HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

9 July 2014

PROTELOS 2 g, granules for oral suspension

B/28 sachets (CIP: 34009 365 170 3 5)
B/56 sachets (CIP: 34009 565 830 7 2)

Applicant: SERVIER

INN	Strontium ranelate
ATC Code (2013)	M05BX03 (Drugs affecting bone structure and mineralisation)
Reason for the review:	**Re-assessment of the actual benefit at the request of the DGS [Directorate-General for Health], in accordance with article R 163-19 of the French Social Security Code.** **Variations to the SPC (indication, contraindications and precautions for use)**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"Treatment of severe osteoporosis:** **- in postmenopausal women,** **- […]** **at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. In postmenopausal women, PROTELOS reduces the risk of vertebral and hip fractures.** **The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks."**

Actual Benefit	**The actual benefit of PROTELOS in the new indication of the Marketing Authorisation is insufficient to justify reimbursement by National Health Insurance.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Marketing Authorisation of 21 September 2004 (centralised procedure, rapporteur state: Sweden) 25 May 2012: Changes to the Marketing Authorisation in the sections: - Contraindications (addition of venous thromboembolic events, VTE and immobilisation) - Warnings about the risk of VTE and DRESS) - Adverse effects 27 June 2012: Extension of the indication to the "treatment of osteoporosis in adult men at high risk of fracture". 21 June 2013: Changes to the Marketing Authorisation in the sections: - Indications (restriction to severe osteoporosis in patients at high risk of fracture) - Method of administration - Contraindications - Warnings - Adverse effects 15 April 2014: Restriction of the indication of the Marketing Authorisation to severe osteoporosis in patients at high risk of fracture in whom other alternative treatments do not exist. Medicine subject to enhanced monitoring since 2007
Prescribing and dispensing conditions /special status	List I

ATC Classification	2013	
	M	Musculo-skeletal system
	M05	Drugs for treatment of bone diseases
	M05B	Drugs affecting bone structure and mineralisation
	M05BX	Other drugs affecting bone structure and mineralisation
	M05BX03	strontium ranelate

02 BACKGROUND

In 2011 (renewal of inclusion of 11 May 2011) the Committee, owing to the risk of occurrence of DRESS and venous thromboembolic events associated with PROTELOS, had assessed its actual benefit as moderate. The Committee had restricted the scope of reimbursement to the treatment of postmenopausal osteoporosis in patients at increased risk of fracture in whom bisphosphonates are contraindicated or not tolerated and who have no history of venous thromboembolic events or other risk factors for venous thromboembolism, in particular being over 80 years of age.

In 2013 an increased risk of myocardial infarction was identified from clinical study data. This new risk is in addition to the risk of venous thromboembolic events and DRESS[1] already identified. A re-assessment of the relative risks and benefits was instigated by the PRAC in April 2013.

Following its initial recommendations in April 2013, the indication for strontium ranelate was restricted on 21 June 2013 to the treatment of severe osteoporosis in patients at increased risk of fracture. In addition, from this date, new contraindications were added to the SPC for patients with arterial cardiovascular disease and the precautions for use were strengthened for patients with risk factors for cardiovascular events.

After re-assessing the relative benefits and risks of PROTELOS, in January 2014 the PRAC recommended the suspension of its Marketing Authorisation. In February 2014, the CHMP decided not to follow this recommendation and suggested further narrowing the indication to when "treatment with other medicinal products approved for the treatment of osteoporosis is not possible" and asked the company to submit studies demonstrating compliance with these measures and evidence of their efficacy in reducing adverse effects in routine use.

In addition, in May 2013, following the PRAC recommendations, the Directorate-General for Health asked the Transparency Committee to re-assess the actual benefit and scope of reimbursement of this proprietary medicinal product.

This medicinal product has now been re-assessed on the basis of the dossier supplied by the applicant and the conclusions of the CHMP published in February 2014 following the PRAC recommendations.

It should be noted that, in 2012, the Marketing Authorisation had been extended to the "treatment of osteoporosis in adult men at high risk of fracture". In the absence of the submission of a dossier in support of the application for inclusion on the list of reimbursed products for this new indication, osteoporosis in men is not assessed in this Opinion.

03 THERAPEUTIC INDICATIONS

"Treatment of **severe** osteoporosis:

- **in postmenopausal women,**
- in adult men,[2]

at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.
In postmenopausal women, PROTELOS reduces the risk of vertebral and hip fractures.

The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks."

04 PRINCIPAL CHANGES TO THE SPC

Posology
The recommended dose is one 2 g sachet once daily by oral administration.

[1] DRESS: Drug Rash with Eosinophilia and Systemic Symptoms. This is a severe hypersensitivity syndrome.
[2] Indication in humans not examined by the Committee.

Method of administration

[…] Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
Temporary or permanent immobilisation due to e.g.post-surgical recovery or prolonged bed rest.
Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
Uncontrolled hypertension.

Precautions for use

[…] Cardiac ischaemic events:
In pooled randomised placebo-controlled studies of postmenopausal osteoporotic patients, a significant increase in the risk of myocardial infarction has been observed in PROTELOS treated patients compared to placebo.
Before starting treatment, patients should be evaluated with respect to cardiovascular risk.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.
Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled.
[…]

05 THERAPEUTIC NEED

Osteoporosis is defined as a T score ≤ -2.5 in the absence of any other causes of demineralising or bone-weakening osteopathy. The aim of treatment of osteoporosis is to prevent fractures.
According to the WHO, 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 any such deficiency corrected. Vitamin and/or calcium replacement must be continued during osteoporosis treatment if needed.

According to the AFSSAPS recommendations published in January 2006, 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 medicinal products used to treat osteoporosis (bisphosphonates, raloxifene, teriparatide and strontium ranelate), the choice of treatment has been determined up to now by the risk of vertebral and non-vertebral fracture, age, the number and localisation of fractures and the predisposition of the patient, as well as possible contraindications to one or more of these medicinal products.

Only 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.

