HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 September 2011

Review of the dossier for the proprietary medicinal product listed for a period of 5 years by the order of 16 December 2005 (*Journal Officiel* of 29 December 2005)

PROTELOS 2 g, granules for oral suspension
B/28 (CIP code: 365 170.3)

Applicant: LES LABORATOIRES SERVIER

strontium ranelate
ATC code (2011): M05BX03

List I

Date of Marketing Authorisation: 21 September 2004 (centralised procedure, rapporteur: Sweden)

Reason for request: Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

strontium ranelate

1.2. Indications

"Treatment of osteoporosis in postmenopausal women. PROTELOS reduces the risk of vertebral and hip fractures."

1.3. Dosage

"The recommended dose is one 2 g sachet once daily by oral administration. Due to the nature of the treated disease, strontium ranelate is intended for long-term use.

The absorption of strontium ranelate is reduced by food, milk and derivative products and therefore, PROTELOS should be administered in-between meals. Given the slow absorption, PROTELOS should be taken at bedtime, preferably at least two hours after eating.

Patients treated with strontium ranelate should receive vitamin D and calcium supplements if dietary intake is inadequate.

Elderly patients

The efficacy and safety of strontium ranelate have been established in a broad age range (up to 100 years at inclusion) of postmenopausal women with osteoporosis. No dose adjustment is required in relation to age.

Renal impairment

Strontium ranelate is not recommended for patients with severe renal impairment (creatinine clearance below 30 mL/min). No dose adjustment is required in patients with mild-to-moderate renal impairment (30-70 mL/min creatinine clearance).

Hepatic impairment

As strontium ranelate is not metabolised, no dose adjustment is required in patients with hepatic impairment.

Paediatric population

The safety and efficacy of PROTELOS in children aged below 18 years have not been established. No data are available.

2 SUMMARY OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

Transparency Committee opinion of 2 March 2005

"The actual benefit contributed by PROTELOS is substantial.

Despite the absence of direct comparative trials, the Transparency Committee assessed the efficacy and tolerance of PROTELOS in comparison with medicines indicated in the treatment of postmenopausal osteoporosis.

- In the population of women aged under 80 years, trials carried out with PROTELOS have demonstrated efficacy against vertebral and nonvertebral fractures that was globally similar to that observed in the available trials with bisphosphonates (risedronate, alendronate). In terms of adverse effects, although PROTELOS seems to cause more venous thromboembolism, it seems to have fewer gastrointestinal and renal adverse effects. PROTELOS is an alternative to bisphosphonates, including in patients for whom bisphosphonates are not recommended or are contraindicated. It does not cause renal impairment. In conclusion, in this population, PROTELOS contributes a minor improvement in actual benefit (IAB IV) in the treatment of these patients. The Committee notes the novelty of the active ingredient and its method of action.

- In the population of female patients aged over 80 years, PROTELOS is the first medicine that has demonstrated benefit in terms of a reduction in vertebral and hip fractures. The adverse effects of venous thromboembolism and nervous system disorders might be more common in this population of elderly women. In this population, PROTELOS contributes a moderate improvement in actual benefit (IAB III) compared with the usual treatment for these patients (bisphosphonates)."

The Transparency Committee would like an observational study to be set up in female patients treated with PROTELOS, particularly those aged over 80 years. The aim of this study would be to assess the impact of long-term treatment with PROTELOS under actual conditions of use in terms of morbidity and in particular, frequency of occurrence of thromboembolism. The Committee would like the intermediate results of the study to be available within two years.

Transparency Committee opinion of 05 July 2006 (requested by UNCAM (the French association of national health insurance funds), redefinition of the reimbursement conditions for indications for medicines for osteoporosis)

Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures:
- in female patients who have had one fracture caused by bone fragility,
- in the absence of fractures, in women with substantially reduced bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current use of systemic corticosteroids at a daily dose of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40).

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2011)

M: Musculo-skeletal system
M05: Drugs for the treatment of bone diseases
M05B: Drugs affecting bone structure and mineralisation
M05BX: Other drugs affecting bone structure and mineralisation
M05BX03: Strontium ranelate

3.2. Medicines in the same therapeutic category

There are no other medicines in the same therapeutic category.

3.3. Medicines with a similar therapeutic aim

Medicines indicated in the treatment of postmenopausal osteoporosis which have demonstrated their efficacy in preventing vertebral and peripheral fractures, including femoral neck fractures

- the following bisphosphonates:

- ACLASTA 5 mg (zoledronic acid), IV infusion (once a year),
- ACTONEL (risedronic acids) 5 mg tablets (every day), 35 mg (every week), 75 mg (two consecutive days a month), ACTONELCOMBI (risedronate 35 mg + calcium 1000 mg + vitamin D 880 IU) tablets (every week),
- FOSAMAX (alendronic acid) 10 mg tablets (every day), 70 mg (every week) and the other proprietary medicinal products containing 10 mg and 70 mg of alendronic acid, FOSAVANCE and ADROVANCE (alendronate or combination of alendronate + vitamin D) tablets every week.

