infarction and stroke) demonstrated in women treated with romosozumab in the ARCH study,

- but subgroup analyses suggesting a reduction in the absolute risk in women aged < 75 years and in women with no history of myocardial infarction/stroke or coronary heart disease (including revascularisations and hospitalisations for unstable angina) as well as safety results contradicting those of the FRAME study (placebo-controlled, conducted in younger women with less severe osteoporosis), which did not find any difference between the groups.

the Transparency Committee considers that, on the basis of currently available data, the proprietary medicinal product EVENITY (romosozumab) is a new therapeutic option to be used only in postmenopausal women aged < 75 years with severe osteoporosis and a history of severe fracture and in the absence of a history of coronary heart disease (including revascularisations and hospitalisations for unstable angina).

In view of the available data demonstrating an excess risk of mortality and serious cardiovascular events in women aged ≥ 75 years or with a history of coronary heart disease, EVENITY (romosozumab) has no role in the care pathway for these patients.

The Committee reiterates that this treatment is contraindicated in women with a history of myocardial infarction and stroke and highlights the importance of assessing the cardiovascular risk factors before

initiating treatment (in particular, hypertension, hyperlipidaemia, diabetes, smoking, severe renal impairment, etc.). If in doubt, a cardiological opinion should be sought.

In accordance with the SPC for EVENITY (romosozumab), the Committee also reiterates that:
- treatment discontinuation should be followed by a switch to bisphosphonates,
- prescription is reserved for osteoporosis treatment specialists.

◗ Special recommendations

The Committee reiterates that this treatment is contraindicated in women with a history of myocardial infarction and stroke and highlights the importance of assessing the cardiovascular risk factors before initiating treatment (in particular, hypertension, hyperlipidaemia, diabetes, smoking, severe renal impairment, etc.). If in doubt, a cardiological opinion should be sought.

In accordance with the SPC for EVENITY (romosozumab), the Committee also reiterates that:
- treatment discontinuation should be followed by a switch to bisphosphonates,
- prescription is reserved for physicians specialised in osteoporosis treatment.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Osteoporosis is a condition for which the seriousness is related to the fracture risk. Severe fractures, particularly femoral neck fractures, can seriously impair quality of life and are associated with excess mortality. The occurrence of a fracture is also a risk factor for repeat fracture, particularly if the fracture is recent.

◗ EVENITY (romosozumab) is a preventive treatment for osteoporotic fractures in women at high risk of fractures.

◗ Its efficacy/adverse effects ratio is high in women with postmenopausal osteoporosis aged < 75 years, with a history of severe fracture and in the absence of a history of coronary heart disease, given subgroup analyses suggesting a reduction in the absolute risk of serious cardiovascular events and the risk of mortality in these patients and the demonstration of the efficacy of romosozumab compared to alendronate on the vertebral, clinical and non-vertebral fracture risk (ARCH study) in patients with a history of severe fracture.
The efficacy/adverse effects ratio of EVENITY (romosozumab) cannot be determined in women aged ≥ 75 years or < 75 years with a history of coronary heart disease given the excess risk of serious cardiovascular events and mortality identified in these patients.

◗ There are medicinal alternatives (see section 06 of this opinion).

◗ EVENITY (romosozumab) is a treatment to be used only in postmenopausal women aged < 75 years with severe osteoporosis and a history of severe fracture and in the absence of a history of coronary heart disease (see section 09 of this opinion).

Public health impact

Considering:
- the seriousness of severe fractures, which impair quality of life, reduce mobility and are life-threatening, as reported by patient associations,
- the prevalence of osteoporosis,

- the medical need for alternatives given the limitations of the available treatments, particularly in terms of long-term efficacy, safety, contraindications, maximum recommended or possible use duration and compliance,
- the partial response to the identified medical need in women aged < 75 years in the absence of a history of coronary heart disease, given subgroup analyses suggesting a reduction in the absolute risk of serious cardiovascular events in these patients and the demonstration of the efficacy of romosozumab compared to alendronate on the fracture risk in patients with a history of severe fracture in the ARCH study,
- the absence of response to the identified medical need in the other MA situations (i.e. in women aged ≥ 75 years or < 75 years with a history of coronary heart disease), given the excess risk of serious cardiovascular events identified in these patients,
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway in the absence of robust quality of life data,
- the lack of any demonstrated impact on the organisation of care (hospitalisation, AE, etc.)

EVENITY (romosozumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of EVENITY (romosozumab) is:

- **substantial only in postmenopausal women aged < 75 years with severe osteoporosis and a history of at least one severe fracture, in the absence of a history of coronary heart disease (including revascularisations and hospitalisations for unstable angina),**
- **insufficient to justify public funding cover in view of the available alternatives in the other situations.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication "treatment of postmenopausal women aged < 75 years with severe osteoporosis and a history of severe fracture and with no history of coronary heart disease (including revascularisations and hospitalisations for unstable angina)" and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication "treatment of postmenopausal women with severe osteoporosis and a history of severe fracture aged ≥ 75 years or < 75 years with a history of coronary heart disease" and at the MA dosages.

- **Recommended reimbursement rate: 65% (only for women aged < 75 years with a history of severe fracture and with no history of coronary heart disease)**

Clinical Added Value

<u>In women aged < 75 years with a history of severe fracture and with no history of coronary heart disease</u>
Considering:

- **demonstration of the superiority of EVENITY (romosozumab) treatment administered for 12 months followed by alendronate compared to alendronate alone in women with severe osteoporosis and a history of severe fracture during first-line treatment (ARCH study, 4,093 patients randomised), particularly in terms of the incidence of:**
  - **new vertebral fractures at 24 months (primary endpoint; 4.1% vs 8.0%; Δ = 3.9%; $CI_{95\%}$ [3.50; 5.57]; RR = 0.50; OR = 0.48; p < 0.001),**
  - **clinical fractures (clinical non vertebral or vertebral fractures) on the main analysis with a median follow-up of 33 months (primary endpoint; 9.7% vs 13.0%; Δ = 3.3%; HR = 0.73; $CI_{95\%}$ [0.61; 0.88]; p < 0.001) and,**
  - **non-vertebral fractures on the main analysis (ranked secondary endpoint; 8.7% vs 10.6%; Δ = 1.9%; OR = 0.81; $CI_{95\%}$ [0.66; 0.99]; p = 0.019)**
    but taking into account:
- **the absence of clinical data relative to the fracture risk in women previously treated with bisphosphates (i.e. receiving second or later-line treatment) in the STRUCTURE study,**
- **the exploratory nature of the data on the high and serious risk of femoral neck extremity fracture in the ARCH study (non-ranked secondary endpoint),**
- **the absence of any conclusion that can drawn based on the quality of life results given the exploratory nature of the analyses,**
- **and the absence of long-term safety data,**

the Transparency Committee considers that EVENITY (romosozumab) provides a minor clinical added value (<u>CAV IV</u>) compared to alendronate in postmenopausal women aged < 75 years with severe osteoporosis and a history of at least one severe fracture and no history of coronary heart disease.

<u>In other patients</u>
Not applicable