Osteoporosis medicinal products are taken on a long-term basis and all types have a tendency to cause adverse effects necessitating permanent discontinuation of the drug. It is therefore useful to have a wide range of available treatments.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

PROTELOS is the only medicinal product in the strontium ranelate class indicated in osteoporosis and is the only medicinal product indicated in severe osteoporosis as a second-line treatment.

The following bisphosphonates are indicated in the treatment of postmenopausal osteoporosis and have all demonstrated their efficacy in the prevention of both vertebral and non-vertebral fractures, including femoral neck fractures.

Name (INN) *Company*	Indication	Date of last Opinion/AB	IAB (wording)
ACLASTA 5 mg (1 tablet/day) 35 mg (1 tablet/week) 75 mg (2 tablets/month) 5 mg IV (1 infusion/year) Zoledronic acid NOVARTIS PHARMA SAS	Treatment of osteoporosis: - in postmenopausal women - […] at increased risk of fracture, including those with a recent low-trauma hip fracture.	3 October 2007 Substantial AB	IAB V compared with ACTONEL (2005)
ACTONEL 5 mg (1 tablet/day) Risedronic acid WARNER CHILCOTT FRANCE		25 October 2010 Substantial AB	IAB III (2000)
ACTONELCOMBI Risedronic acid 35 mg + calcium 1000 mg + vitamin D 880 IU (1 tablet/week)	Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.	19 December 2013 Substantial AB	IAB V (2007)
FOSAMAX Tablets 10 mg (1 tablet/day), 70 mg (1 tablet/week) Alendronic acid *MERCK SHARP & DOHME CHIBRET*	Treatment of postmenopausal osteoporosis. FOSAMAX reduces the risk of vertebral and hip fractures.	21 July 2010 Substantial AB	IAB III (1997)
FOSAVANCE and ADROVANCE Tablets (exact copy) 1 tablet/week Combination of risedronic acid + vitamin D MERCK SHARP & DOHME-CHIBRET and IPSEN PHARMA	Treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency who are not receiving vitamin D supplements. This product reduces the risk of vertebral and hip fractures	21 July 2010 Substantial AB	IAB V (2005)

*Therapeutic category.

Other classes of medicinal product are indicated in osteoporosis.

Name (INN) *Company*	Indication	Date of last Opinion/AB	IAB (wording)
FORSTEO* 1 injection/day Teriparatide Exception drug status LILLY France SAS	Treatment of osteoporosis in: postmenopausal women and […]. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.	22 July 2009 Substantial	IAB IV (2009) compared with bisphosphonates administered orally
PROLIA*** 1 injection/6 months Denosumab AMGEN	Treatment of postmenopausal osteoporosis in women at increased risk of fractures. PROLIA significantly reduces the risk of vertebral, non-vertebral and hip fractures	16 November 2011 Substantial	IAB IV (2004) as second-line treatment as alternative to bisphosphonates
EVISTA Raloxifene 1 tablet/day DAIICHI SANKYO FRANCE SAS	Treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.	17 October 2012 Substantial	IAB V (2000) compared with HRT
OPTRUMA Raloxifene 1 tablet/day Pierre Fabre Médicament	Treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.	17 October 2012 Substantial	IAB V (2000) compared with HRT

* FORSTEO is reimbursed only if at least two fractures have occurred.
** The other medicinal products are reimbursed only in patients with osteoporosis complicated by at least one fracture.
*** Of these four proprietary medicinal products, only PROLIA has demonstrated its efficacy in the prevention of both vertebral and non-vertebral fractures, including femoral neck fractures.

◗ Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

PROTELOS is registered in 74 other countries outside Europe, but is not registered in Japan, the United States or Canada.

In Europe it is reimbursed in 25 countries, but not in Malta or Poland. In almost half of these there are restrictions on the scope of reimbursement or on prescribers.

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion	2 March 2005
Reason for review	Inclusion
Indication	Treatment of postmenopausal osteoporosis. PROTELOS reduces the risk of vertebral fracture.
AB	**Substantial**
IAB	Despite the absence of direct comparative studies, the Transparency Committee assessed the efficacy and safety of PROTELOS compared with medicinal products indicated in the management of postmenopausal osteoporosis. In women under 80 years of age, studies carried out with PROTELOS demonstrated an efficacy against vertebral and non-vertebral fractures of broadly the same order as that observed in the available studies with bisphosphonates (risedronate, alendronate). In terms of adverse effects, although PROTELOS appears to cause more venous thromboembolic events, it appears to show better gastrointestinal and renal tolerability. PROTELOS is an alternative to bisphosphonates, including when these are not recommended or are contraindicated. It does not cause renal failure. In conclusion, in this population PROTELOS provides a minor improvement in actual benefit (level IV) in the management of these patients. The Committee notes the uniqueness of the active substance and its mechanism of action. In the population of patients over 80 years of age, PROTELOS is the first medicinal product that has been shown to be beneficial in reducing vertebral and hip fractures. In this population of elderly women, the most common adverse effects are likely to be venous thromboembolic events and nervous system disorders. In this population, PROTELOS provides a moderate improvement in actual benefit (level III) compared with standard management of these patients (bisphosphonates)."
Scope of reimbursement	No restriction

Date of opinion	5 July 2006
Reason for review	Redefinition of the scope of reimbursement
Scope of reimbursement	Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. - in patients who have had a fracture due to bone fragility, - in the absence of fractures, in women with a substantial decrease in bone density (T score < -3) or with a T score ≤ -2.5 associated with other risk factors for fracture, in particular age > 60 years, past or present systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day of prednisone equivalent, body mass index < 19 kg/m², history of femural neck fractures in a first-degree relative (mother), premature menopause (before the age of 40 years).

Date of Opinion 11 May 2011
Reason for review Renewal of inclusion

AB

Because of its concerns regarding the risk of occurrence of DRESS and venous thromboembolic events, the Transparency Committee considers that the actual benefit of PROTELOS is **moderate** in the population limited to:

- patients in whom bisphosphonates are contraindicated or are not tolerated,
- patients with no risk factors for venous thromboembolic events (history of venous thromboembolic events, age over 80 years, immobilisation, etc.).