Medicines indicated for the treatment of postmenopausal osteoporosis but which have not demonstrated their efficacy in preventing femoral neck fractures

- DIDRONEL 400 mg tablets (etidronic acid), 1 tablet/14 days/3 months
- BONVIVA 150 mg/1 month tablets and 3 mg/3 months solution for injection

In December 2010 the AB for these medicines was judged to be insufficient.

- FORSTEO (teriparatide), subcutaneous injection every day, refundable for patients with severe osteoporosis (at least two vertebral fractures), efficacy demonstrated against peripheral fractures but not hip fractures.
- EVISTA and OPTRUMA (raloxifene), tablets (every day) efficacy against vertebral fractures only.

Calcium and vitamin D are generally given as adjuvant therapy.

4 FURTHER UPDATING OF DATA MADE AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

In the context of its request for renewal of inclusion of PROTELOS on the list of proprietary medicinal products refundable by National Health Insurance, the applicant Les Laboratoires Servier has claimed:

- a number of analyses of the two initial phase III trials SOTI and TROPOS which evaluated the efficacy of PROTELOS against fractures after three years[1] against placebo, notably:
  - five-year data, with the double-blind maintained (main analysis scheduled in the initial protocol),
  - data from an additional open extension phase for a three-year period carried out in patients who had been treated for five years in the SOTI and TROPOS trials (i.e. eight years' follow-up) and
  - five-year data from a combined analysis scheduled in the protocol for each of the SOTI and TROPOS trials in the subgroup of elderly patients aged over 80 years (subgroup not defined in the initial trial protocol).
- results of the trial against alendronate 70 mg on bone quality and microarchitecture (Rizzoli 2010).

Data at 3-5 years[2] from the SOTI trial

Design of the SOTI trial:

- Controlled, randomised, double-blind trial to demonstrate the efficacy and tolerance of PROTELOS (n=828) compared with placebo (n=821), in women with postmenopausal osteoporosis with at least one vertebral fracture.
- Inclusion criteria: women who had been postmenopausal for at least five years, with a lumbar T-score $\leq$ -2.4 SD and at least one osteoporotic vertebral crush fracture.
- Primary endpoint: number of patients with new vertebral fractures determined from annual radiological examination.
- PROTELOS (2 g/day) was given either once daily in the evening at bedtime (87% of patients), or twice a day (13%), at the patient's choice. All patients received calcium and/or vitamin D supplements at dosages determined for each individual according to any deficiency.

Mean age of patients was 69.7 years, lumbar T score was -3.6 and 87.5% of patients had a history of fracture at inclusion.

Three-year results: the reduction in absolute risk of vertebral fracture (determined by radiological examination) compared with placebo was 11.9%: incidence = 32.8% (222/723) under placebo versus 20.9% (139/719) under PROTELOS, p<0.001. The reduction in absolute risk of clinical vertebral fracture compared under placebo at three years was 6.1%: incidence = 17.4% (117/723) under placebo versus 11.3% (75/719) under PROTELOS, p<0.001.

Five-year results from the SOTI trial:
Of the 1649 patients originally randomised in the SOTI trial to receive either strontium ranelate (n =828) or placebo (821), 1149 patients (69.7%) completed the trial at four years with the double-blind maintained. After four years these patients were included in an additional one-year extension phase during which patients previously treated with placebo

[1] The protocols for the SOTI and TROPOS trials specified a total study period of five years, with a main analysis at three years.
[2] Meunier PJ, Roux C, Ortolani S, az-Curiel M, Compston J, Marquis P, et al. Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis. Osteoporos Int 2009 ; 20:1663-1673.

received strontium ranelate (434) and those who had received strontium ranelate could either be treated with placebo (225) or could continue their treatment (221).
At four years, the absolute reduction in risk of radiological vertebral fractures compared with placebo was 9.34%, p<0.001; fracture incidence = 27.02% (173/719) under PROTELOS versus 36.36% (245/726) under placebo. The absolute reduction in risk of clinical vertebral fractures was 6.7%, p<0.001; fracture incidence = 14.49% (93/719) under PROTELOS versus 21.18% (139/726) under placebo (139/726).
Quality of life measured using the specific QUALIOST scale showed that the benefit of PROTELOS over placebo was maintained at four years.
The five-year efficacy data concerned an intermediate criterion, BMD (bone mineral density), so will not be described here.

