BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

PROTELOS (strontium ranelate), anti-osteoporosis agent

The Committee does not recommend reimbursement due to the insufficient clinical benefit in severe osteoporosis.

Main points

- PROTELOS now has Marketing Authorisation only in patients at high risk of fracture, for whom treatment with other medicinal products approved for osteoporosis is not possible due to, for example, contraindications or intolerance.
- Recent new data has shown an increase in the arterial cardiovascular risk. This new risk is in addition to the known life-threatening venous thromboembolic risks and serious hypersensitivity syndromes (Drug Rash with Eosinophilia and Systemic Symptoms or DRESS).
- Some doubt remains concerning its efficacy in the rare patients that might use it.

Pre-existing indication

- PROTELOS also has Marketing Authorisation in the treatment of osteoporosis in adult men. This summary does not cover this indication.

Therapeutic use

- Osteoporosis is defined as a T score ≤ -2.5 in the absence of all other causes of demineralised or fragile bone disease. The aim of treatment for osteoporosis is to prevent fractures. Osteoporosis is classified as severe when a patient has experienced at least one osteoporotic fracture.
- Before starting any osteoporosis treatment, the patient should be tested for deficiency in calcium and vitamin D and have any such deficiency corrected. Vitamin and/or calcium replacement must be continued during osteoporosis treatment if needed.
- Treatment is prescribed as a matter of routine in cases of osteoporosis complicated by fracture.
- In the absence of a direct comparison between the different first-line medicinal products used to treat osteoporosis (bisphosphonates, raloxifene, and teriparatide), the choice of treatment is determined by the risk of vertebral and/or nonvertebral fracture, age, the number and localisation of fractures, and possible contraindications to one or more of these medicinal products.
- Bisphosphonates, denosumab, and strontium ranelate have been shown to reduce the risk of vertebral and hip fractures.
- If a fracture occurs after the first year of treatment despite satisfactory compliance, treatment must be reconsidered. A different medicinal product may be proposed, which could be one from the same pharmacological class.

Clinical data

- Cardiovascular events (primarily myocardial infarction) were recently shown to occur with a relative risk of 1.6 (4 per 1000 patients) in a pooled analysis of all development studies and confirmed by pharmacovigilance data. These effects are in addition to the venous thromboembolic effects (including pulmonary embolism) known since the initial assessment, for which the relative risk is 1.42, and to DRESS, a very rare, but life-threatening condition that has been reported since market launch.
In the initial studies, efficacy had been demonstrated in studies of vertebral fractures (absolute risk reduction versus placebo of 9.34% in the risk of fracture after 4 years, \( p < 0.001 \)) and nonvertebral fractures (absolute risk reduction of 2.3% in the risk of fracture after 5 years, \( p < 0.001 \)). A reduction of 3% in hip fracture was demonstrated in a subgroup of the most high-risk patients (T score \( \leq -2.4 \) SD and age \( \geq 74 \) years).

To establish whether the initial efficacy persists in the population restricted to female patients with severe osteoporosis and with no contraindication associated with venous or arterial risk, the applicant submitted a new multivariate post-hoc analysis. In this analysis, PROTELOS was not found to be effective against hip fracture in any of the subgroups, including patients with and without cardiovascular risk. However, these data, which were obtained in post-hoc studies of subgroups with small patient populations, do not permit any conclusions to be drawn about the efficacy of PROTELOS in the subgroup of patients corresponding to the new indication.

Similarly, post-hoc analyses were carried out to compare cardiovascular risk and mortality in all osteoporosis female patients and in lower-risk populations. In the population restricted to female patients without cardiovascular risk and with severe osteoporosis, no increased cardiovascular risk versus placebo was found. It is possible, however, that the fact that no difference was found may be attributable to the lack of statistical power, owing to the small number of patients.

There are no data for the patients who showed no response or had a contraindication to all the other osteoporosis medicines or versus the active comparator.

**Benefit of the medicinal product**

* The actual benefit* of PROTELOS is insufficient in the new indication in postmenopausal women to justify reimbursement by National Health Insurance.
* Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

---

This document was created on the basis of the Transparency Committee Opinion of 09 July 2014 (CT-12966) and is available at [www.has-sante.fr](http://www.has-sante.fr)

---

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient insufficient for reimbursement by the National Health Insurance.

© Haute Autorité de Santé 2015