IAB

Like bisphosphonates (alendronate, risedronate, zoledronate), PROTELOS has demonstrated its efficacy in the prevention of vertebral and non-vertebral fractures, including femoral neck fractures. However, safety data reveal a risk of venous thromboembolic events and a risk of serious hypersensitivity syndrome (DRESS), the occurrence of which is difficult to predict. In the light of these points it does not seem appropriate, given the available therapeutic alternatives, to retain the improvement in actual benefit for this product. The Transparency Committee consequently considers that PROTELOS does not provide any improvement in actual benefit (level V) in the management strategy for postmenopausal osteoporosis.

Scope of reimbursement

Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures in patients at increased risk of fractures:

- in whom bisphosphonates are contraindicated or are not tolerated,
- with no history of venous thromboembolic events or other risk factors for venous thromboembolism, in particular being over 80 years of age.

Patients considered to be at increased risk of fracture are:

- patients who have had a fracture due to bone fragility,
- in the absence of fractures, women with a substantial decrease in bone density (T score < -3) or with a T score ≤ -2.5 associated with other risk factors for fracture, in particular age > 60 years, past or present systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day of prednisone equivalent, body mass index < 19 kg/m², history of femural neck fractures in a first-degree relative (mother), premature menopause (before the age of 40 years).

09 ANALYSIS OF AVAILABLE DATA

The applicant was asked to submit:

- the available new efficacy data, in particular comparative data versus other osteoporosis medicinal products,
- recent safety data on known adverse effects and cardiac effects,
- data on the risk of atypical fractures,
- data specific to the population benefiting the most from this product.

09.1 Efficacy

The applicant has submitted only a multivariate analysis on the SOTI and TROPOS studies.

In the PRAC report, a pooled analysis of all the available randomised data for the population restricted to patients corresponding to the 2013 indication (severe osteoporosis without contraindications) was examined.

In the dossier submitted at the request of the Committee, the applicant presented no new clinical efficacy study, in particular no new comparative data versus another osteoporosis medicinal product.

The definition of severe osteoporosis used in this dossier is the WHO definition:

- BMD ≤ -2.5 irrespective of bone site measured and at least one prior fragility fracture.

This definition likewise remains in use by the EMA.

9.1.1 Initial data

To recap, the initial efficacy data were based on two clinical studies, SOTI and TROPOS, which were randomised double-blind placebo-controlled studies over a 3-year period in osteoporosis in postmenopausal women. These studies were subsequently extended to 5 years. The primary endpoint was the number of patients with documented new fractures (vertebral for the SOTI study and non-vertebral for TROPOS). The conclusions of the Committee were:

- an absolute reduction versus placebo in the risk of vertebral fracture of 9.34%, $p < 0.001$ after 4 years (this was 11.9% after 3 years);
- an absolute reduction in the risk of non-vertebral fracture of 2.3%, $p < 0.001$ after 5 years (this was 1.8% after 3 years);
- efficacy data in terms of prevention of hip fractures from a post-hoc analysis of a subgroup of patients at high risk of hip fracture (T score ≤ -2.4 SD (level III in the NHANES classification) and aged ≥ 74 years. In this subgroup of patients with a mean age of 83 years, PROTELOS achieved a 2.1% reduction versus placebo in the absolute risk of hip fracture after 3 years. The reduction in this risk after 5 years was 3% ($p = 0.036$).

9.1.2 Pooled analysis submitted to the EMA

For the re-assessment of the relative benefits and risks by the EMA, the applicant had submitted a new post-hoc pooled analysis of all the available efficacy data from randomised placebo-controlled studies, which comprised seven phase II and phase III studies in postmenopausal osteoporosis. Two of these, SOTI and TROPOS, were phase III studies, and the other five were phase II studies with smaller patient populations. A total of 7572 patients were included (3803 treated with strontium ranelate and 3769 with placebo).

This new analysis, which was originally intended to provide answers to questions concerning safety, also allowed the EMA to analyse the efficacy findings within various subgroups (according to population under consideration and according to fracture type) with the objective of determining whether efficacy was still observed in the different subgroups.

Various populations were examined: women with postmenopausal osteoporosis, patients with a contraindication[3] (arterial or venous risk) and patients with severe osteoporosis at increased risk of fracture. The principal efficacy findings in these populations are as follows:

[3] The contraindications for the purposes of this analysis were the contraindications introduced in the SPC in June 2013 relating to the prevention of arterial or venous cardiovascular risk:

- Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
- Temporary or permanent immobilisation due to e.g. recovery from surgery or prolonged bed rest.
- Current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Uncontrolled hypertension.

Table 1: Pooled results of seven clinical studies

Efficacy of PROTELOS in postmenopausal osteoporosis in various subgroups.