Results of the TROPOS trial at 3 and 5 years[3]

Design:

- Randomised controlled double-blind trial conducted simultaneously and in the same centres as the SOTI trial, to demonstrate the efficacy and tolerance of PROTELOS (n=2554) compared with placebo (n=2537) in women with postmenopausal osteoporosis.
- Inclusion criteria: postmenopausal women (≥ 5 years), with a lumbar T-score ≤ -2.5, aged ≥ 74 years or aged ≥ 70 years with a risk factor.
- Primary endpoint: number of patients with confirmed new nonvertebral fractures.
- PROTELOS (2 g/day) was given either once daily in the evening at bedtime (90% of patients), or twice a day (10%), at the patient's choice. All patients received calcium and/or vitamin D supplements at dosages determined for each individual according to any deficiency.

Mean patient age was 76.8 years, mean femoral T-score was -3.1, and 54.8% of patients had had an osteoporotic fracture. At three years, PROTELOS was superior to placebo for reduction in incidence of new nonvertebral fractures; the reduction in absolute risk of nonvertebral fracture was 1.8% (p<0.04).

The efficacy data (prevention of hip fractures under PROTELOS after three years) were derived from an *a posteriori* analysis performed in a subgroup of patients at high risk of hip fracture as defined by femoral neck T-score ≤ -2.4 SD (NHANES III classification) and age ≥ 74 years (n=1 977, i.e. 39% of the population of the TROPOS trial). In this group of patients, mean age 83 years, after three years of treatment PROTELOS reduced the absolute risk of hip fracture by 2.1% compared with placebo, p=0.046.

Five-year results for the TROPOS trial[5]:
2720 (55%) of the 4935 patients originally randomised completed five years of the study. The reduction in absolute risk of non vertebral fracture at five years was 2.3% compared with placebo, p<0.001: incidence of non vertebral fracture was 18.6% (312/2479) under PROTELOS compared with 20.9% (359/2456) under placebo.

In the subgroup of patients at high risk of hip fracture defined as a femoral neck T-score ≤ -2.4 SD (NHANES III classification) and age ≥ 74 years, an analysis carried out after five years including 571 patients treated with placebo and 557 treated with strontium ranelate showed that the absolute reduction in risk of hip fracture compared with placebo was 3% (p=0.036). Hip fracture incidence was 7.2% under PROTELOS and 10.2% under placebo at 5 years.

[3] Reginster JY *et al*. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a 5-year, randomized, placebo-controlled trial. Arthritis Rheum 2008; 58: 1687-1695.

Combined results of the three-year open extension of the TROPOS and SOTI trials (total treatment duration = 8 years)[4].

Eight hundred and seventy-nine (879) patients treated for five years with PROTELOS were included in this extension phase for a further three years (17% from the SOTI trial and 83% from the TROPOS trial). Cumulative incidence of vertebral fractures during these three additional years' follow-up was 13.7%, and for nonvertebral fractures, 12%.

Updating of efficacy data in the subgroup of patients aged over 80 years

In the 2005 opinion on the listing of PROTELOS, the Transparency Committee took account of a combined analysis of the SOTI and TROPOS trials in the subgroup of patients aged 80-100 years (n=1556).
The protocol included a combined analysis of results from these two studies but the analysis of the "elderly patients" subgroup was not pre-specified in the protocol; there was no alpha risk adjustment.

Vertebral radiographs were available for 452 patients in the placebo group and 443 in the PROTELOS group, and data on nonvertebral fractures were available for 1488 patients (749 patients in the placebo group and 739 in the PROTELOS group). Patients had a lumbar T-score of -2.7, and a femoral T-score of -3.3; mean age was 83.5 years; at inclusion 48.9% of patients had had a vertebral osteoporotic fracture and 36.1% had had a nonvertebral osteoporotic fracture.
In elderly patients aged over 80 years, PROTELOS reduced the absolute risk of new vertebral fractures at three years by 7.4% compared with placebo (p = 0.013) and by 8.7% at five years (p=0.01). The absolute risk of new nonvertebral fractures in women treated with PROTELOS was reduced by 5.3% at three years compared with placebo (p=0.011) and by 4.2% at five years (p=0.018).

Five-year results[5]:
A subgroup analysis based on the combined five-year results of the SOTI and TROPOS trials in elderly patients aged over 80 years (n = 1489) showed that PROTELOS reduced the risk of new vertebral and nonvertebral fractures compared with placebo. The absolute reduction in risk of vertebral fracture was 8.7% compared with placebo (p=0.01); fracture incidence was 26.6% (83/443) under PROTELOS versus 35.3% (118/453) under placebo.
The absolute reduction in new nonvertebral fractures was 4.2%, p=0.018; fracture incidence was 24.7% (101/739) under PROTELOS versus 28.9% (135/750) under placebo.