		PMO		Without CI		Without CI without warnings		Severe OP		Severe OP without CI without warnings	
		N = 7572	PY = 22519	N = 4040	PY = 11690	N = 3030	PY = 8898	N = 3744	PY = 11312	N = 1445	PY = 4373
		SR N = 3803 PY = 11269	Placebo N = 3769 PY = 11250	SR N = 2035 PY = 5860	Placebo N = 2005 PY = 5829	SR N = 1519 PY = 4456	Placebo N = 1513 PY = 4442	SR N = 1865 PY = 5332	Placebo N = 1879 PY = 5680	SR N = 718 PY = 2193	Placebo N = 727 PY = 2179
Assessment of the risk of:											
Non-vertebral fracture	N	3748	3711	2010	1975	1505	1489	1839	1849	711	717
	n [%]	427 (11.4)	492 (13.3)	218 (10.9)	240 (12.2)	160 (10.6)	180 (12.1)	269 (14.6)	293 (15.9)	102 (14.4)	100 (14.0)
	PY	36.7	42.1	36.1	36.9	34.9	39	45.9	49.3	44.7	43.8
	OR [95% CI]	0.841 [0.733; 0.966]		0.879 [0.724; 1.069]		0.865 [0.690; 1.085]		0.910 [0.760; 1.089]		1.033 [0.767; 1.392]	
	p	0.014		0.196		0.209		0.303		0.829	
Hip fracture	N	3748	3711	2010	1975	1505	1489	1839	1849	711	717
	n [%]	111 (3.0)	114 (3.1)	58 (2.9)	52 (2.6)	48 (3.2)	40 (2.7)	67 (3.6)	60 (3.2)	29 (4.1)	17 (2.4)
	PY	9.5	9.8	9.6	9.6	10.5	8.7	11.4	10.1	12.7	7.4
	OR [95% CI]	0.963 [0.739; 1.256]		1.099 [0.752; 1.606]		1.193 [0.780; 1.827]		1.127 [0.791; 1.607]		1.751 [0.953; 3.216]	
	p	0.781		0.627		0.416		0.507		0.071	
Major non-vertebral fracture	N	3748	3711	2010	1975	1505	1489	1839	1849	711	717
	n [%]	330 (8.8)	390 (10.5)	166 (8.3)	186 (9.4)	121 (8.0)	137 (9.2)	211 (11.5)	218 (11.8)	75 (10.6)	71 (9.9)
	PY	28.4	33.5	27.6	30.8	26.4	29.8	36.1	36.9	33	31.3
	OR [95% CI]	0.822 [0.705; 0.959]		0.86 [0.695; 1.078]		0.863 [0.668; 1.114]		0.970 [0.793; 1.186]		1.073 [0.762; 1.511]	
	p	0.013		0.198		0.258		0.764		0.687	
Vertebral fracture	N	2917	2939	1588	1599	1175	1205	1488	1514	587	597
	n [%]	507 (17.4)	661 (22.5)	269 (16.9)	355 (22.2)	205 (17.5)	251 (20.8)	386 (25.9)	462 (30.5)	158 (26.9)	167 (28.0)
	PY	48.5	63.7	49.3	64.8	50.5	60.7	70.8	85.8	74.8	80
	OR [95% CI]	0.725 [0.637; 0.825]		0.715 [0.599; 0.853]		0.803 [0.654; 0.986]		0.798 [0.680; 0.935]		0.948 [0.735; 1.224]	
	p	< 0.001		< 0.001		0.036		0.005		0.684	

PMO: Total population with postmenopausal osteoporosis

CI: Contraindications

OP: Osteoporosis

PY: Number of patients per 1000 patient-years

SR: Strontium ranelate

Severe OP : Severe osteoporosis, defined as a T score ≤ -2.5 and at least one previous fracture

The following comments can be made based on the results presented in this table:

- In the general population, strontium ranelate shows efficacy only in vertebral and non-vertebral fractures, but not in hip fractures.
- In the subgroup of patients without contraindications and that of patients with severe osteoporosis, efficacy was demonstrated only in vertebral fractures. In these subgroups, efficacy against other types of fracture was not demonstrated.

The principal criticisms are that this was a post-hoc analysis on a contentious selection of studies (heterogeneity of the studies: phase II and III with clinical and nonclinical endpoints, variable duration of the studies). The fact that the analysis was carried out on subgroups defined post hoc to conform to a restricted indication can lead to false-positive results. Similarly, results may be negative owing to a lack of statistical power resulting from the reduced patient populations. These results must therefore be interpreted with extreme caution.

9.1.3 New multivariate analysis of the initial studies

The applicant has carried out a multivariate analysis defined post hoc on the pooled data of the SOTI and TROPOS studies described in the initial evaluation dossier, in accordance with the comments of the CHMP.

The SOTI study related to vertebral fractures and the TROPOS study to non-vertebral fractures.
The studies examined the variation in the occurrence of fracture as a function of the presence of contraindications[2] concerning arterial or venous risk or the severity of the osteoporosis. The primary endpoints of this analysis were the incidence of clinical osteoporotic fracture and the incidence of morphometric vertebral fractures.
A total of 6374 patients were included, of whom 51% had severe osteoporosis and 50% had a contraindication.

The global efficacy findings presented in the evaluation dossier are as follows:

Table 2: Pooled phase III studies – Global efficacy versus placebo

	HR[1]	95% CI	p
Clinical osteoporotic fractures	0.80	0.71-0.91	< 0.001
Non-vertebral osteoporotic fractures	0.84	0.72-0.98	0.028
Morphometric vertebral fractures	0.60	0.52-0.69	< 0.001
Hip fractures	0.95	0.70-1.28	> 0.30

[1] HR: Hazard ratio.

The findings presented according to severity and presence of a contraindication are as follows:

Table 3: Pooled phase III studies – Efficacy according to presence of a contraindication

	With contraindications		Without contraindication	
	HR[1]	95% CI	HR[1]	95% CI
Clinical osteoporotic fractures	0.78	0.66-093	0.84	0.70-1.00
Morphometric vertebral fractures	0.61	0.50-0.74	0.60	0.49-0.72
Hip fractures	0.94	0.61-1.45	0.96	0.63-1.46

Table 4: Pooled phase III studies – Efficacy according to severity of osteoporosis

	With severe osteoporosis		Non-severe osteoporosis	
	HR[1]	95% CI	HR[1]	95% CI
Clinical osteoporotic fractures	**0.84**	**0.72-0.98**	**0.76**	**0.61-0.94**
Morphometric vertebral fractures	**0.65**	**0.56-0.76**	**0.47**	**0.35-0.63**
Hip fractures	**1.14**	**0.76-1.70**	**0.78**	**0.49-1.23**

No significant difference relating to fracture type was observed between the subgroups with and without contraindications ($p > 0.30$) or between the subgroups with and without severe osteoporosis ($p = 0.10$).

In this new subgroup analysis, PROTELOS was not found to show efficacy against hip fractures (it should be noted that, in the initial studies, efficacy had been demonstrated in a subgroup of patients aged 74 years and over).

09.2 Adverse effects

As a consequence of the adverse effects profile, a risk management plan (RMP) has been in place since the 2004 assessment.

9.2.1 Known adverse effects

9.2.2 Nervous system disorders

The initial clinical studies, had reported central nervous system disorders, in particular disturbances of consciousness (2.5% with strontium ranelate versus 2.0% with placebo), memory loss (2.4% with strontium ranelate versus 1.9% with placebo) and seizures (0.3% with strontium ranelate versus 0.1% with placebo).
In April 2004, the PRAC judged that these known effects did not necessitate any new measures.

9.2.3 Venous thromboembolic events

In the initial clinical studies, the incidence of venous thromboembolic events after 3 years was 9.2/1000 patient-years with PROTELOS versus 6.1/1000 patient-years, with a relative risk of 1.42 ([95% CI: 1.02; 1.98] $p = 0.036$).

The 2011 analysis of safety data from clinical studies extended to 5 years, from pharmacoepidemiological studies and from pharmacovigilance data confirmed an increased incidence in venous thromboembolic events including pulmonary embolism. The cause of these events is unknown.

It was found that the thromboembolic risk associated with PROTELOS was promoted by the presence of thromboembolic risk factors and that this was greatest in patients over 80 years of age. This led in 2012 to the addition to the SPC of a contraindication if thromboembolic risk factors are present and a warning for patients aged ≥ 80 years.

9.2.4 DRESS

The SPC states that life-threatening skin reactions, such as Stevens-Johnson syndrome (very rare), toxic epidermal necrolysis (very rare) and DRESS (drug rash with eosinophilia and systemic symptoms) have been reported in patients treated with PROTELOS.

According to the latest pharmacovigilance data,[4] there have been approximately 3.4 million patient-years of treatment with strontium ranelate worldwide. Among these patients there have been 2074 reported cases of hypersensitivity, 71 cases of DRESS confirmed as at least possibly attributable to strontium ranelate and 21 confirmed cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.

9.2.5 Other effects

The adverse effects most commonly reported during clinical development were nausea and diarrhoea, which are typically reported at the start of treatment. Mild muscle pain and minor CK elevations have been also reported.

Cases of hepatitis and bone marrow failure have also been reported. Their frequency is unknown.

9.2.6 Cardiac events

9.2.7 PSUR data

Routine assessment of the periodic safety update report (PSUR) covering the period 22 September 2011 to 21 September 2012 identified a risk of cardiac events associated with PROTELOS. An increased risk of serious cardiac events of 4/1000 patient-years was found. These data originated mainly from pooled results of studies carried out during development.

Following the PRAC opinion of April 2013, the SPC of PROTELOS was amended to restrict the target population of PROTELOS: limitation of the indication to severe osteoporosis, contraindications in persons with cardiovascular disease and warnings recommending monitoring of risk factors.

9.2.8 Pooled data from clinical studies

In its report re-assessing the relative benefits and risks, the PRAC examined the pooled data from all the randomised studies carried out during the development of PROTELOS. The cardiovascular risk was examined in the population of the indication of the original Marketing Authorisation and in the population corresponding to restriction of the indication to severe osteoporosis and taking into account the contraindications[2] introduced in 2013. The table below presents the results for the principal adverse effects.

[4] PRAC report of 20 August 2013.

Table 5: Cardiovascular adverse effects in various target populations

		PMO[1] N = 7572		PMO without CI N = 5640		Severe OP without CI[2] N = 1952	
		SR[3] n = 3803	Placebo n = 3769	SR n = 2035	Placebo n = 2005	SR n = 975	SR n = 977
Serious cardiac events	Incidence n [%]	*262 (6.9)*	*215 (5.7)*	*83 (4.1)*	*73 (3.6)*	*42 (4.3)*	*40 (4.1)*
	PY[5]	*23.2*	*19.1*	*14.2*	*12.5*	*14.4*	*13.8*
	OR [95% CI]	*1.22 [1.2; 1.48]*		*1.13 [0.82; 1.57]*		*1.05 [0.67; 1.64]*	
	p	*0.034*		*0.443*		*0.833*	
Myocardial infarction[4]	Incidence n [%]	*64 (1.7)*	*40 (1.1)*	*15 (0.7)*	*15 (0.7)*	*5 (0.5)*	*6 (0.6)*
	PY	*5.7*	*3.6*	*2.6*	*2.6*	*1.7*	*2.1*
	OR [95% CI]	*1.60 [1.07; 2.38]*		*0.99 [0.48; 2.04]*		*0.86 [0.26; 2.86]*	
	p	*0.020*		*0.988*		*0.807*	
Cardio-vascular death	Incidence n [%]	*80 (2.1)*	*81 (2.1)*	*28 (1.4)*	*29 (1.4)*	*13 (1.3)*	*12 (1.2)*
	PY	*7.1*	*7.2*	*4.8*	*5.0*	*4.5*	*4.1*
	OR [95% CI]	*0.98 [0.71; 1.34]*		*0.96 [0.57; 1.61]*		*1.07 [0.49; 2.36]*	
	p	*0.887*		*0.866*		*0.864*	
Sudden death	Incidence n [%]	*18 (0.5)*	*30 (0.8)*	*5 (0.2)*	*12 (0.6)*	*2 (0.2)*	*5 (0.5)*
	PY	*1.6*	*2.7*	*0.9*	*2.1*	*0.7*	*1.7*
	OR [95% CI]	*0.59 [0.33; 1.06]*		*0.41 [0.14; 1.17]*		*0.39 [0.08; 2.03]*	
	p	*0.076*		*0.085*		*0.248*	

[1] PMO : Total population with postmenopausal osteoporosis
[2] CI: Contraindication according to 2013 SPC
[3] SR: Strontium ranelate
[4] Strict definition of the MedDRA classification
[5] PY: Number of patients per 1000 patient-years
[6] Severe OP: Severe osteoporosis, defined as a T score ≤ -2.5 and at least one previous fracture

The incidence of cardiovascular events (OR = 1.22, 95% CI [1.2; 1.48], p = 0.034) and myocardial infarction (OR = 1.60, 95% CI [1.07; 2.38], p = 0.02) was significantly higher in the original population. There is no apparent significant difference in the restricted population, but this was a post-hoc study on a smaller population and the statistical analysis carried out is unable to quantify rare events.
These data do not therefore allow any conclusions to be drawn regarding the effectiveness of the restrictions to the SPC in limiting the risk of adverse effects.