Comparative trial against alendronate[6]

A randomised controlled double-blind two-year trial against alendronate (with a scheduled intermediate analysis at one year). A total of 88 female patients with postmenopausal osteoporosis, who had not received any anti-osteoporosis therapy for at least one year were included, 46 in the PROTELOS 2g/day group and 42 in the alendronate 70 mg/week group. The primary endpoint was change in parameters of bone microarchitecture (cortical thickness and trabecular volume) measured every six months by high resolution CT scan. Cortical thickness and trabecular volume increased from baseline in the patients treated with PROTELOS (+6.3% for cortical thickness, p = 0.004 and +2.5% for trabecular volume, p = 0.04), which was not the case for patients treated with alendronate.

[4] Reginster JY *et al*. Long-term treatment of postmenopausal osteoporosis with strontium ranelate: results at 8 years, Bone 2009; 45(6): 1059-1064.
[5]Seeman E *et al.* Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life years in women over 80 years of age. Bone 2010; 46: 1038-1042.
[6] Rizzoli R, Felsenberg D, Laroche M, Krieg M, Frieling I, Thomas T, et al. P107: Beneficial effects of strontium ranelate compared to alendronate on bone micro- structure - A 2-year study. Osteoporos Int 2010b; 21 (Suppl. 1): S28-S29.

4.2. Tolerance

When PROTELOS 2 g/day was listed in 2005, the tolerance data available concerned 3352 female patients treated for up to 56 months with PROTELOS.
The most common adverse effects were nausea and diarrhoea, usually reported at the beginning of treatment with no marked difference between the two groups subsequently. The incidence of venous thromboembolism at three years was 9.2/1000 patient-years under PROTELOS versus 6.1/1000 patient-years with a relative risk of 1.42 (CI [1.02-1.98], p=0.036).
Nervous system disorders were reported, particularly disorders of consciousness, with a frequency of 2.5% under strontium ranelate and 2.0% under placebo, memory loss (2.4% under strontium ranelate vs. 1.9% under placebo) and convulsions (0.3% with strontium ranelate vs. 0.1% under placebo).

In view of the finding of a higher incidence of venous thromboembolism and nervous system disorders, a risk management plan (RMP) was produced and a post-listing study requested by the Transparency Committee was started.

The updating of the tolerance data for PROTELOS took the following into account:
- data from clinical trials,
- pharmacovigilance data,
- UK GPRD (General Practice Research Database) and DSRU (Drug Safety Research Unit) observational data,
- results of the post-listing study

Global tolerance:
Analysis of the five-year data from clinical trials including 3352 patients exposed to PROTELOS for up to 60 months (mean = 1142 ± 661 days) did not reveal any adverse effects that were not identified in the SPC and not monitored under the risk management plan.

In the observational study requested by the Transparency Committee in a population of 11 853 patients, 16.4% of subjects reported an adverse event. The most common were gastrointestinal disorders (5.9%). Two hundred and eleven (211) patients (1.8%) had an adverse event that was fatal (cardiac, tumour, central nervous system disorders). The investigator considered that none of these deaths was related to treatment.

According to international pharmacovigilance data, between the end of 2004 and March 2010 the total number of patients exposed to PROTELOS was 1 717 411 patient-years, including 379 811 patient-years in France.
According to the French follow-up data, between January 2006 and 31 March 2009, 884 adverse effects were notified (36% skin, 17% gastrointestinal and 16% cardiovascular), i.e. an estimated incidence of 1/3583 treatment months. These adverse effects were serious in 23% of cases, including eight deaths. A causal relationship between these deaths and PROTELOS was not discussed.

Adverse events of particular interest:

Venous thromboembolism (VTE)
A risk of VTE was identified in clinical trials at three years.
During five-year follow-up of the clinical trials, 89 patients reported VTE, 2.7% of them in the PROTELOS group compared with 1.9% in the placebo group, i.e. an incidence of 9.2 per 1000 patient-years under PROTELOS and 6 per 1000 patient-years under placebo (relative risk= 1.4 [1; 2], p = 0.031).

Between the end of 2004 and March 2010, 275 cases of VTE (pulmonary embolism in 37% of cases) had been reported worldwide, i.e. an estimated incidence of 0.16/1000 patient-years. Twenty percent (20%) of the patients had a history of VTE.

The French pharmacovigilance monitoring carried out by the Tours pharmacovigilance centre after PROTELOS had been placed on market[7] contained reports of 93 venous thromboembolisms (39 pulmonary embolisms and 54 deep vein thromboses) between 21 January 2006 and 31 March 2009; median time to onset was 3 months. Cumulative incidence of VTE was 1/31 052 treatment months. At least a third of the patients had a risk factor for thrombosis (a proportion which was probably underestimated as a history was not routinely collected at the time of notification). The pathophysiological mechanism for the VTE was unknown (haemostasis parameters were unchanged before compared with after two months' treatment in 35 patients studied[8]).