9.2.9 Retrospective case-control study in the British CPRD database

This was a retrospective case-control study carried out using data from the British CPRD database[5].This study was proposed by the CHMP as part of the risk management plan, to document the risk of cardiac ischaemia. The protocol was approved in July 2012.
A nested case-control analysis in a cohort of newly treated women was carried out with the objective of examining the association between PROTELOS and ischaemic cardiac events (primary endpoint). The ischaemic cardiac events examined were first definite myocardial infarction, infarction resulting in hospitalisation and cardiovascular death. Incident cases were matched to six to ten controls. The same analysis was carried out with alendronate.

The results are shown in the table below:

[5] CPRD: Clinical Practice Research Datalink. Database containing anonymised medical data from more than 10 million patients monitored by British general practitioners.

Table 6: CPRD study – Association of alendronate/PROTELOS and ischaemic cardiac events

	First definite MI (1) Cases = 1336 / Controls =13,330 Adjusted OR and [95% CI]	**MI with hospitalisation** Cases = 1433 / Controls = 14,261 Adjusted OR and [95% CI]	**Cardiovascular death** Cases = 3516 / Controls = 34,982 Adjusted OR and [95% CI] (1)
PROTELOS			
Never	1 (reference)	1 (reference)	1 (reference)
Current	*1.05 [0.69; 1.62]*	*0.84 [0.54; 1.30]*	*0.96 [0.76; 1.21]*
Past	*1.12 [0.79; 1.58]*	*1.17 [0.83; 1.66]*	*1.16 [0.94; 1.43]*
Alendronate			
Never	1 (reference)	1 (reference)	1 (reference)
Current	*0.98 [0.83; 1.15]*	*0.85 [0.73; 0.99]*	*0.80 [0.72; 0.88]*
Past	*1.09 [0.92; 1.30]*	*1.17 [0.99; 1.37]*	*1.11 [1.01; 1.23]*
Current			
Alendronate	1 (reference)	1 (reference)	1 (reference)
PROTELOS	*1.13 [0.74; 1.73]*	*1.12 [0.72; 1.74]*	*1.27 [1.00; 1.61]*
Past			
Alendronate	1 (reference)	1 (reference)	1 (reference)
PROTELOS	*0.83 [0.48; 1.43]*	*1.00 [0.61; 1.63]*	*1.01 [0.76; 1.33]*

MI: Myocardial infarction.(1)

Adjusted for region, duration of follow-up, obesity, tobacco consumption, socioeconomic status, cardiovascular treatments by class (statins, fibrates, beta-blockers, calcium-channel blockers, medicinal products acting on the renin-angiotensin system, diuretics, other antihypertensives, nitrates, platelet-aggregation inhibitors), antidiabetic treatments, hormone replacement therapy, calcium and vitamin D replacement, other osteoporosis drugs, history of MI (MI with hospitalisation).

This study found no increase in the risk of myocardial infarction and cardiovascular mortality associated with use of PROTELOS in women treated for osteoporosis by British general practitioners.

As regards the controls, it would have been interesting to know whether this study found thromboembolic effects, the existence of which is not discussed.

9.2.10 Data on atypical fractures

The applicant was asked to provide data on atypical fractures.

According to the American Society for Bone and Mineral Research (ASBMR), for a fracture to be considered atypical, it must be localised on the femoral shaft between the subtrochanteric region and its distal third, associated with no or minimal trauma, such as a fall from the patient's standing height, and be of transverse or short oblique configuration and not comminuted.

Such fractures have been described primarily in patients treated with bisphosphonates. They are rare and may be promoted by strong and prolonged suppression of bone remodelling. Such fractures have also been recently described with denosumab (PROLIA).

The mechanism of action of PROTELOS, which reduces bone resorption and increases bone formation, is different to that of bisphosphonates and denosumab, suggesting that such fractures would not necessarily be expected.
In clinical studies carried out with PROTELOS, there have been no reported cases of atypical fracture, even after long-term follow-up of 237 patients for up to 10 years. No cases of atypical fracture have been reported in pharmacovigilance databases.

09.3 EMA conclusions

9.3.1 PRAC assessment of 9 January 2014

Strontium ranelate is associated with serious risks: cardiac risk, in particular myocardial infarction, severe skin reactions, disturbances of consciousness, seizures, hepatitis, etc. In controlled studies there were four cardiac events per 1000 patient-years, of which two were myocardial infarction. The number of thromboembolic events was four per 1000 patient-years.

The applicant has submitted a new post-hoc subgroup analysis assessing the impact of the contraindications of the SPC covering arterial and venous cardiovascular risk. The decrease in the number of patients has reduced the statistical power of the study. Doubts remain about the meaningfulness of the measures to minimise risk given the methodological limitations of this analysis (post-hoc analysis, reduced statistical power, rareness of observed adverse events).

The PRAC expressed some serious concerns about the practical difficulties in taking account of thromboembolic and cardiac risk factors as a consequence of a possible deterioration over time in the cardiovascular condition of patients, who are generally elderly.

In addition, the PRAC consulted an ad-hoc group of experts. Some experts believe that PROTELOS could be beneficial to a subgroup of patients and the group of experts took the view that if PROTELOS were to remain available, it could be prescribed only as second-line treatment in patients with severe osteoporosis who are unable to tolerate other osteoporosis treatments.

In the analysis of the pooled placebo-controlled studies, PROTELOS showed a reduction of 15 vertebral fractures, 5 non-vertebral fractures and 0.4 hip fractures per 1000 patient-years (results not significant). The magnitude of the effect was thus modest, particularly in more serious fractures. Non-vertebral fractures were mainly fractures of the ribs, pelvis or humerus. This new analysis raises the question whether the magnitude of the effects observed in the initial studies is maintained in restricted patient population.

Given the serious risks identified, uncertainty as to whether they can realistically be kept in check in the long term, and the modest efficacy, the PRAC concluded that the benefits did not justify the risks and recommended suspension of the Marketing Authorisation.

9.3.2 CHMP conclusions of 28 February 2014

The CHMP confirms the risks associated with strontium ranelate, including the increase in serious ischaemic cardiac events observed in postmenopausal women.

Although the CHMP accepts there are some uncertainties concerning the retrospective subgroup analysis submitted, it considers that the study clearly demonstrates a tendency for cardiovascular risk to be neutralised when the population is restricted to patients with severe osteoporosis without contraindications, thus showing that the measures to minimise risk previously implemented are effective in reducing identified cardiovascular risk in postmenopausal women.

The CHMP appreciates that compliance with all measures to minimise risk is very difficult in practice, but, as members of an ad-hoc group of experts have noted, repeated assessment of risk should not be considered impractical in clinical practice.

Taking together all the risks associated with strontium ranelate, the CHMP considers that it is appropriate to restrict use to patients for whom treatment with a different medicinal product is not possible, e.g. because of intolerance or contraindications.

The CHMP would like the applicant to carry out a post-inclusion safety study in the new target population in order to evaluate compliance with the new restrictions, collect new safety data, and evaluate the efficacy of the measures to minimise risk.

The analysis of the pooled data from all the studies in postmenopausal women was considered relevant for the analysis of safety. However, the CHMP considers that the efficacy against fractures needs to be examined in an analysis based only on clinical studies in which the primary endpoint was fracture. This being so, the level of benefit of strontium ranelate in the prevention of fractures is unchanged.

09.4 Prescription data

According to IMS data (moving annual total winter 2013), 122,000 prescriptions have been issued for the proprietary medicinal product PROTELOS in private practice. The reason for prescription was osteoporosis in 92% of cases. The dosage instructions were complied with in 99% of cases where they were specified.

A telephone survey was conducted by the applicant in 2013 to assess prescribers' level of understanding of the contraindications and precautions for use (the most recent, dated April 2012). This was a declarative survey on the purpose of prescriptions and does not provide any relevant information as regards the practical details of the prescription of PROTELOS. Among the results of this study, 98.4% of French doctors said that, in the event of hypersensitivity to the product, they would stop treatment with PROTELOS and 93.4% of doctors said they would do the same if patients had a current or past thromboembolic event.

09.5 Final report of the post-inclusion study requested by HAS

The Transparency Committee has requested a post-inclusion study on PROTELOS (Opinion of 02/03/2005 and in the amendment of the CEPS [Healthcare Products Pricing Committee] of 13/12/05). The wording of this request was as follows:
"The Transparency Committee requests the performance of an observational study of patients treated with PROTELOS, in particular patients over 80 years of age. The objective of this study would be to assess, under the conditions of routine and long-term use, the impact of treatment with PROTELOS in terms of morbidity and in particular the frequency of thromboembolic complications. The Committee would like the interim results of this study to be available within 2 years."
In response to this request, the applicant has instituted a multicentre study in seven European countries, with follow-up for 3 years of patients treated with PROTELOS.
The interim results of this study were included in the TC Opinion on PROTELOS in 2011 and corresponded to data collected on 08/01/2010.

The final report of this study has been submitted. The principal findings are as follows:
This cohort study carried out between March 2006 and June 2011 involved 853 centres in seven different European countries: Austria (21 centres, 279 patients included), France (276 centres, 2182 patients), Germany (204 centres, 4665 patients), Italy (114 centres, 1867 patients), the Netherlands (48 centres, 374 patients), Spain (179 centres, 3257 patients) and the United Kingdom (11 centres, 78 patients).
A total of 32,446 patients were included in a register and 12,702 in a cohort, of which 12,046 had had at least one follow-up visit.
The population of the register comprised women who had consulted a doctor and in whom osteoporosis treatment (of any kind) had been initiated. The cohort was made up of patients on the register in whom treatment with strontium ranelate had been initiated in the 6 months preceding the inclusion visit.

The mean age of the patients in the cohort was 69 years (± 10.3 years) and 16.5% of patients were aged 80 years or over.

The mean age of these patients at menopause was 48.4 (± 4.7 years). Among the patients in the cohort, 2.4% had had a previous venous thromboembolic event (1.9% a deep vein thrombosis and 0.7% a pulmonary embolism).
A total of 77% of patients presented a risk factor for osteoporosis: previous fracture, lack of physical exercise (26.1%), familial history of osteoporosis (20.7%), inadequate calcium intake (17.9%).
In addition, 59.1% of patients were taking calcium/vitamin D supplements on inclusion.

The mean femoral T score on inclusion was -2.07 ± 0.86 (min = -4.0 and max = 2.0) and the mean vertebral T score was -2.53 ± 0.85 (min = -4.0 and max = 5.4).

During follow-up, 7.4% of patients suffered a new fracture: 2.5% a vertebral fracture and 3.6% a non-vertebral fracture.

Of the patients in the cohort, 36.3% stopped their treatment with PROTELOS: 12.5% in the first 6 months of treatment, 19.4% in the first year, 10.4% in the second year and 6.4% after 2 years.
The most common reason was adverse effects (10.2% of patients).

During follow-up, 22.1% of patients presented at least one adverse event and 6.6% at least one serious adverse event.
The most common were gastrointestinal disorders (7.4%), musculoskeletal disorders (4.0%), neurological disorders (2.9%, of which 0.3% were stroke) and infections (2.3%).
Cardiac problems were reported by 1.7% of patients: arrhythmias (0.6%), coronary disease (0.5%), MI (0.2%) and heart failure (0.5%).
Vascular disorders were reported in 1.4% of patients (hypertension 0.4%).

A total of 339 patients (2.8%) died during follow-up. WHO data report mortality rates of 2.6% to 2.9% in women aged 55 years or over in a group of four European countries comprising Germany, France, Italy and Spain.
The principal causes of death were heart conditions (0.6%), coronary disease (0.3%), benign or malignant tumours (0.4%) and stroke (0.2%).