In the observational study requested by the Committee, 51 cases of VTE were reported in 44 patients (0.37%): deep vein thrombosis (33 patients, 0.28%), pulmonary embolism (16 patients, 0.14%) and retinal vein occlusion (2 patients, 0.02%). The global incidence of these events was 2.5 [1.8; 3.3] / 1 000 patient-years; incidence for patients aged 80 years or over was 3.4 [1.63; 6.26] / 1 000 patient-years, and for patients aged under 80 years it was 2.3 [1.58; 3.18] per 1 000 patient-years. Mean time to onset of these events was 371 days [22-989 days]. The main potential risk factors found were history of VTE and/or thrombosis (10 patients) or prolonged immobilisation (11 patients).

In a retrospective observational study[9] using the UK General Practice Research Database, VTE frequency was higher in untreated osteoporotic women than in non-osteoporotic women (RR 1.75 [1.09-1.84]). After adjustment for age, BMI, use of corticosteroids and history of VTE, the difference remained significant between the two groups (RR =1.38 [1.03; 1.86].

The incidence of VTE between 02 December 2004 and 04 January 2009 was:

- for patients treated with PROTELOS, 8.3/ 1 000 patient-years;
- for patients treated with alendronate, 7.5/ 1 000 patient-years;
- for untreated patients, 6.2/1 000 patient-years.

See Annex.

Another retrospective study[10] carried out using the UK General Practice Research Database (Drug Safety Research Unit - DSRU) between October 2004 and January 2008 followed a cohort of 10782 women, 91.3% of whom were treated with strontium ranelate and 2.6% of whom had a history of VTE. During the first year of treatment with strontium ranelate, 48 cases of VTE including pulmonary embolism were reported, i.e. an incidence of 6.24 per 1000 patient-years exposed. The results of this study showed that a history of VTE was a risk factor for VTE: the incidence of VTE was 11.63% in patients with a history of VTE and treated with strontium ranelate compared with 2.58% in patients without a history of VTE treated with PROTELOS.

Overall, the data from clinical trials, observational studies and pharmacovigilance monitoring confirm a risk of venous thromboembolism under PROTELOS. The cause of VTE remains unknown.

Skin hypersensitivity reactions:
Since PROTELOS was placed on the market, the risk of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has been added to the SPC (25 January 2008) following reports of 16 cases in Europe, two of which were fatal: "Cases of severe

[7] French national pharmacovigilance committee report. Report of meeting held on Tuesday 06 July 2010
[8] Halil M, *et al.* Short-term hemostatic tolerance of strontium ranelate treatment in elderly women with osteoporosis. Ann Pharmacother. 2007; 41: 41-5
[9] Study report.
[10] Osborne V *et al*. Incidence of venous thromboembolism in users of strontium ranelate: an analysis of data from a prescription-event monitoring study in England. Drug Saf 2010; 33: 579-591.

hypersensitivity syndromes, including, in particular, drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, have been reported with the use of PROTELOS". A pharmacovigilance alert was set up and a letter was sent to prescribers in November 2007. The syndrome, which may be life-threatening, is characterised by skin rash, fever, hypereosinophilia, adenopathy and systemic symptoms, particularly hepatic, renal and pulmonary. Time to onset is 3-6 weeks. In most cases the outcome is favourable after withdrawal of PROTELOS and after initiation of corticosteroid therapy. Recovery may be slow and recurrences of the syndrome are possible after corticosteroids have been stopped. The mechanism of this syndrome is not known. The onset of DRESS is therefore not predictable and apart from warning patients to stop taking the medicine immediately if they have a skin rash with fever, it is difficult to reduce the risk.

According to international pharmacovigilance data for the period since PROTELOS was placed on the market, end of 2004 to March 2010, 32 cases (11 confirmed, 6 probable, and 15 possible) of DRESS possibly related to treatment with PROTELOS have been established by a committee of experts, i.e. a global incidence of 1 case per 53 669 patient-years.
In France, 14 cases of DRESS have been notified, 6 of which (including 1 death) are considered as confirmed, 2 as probable and 6 as possible.

Central nervous system disorders
The risk of onset of central nervous system disorders was identified during clinical trials at three years.
The clinical data extended to five years showed that the frequency of disorders of consciousness was 2.6 % under PROTELOS compared with 2.1% under placebo; for memory loss, the figure was 2.5% under PROTELOS compared with 2.0% under placebo, and for convulsions, 0.4% under PROTELOS compared with 0.1% under placebo.

In the post-listing study, 39 patients experienced a nervous system disorder such as memory loss (25 patients, 0.21%), disorders of consciousness (11 patients, 0.09%) or epileptic seizure (4 patients, 0.03%).