During follow-up, 7.7% of patients reported an adverse event that was judged to be possibly associated with PROTELOS treatment, corresponding to 25.8% of reported adverse events. The most common were gastrointestinal disorders (5.3%), dermatological disorders (0.9%) and neurological disorders (0.7%, of which headache and memory loss were the most common).

In total, a venous thromboembolic event was reported in 55 patients (0.5%), which corresponds to an annual incidence of 2.1/1000 PY. This incidence was 3/1000 PY in women over 80 years of age (12 cases) and 2/1000 PY in women under 80 years of age (43 cases).
These declarative results give the lowest incidences of venous thromboembolic events in patients treated with PROTELOS compared with the results of the placebo-controlled studies (7.9/1000 PY in the PROTELOS arm and 5.8/1000 in the placebo arm) and results taken from the British GPRD (8.7/1000 PY in the PROTELOS arm, 7.7/1000 in the alendronate arm and 8.3/1000 in untreated women).

In conclusion, these final results confirm the preliminary results submitted in 2010 and included in the TC Opinion of 11 May 2011.
As regards the conditions of use, it should be noted that 16.5% of the women in the cohort were aged 80 years or over. There is no information available on the cardiovascular and neurological history of patients treated with PROTELOS.
As regards the highlighted cardiovascular adverse effects, although this study reports a certain number of cardiovascular and neurological adverse events, the observational, declarative and non-comparative nature of these data does not permit any conclusions to be drawn about this risk.

09.6 Summary and discussion

Following the identification, in April 2013, of an increased cardiovascular risk associated with use of PROTELOS and the narrowing of the indication to limit the risk of cardiovascular adverse effects, the Transparency Committee was asked to re-assess the actual benefit of PROTELOS.

Cardiovascular effects (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 potentially life-threatening condition that has been reported since market launch.

In the initial studies, efficacy had been demonstrated in studies of vertebral fractures (absolute reduction versus placebo of 9.34% in the risk of fracture after 4 years, $p < 0.001$) and non-vertebral fractures (absolute reduction of 2.3% in the risk of fracture after 5 years, $p < 0.001$). A reduction of 3% in hip fracture (the most serious fractures) was demonstrated in a subgroup of the most high-risk patients (T score ≤ -2.4 SD and age ≥ 74 years).

To establish whether the initial efficacy persists in the population restricted to patients with severe osteoporosis and with no contraindication associated with venous or arterial risk, the applicant submitted a new post-hoc subgroup analysis. In this analysis, PROTELOS was not found to be effective against hip fracture in the different 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, to check whether the measures to minimise risk are effective, post-hoc analyses were carried out to compare cardiovascular risk and mortality in all osteoporosis patients and in lower-risk populations. In the population restricted to patients without cardiovascular risk and with severe osteoporosis, the increased cardiovascular risk versus placebo was not observed. However, it is difficult to know if the observed absence of difference is due to a lack of statistical power resulting from the small patient population or to the efficacy of these measures.

There are no data for the population defined in the SPC of 15 April of this year which, in addition to the above restrictions, limits the indication to patients in whom all other osteoporosis medicinal products are ineffective or contraindicated. It may be assumed that, in this very limited target population with no venous or arterial risk cardiovascular factors and generally treated for osteoporosis for many years, the risk of fracture is lower and consequently the efficacy of PROTELOS is lower.

Moreover, the applicant has not supplied any new data versus an active comparator.

09.7 Planned studies

In the context of its new Marketing Authorisation, the applicant was asked to submit a non-interventional safety study to evaluate the efficacy of the measures to minimise risk, including a description of the patients treated in routine clinical practice.

010 THERAPEUTIC USE

The indication for strontium ranelate has now been limited to severe osteoporosis when treatment with a different medicinal product is not possible (e.g. because of contraindication or intolerance), in patients without contraindications (history of thrombotic disease, arterial or venous in particular).

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual clinical benefit

◗ Postmenopausal osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck can be life-threatening.
◗ PROTELOS is a preventive treatment for osteoporotic fractures.
◗ The new data do not allow any conclusions to be drawn regarding the maintenance of efficacy against fractures in the new target population of women at low cardiovascular risk with severe osteoporosis in whom other osteoporosis treatments cannot be used. Moreover, taking into account the risk of cardiovascular events, in particular the recently highlighted risk of myocardial infarction, in addition to venous thromboembolic events including pulmonary embolism and a serious hypersensitivity syndrome (DRESS), the efficacy/adverse effects ratio of this medicinal product is insufficient.
◗ There are treatment alternatives.
◗ This medicinal product is a second-line therapy for use in patients in whom bisphosphonates and other osteoporosis medicinal products are not tolerated or contraindicated,

◗ Public health benefit

Because of the high prevalence of postmenopausal osteoporosis and the seriousness of its consequences, the burden of illness on public health is substantial.
The therapeutic need is only partially covered by existing therapies. Moreover, since the adverse effects caused by such drugs, their contraindications and the precautions for use (digestive system, renal failure) are nontrivial, it is important to have additional alternatives available.
In the light of the available data and in the absence of direct comparative data that allow PROTELOS to be assessed in relation to the other available treatments, it is not possible to quantify the impact of PROTELOS on the reduction in fractures.
More generally, the impact of PROTELOS on morbidity and mortality is difficult to quantify based on the pharmacovigilance data collected since the market launch of PROTELOS (DRESS, thromboembolic events, particularly in at-risk patients).
In addition, PROTELOS has not been found to have any impact on quality of life or on the healthcare system.
Given the substantial modification to the target population of this medicinal product, which does not correspond to that of the studies initially carried out, it is uncertain whether results observed in studies can be transposed to conditions of routine use.
Consequently, in the current state of knowledge and taking into account the other available treatments, PROTELOS cannot have any impact on public health.

Taking account of these points, the Committee considers that the actual benefit of PROTELOS in the new indication of the Marketing Authorisation is insufficient to justify reimbursement by National Health Insurance.

The Committee does not recommend continued inclusion of PROTELOS on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "treatment of severe osteoporosis in postmenopausal women at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance" and at the dosages in the Marketing Authorisation.