According to international pharmacovigilance data, over a 66-month period, 31 cases of disorders of consciousness were reported (incidence = 0.02 per 1000 patient-years), 105 cases of memory loss (incidence = 0.06 per 1000 patient-years) and 24 cases of convulsions (incidence = 0.01 per 1000 patient-years of treatment).
During the same period (between 21 January 2006 and 21 March 2010), 49 cases were reported in France:

- Memory problems: 36 cases, including 6 serious)
- Disorder of consciousness: 7 cases, including 4 serious)
- Convulsions: 6 cases

Other serious adverse effects:
Between January 2006 and 31 March 2009, five cases of liver disorder and two of pancreatitis were reported in France.

4.3. Conclusion

Data available since the inclusion of PROTELOS on the list of reimbursable proprietary medicinal products (2005) in the treatment of postmenopausal osteoporosis confirm the efficacy of the medicine against fractures:

- the absolute reduction in risk of vertebral fracture at 4 years compared with placebo was 9.34%, p<0.001 (versus 11.9% at 3 years);
- the absolute reduction in risk of nonvertebral fracture was 2.3% at 5 years, p<0.001 (versus 1.8% at 3 years).

The only new study added to the dossier was a comparative study against alendronate, but it is not relevant as fracture incidence was not measured. No studies were provided comparing the efficacy of PROTELOS with that of other anti-osteoporosis medicines in terms of fracture prevention.

Overall, these data provide five years' follow-up in terms of duration of treatment with PROTELOS with evidence of an action against fractures compared with placebo and up to eight years' follow-up of treated patients.

The tolerance data derived from clinical trials extended to five years, pharmacoepidemiological studies and pharmacovigilance data have confirmed a risk of venous thromboembolism, including pulmonary embolism, and central nervous system disorders such as disorders of consciousness, memory loss and convulsions. Serious and unpredictable hypersensitivity reactions such as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) which had not been identified in clinical trials were notified during pharmacovigilance monitoring.

5 DATA ON THE USE OF THE MEDICINAL PRODUCT

5.1. Post-listing study requested by the Transparency Committee (intermediate results) - Analysis by ISPEP (the HAS working group on public health benefit and post-listing studies)

A post-listing study for the proprietary medicinal product PROTELOS was requested by the Transparency Committee (opinion of 02 March 2005 and the Committee for Pricing and Reimbursement of Healthcare Products (CEPS) amendment of 13 December 2005). The study was to measure the impact of long-term treatment with PROTELOS under real-life conditions of use, particularly in women aged over 80 years, in terms of morbidity and in particular the frequency of occurrence of thromboembolism. The Committee wanted the intermediate results of the study to be available within two years.
To satisfy this request, the applicant set up a multicentre study, in seven European countries, with three-year follow-up of female patients treated with PROTELOS.
The report presented gives intermediate data as at 08 January 2010. On that date, a registry was established of 32 890 patients seeing their doctor for postmenopausal osteoporosis (retrospective data) and 13 070 patients treated with PROTELOS were included in a prospective follow-up cohort for three years. Patients were to continue to be monitored until February 2011.

The countries which recruited the largest number of patients were Germany (35.7% of inclusions in the cohort), Spain (25.7%), France (16.8%) and Italy (16.2%).
Nearly half of these patients were monitored for one - two years (mean duration was 20.6 months after the initial consultation and mean treatment duration was 17.1 months).

The mean age of patients in the cohort was 69 years (16.3% were aged 80 years or over), with a mean BMI of 25.6 (+/-4.3) kg/m2 and mean age at menopause of 48 years. The representativeness of patients in the cohort was acceptable.
Of these patients, 64.1% had at least one risk factor for osteoporosis and fractures, and 45.3% had already had an osteoporotic fracture (30.1% vertebral fracture, 22.2% nonvertebral fracture).
The risk factors found in the study were: family history of osteoporosis, corticosteroid therapy for > 3 months, smoking> 10 cigarettes /day, alcohol > 2 units/day, low BMI < 20, early menopause < 40 years, history of primary or secondary amenorrhoea, inadequate calcium intake < 80 mg/day, frequent falls, visual disorders, use of sleeping pills, lack of physical exercise < 30 min/day, residence in a nursing home, prolonged immobilisation > 3 months. The definition used in this study for risk factors was broader than that used in the context of reimbursement of the medicine[11].
More than half the patients (58.9%) were given calcium and/or vitamin D supplements.
Densitometry data were available for 37.5% of patients for lumbar score (median T score = 2.6 +/-0.86 SD) and for 35.3% for femoral score (median T score = -2.1 +/-0.86 SD).

For the current duration of follow-up, 662 of the 11 853 patients who had had a follow-up visit since the initial visit (5.6%) had a new fracture: 206 (1.7%) vertebral fracture, 301 (2.5%) nonvertebral fracture and fracture location not given for 155 women (1.3%).
As at 08 January 2010, 27.9% of the patient follow-up cohort had stopped treatment with PROTELOS. Mean treatment duration between inclusion and discontinuation was 9 months (median 7 months). The main reasons for discontinuing PROTELOS therapy were patients being tired of the treatment (7.5%), adverse events (7.3%) and patient's request (5.3%). At 12 months after the inclusion visit, 78% of patients were still taking their treatment; at 24 months, this figure was 69%.

Tolerance data were described in section 4.2.

Concerning data on the use of PROTELOS, particularly in France, the data submitted were not sufficient for an accurate assessment of compliance with the conditions for reimbursement as defined by the Transparency Committee, particularly because results for bone mineral density (BMD) were available at inclusion for fewer than 40% of patients, and because a much broader definition of risk factors was used in this study than was used for reimbursement. These intermediate results should be confirmed by full follow-up of the cohort.

5.2. Thales data

According to the Thales database, 390 000 patients in France were treated with PROTELOS between January 2006 and March 2010. General practitioners were responsible for 96% of prescriptions. Female patients aged 80 years and over accounted for 25% of patients treated with PROTELOS, and 67.5% of patients treated had a history of fracture.

[11] The conditions for reimbursement were defined by the Transparency Committee in its opinion of 05 July 2006, "Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures [in French]":
- in female patients who have had one fracture caused by bone fragility,
- in the absence of fractures, in women with substantially reduced bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current use of systemic corticosteroids at a daily dose of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of fracture of the end of the femoral neck in a first-degree relative (mother), early menopause (before the age of 40).

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

The seriousness of postmenopausal osteoporosis lies in the risk of fracture. In particular, fractures of the femoral neck can be life-threatening.

PROTELOS is a preventive medicine against osteoporotic fractures. Its efficacy has been demonstrated in terms of reduction in risk of vertebral and hip fractures.
However, in view of the confirmation of the risk of venous thromboembolism including pulmonary embolism, and the demonstration of a serious hypersensitivity DRESS-like syndrome, the efficacy/adverse effects ratio of this proprietary medicinal product is average.

Public Health Benefit:
Postmenopausal osteoporosis is a common disease with serious consequences, which makes it a substantial burden on public health.
The treatment requirement is only partially covered by existing therapies. In addition, as the adverse effects caused by these therapies, their contraindications and the precautions for use (gastrointestinal system, renal failure) are non-negligible, it was useful to have access to a further alternative.
In view of the data available (results of the post-listing study and four- and five-year results of the SOTI and TROPOS trials, in particular) and in spite of the absence of direct comparative data that would make it possible to situate PROTELOS in relation to the other treatments available, the actual impact of PROTELOS on fracture reduction is low.
In addition, the impact of PROTELOS on morbidity and mortality is difficult to quantify in view of the pharmacovigilance data collected since PROTELOS was placed on the market (DRESS, thromboembolism particularly in at-risk patients).
In addition, PROTELOS does not have any impact on quality of life or the healthcare system.
It is clear that these results observed in trials may be transposed to actual conditions of use in the medium term, particularly because of the acceptable level of maintenance treatment.
Consequently, in the current state of knowledge and taking account of the other treatments currently available, PROTELOS does not contribute any public health benefit.

This proprietary medicinal product is a second-line medicine, in patients with a contraindication to or adverse effects with bisphosphonates.

There are alternative therapies.

In view of its concerns related to the risk of onset of DRESS and venous thromboembolism, the Transparency Committee considers that the actual benefit of PROTELOS is moderate in a population restricted to:
- patients with a contraindication to or adverse effects with bisphosphonates,
- patients with no risk factors for venous thromboembolism, including a history of venous thromboembolism, aged over 80 years, prolonged immobilisation, etc.

6.2. Re-assessment of the improvement in actual benefit (IAB)

Like the bisphosphonates (alendronate, risedronate, zoledronate), PROTELOS has demonstrated its efficacy in preventing vertebral and nonvertebral fractures, including femoral neck fractures. However, the tolerance data show a risk of venous thromboembolism and a risk of serious hypersensitivity syndrome (DRESS), the onset of which is unpredictable. In view of these factors and in view of the alternative forms of treatment available, it seems inappropriate to maintain an improvement in actual benefit for this medicine. Consequently, the Transparency Committee considers that PROTELOS does not

provide any improvement in actual benefit (V) to the treatment strategy for postmenopausal osteoporosis.

6.3. Therapeutic use

Osteoporosis is defined as a T-score ≤-2.5 in the absence of any other cause of demineralising or weakening bone disease. The aim of treating osteoporosis is to prevent fractures.
Any calcium or vitamin D deficiency should be identified and treated before any anti-osteoporosis therapy is started. If necessary, calcium and vitamin supplements should be continued during anti-osteoporosis therapy.

According to the AFSSAPS (French Healthcare Product Safety Agency) guidelines published in January 2006, treatment is routinely recommended in patients with osteoporosis complicated by fracture. In the absence of fracture in postmenopausal women, the indication for treatment should be discussed on an individual basis, in relation to the individual fracture risk. This risk is assessed on the basis of T-score value and the presence of any other risk factors for fracture. Treatment should therefore be considered in women with:

- a substantial reduction in bone density (T score < -3) or
- T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current systemic corticosteroid therapy at a dose of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of femoral neck fracture in a first degree relative (mother), early menopause (before the age of 40 years).

In the absence of direct comparison between the various anti-osteoporosis medicines (bisphosphonates, raloxifene, teriparatide and strontium ranelate), treatment should be chosen according to risk factors for vertebral and/or nonvertebral fracture, age, the number and location of fractures, and the patient's general health and any contraindications to any of the medicines.
The onset of fracture after the first year of treatment, despite satisfactory compliance, should lead to treatment being reassessed. Another medicine could be proposed, including one from the same pharmacological category.

Place of PROTELOS
Strontium ranelate (PROTELOS) has demonstrated its efficacy in terms of reducing the risk of vertebral and nonvertebral fractures, including femoral neck fractures. According to the data available, there is five years' experience in terms of duration of PROTELOS therapy with evidence of an anti-fracture effect compared with placebo and a maximum duration of follow-up for treated patients of eight years. PROTELOS is a useful alternative in patients with a contraindication to bisphosphonates (impaired renal function) or adverse effects with these medicines.
It should not be used in patients at increased risk of venous thromboembolism, notably in women with a history of venous thromboembolism.
In the event of onset of DRESS, patients should be informed of the need to discontinue PROTELOS immediately and definitively, and to see a doctor as soon as possible. Patients who have discontinued treatment because of onset of a hypersensitivity reaction should not start taking that medicine again.

6.4. Target population

The target population for PROTELOS is women with postmenopausal osteoporosis who have contraindications to or adverse effects with bisphosphonates, or who have no risk factor for thromboembolism (history of venous thromboembolism or other risk factors, including age over 80 years, prolonged immobilisation).

The population can be estimated from the following data:

- Around 25% of women aged 65 and 50% of women aged 80 are thought to have osteoporosis (GTNDO, 2003).
- According to INSEE (the French National Institute for Statistics and Economic Studies) (www.insee.fr), on 1st January 2005 there were 11.5 million women aged over 50 in France, 6 million over 65, and 1.9 million over 80.

According to these data, the estimated population with postmenopausal osteoporosis is around 3 to 3.3 million women, including around 930 000 aged over 80.

Only some of this population is eligible for treatment with PROTELOS, but in the absence of accurate epidemiological data, it is not possible to estimate this population.

6.5. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance.

6.5.1. Indications refundable

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

- who have a contraindication to or intolerance to bisphosphonates
- who have no history of venous thromboembolism or other risk factors for venous thromboembolism, notably age over 80 years.

Patients considered at high risk of fracture are:

- female patients who have had one fracture caused by bone fragility,
- in the absence of fractures, women with substantially reduced bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current use of systemic corticosteroids at a daily dosage of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40).

6.5.2. Packaging: Appropriate for the prescription conditions

6.5.3. Reimbursement rate: 30%

ANNEX

OPINION OF THE ISPEP WORKING GROUP
ON THE INTERMEDIATE RESULTS (June 2010)
OF THE PROTELOS POST-LISTING STUDY

PROTOCOL: Observational study CLE-12911-021
VERSION: Intermediate report, June 2010
PROPRIETARY MEDICINAL PRODUCT: PROTELOS
APPLICANT: **SERVIER**
DATE OF OPINION: 25 November 2010

I. SUMMARY OF THE REQUEST

The request by the Transparency Committee for the study was included in the opinion of 02 March 2005 and repeated in the Pricing and Reimbursement of Healthcare Products (CEPS) amendment of 13 December 2005. The wording was:

"The Transparency Committee would like an observational study to be set up in female patients treated with PROTELOS, particularly those aged over 80 years. The aim of the study would be to assess the impact of long-term treatment with PROTELOS under actual conditions of use, in terms of morbidity and in particular, frequency of occurrence of thromboembolism. The Committee would like the intermediate results of the study to be available within two years."

To satisfy this request, the applicant set up a multicentre study, in seven European countries, with three-year follow-up of female patients treated with PROTELOS.
The report submitted gives intermediate data as at 08 January 2010. On this date, a registry was established of 32 890 female patients seeing their doctor for postmenopausal osteoporosis, containing retrospective data. A prospective cohort of 13 070 patients treated with PROTELOS was formed for a three year follow-up period. Tolerance data were analysed in 11 853 patients (91% of the patients in the cohort) for whom follow-up data were available in January 2010.
Patients were to continue to be monitored until February 2011.

II.COMMENTS ON THE DESIGN

The protocol on the study was approved in September 2006. The preliminary results after two years were examined by the ISPEP group in September 2008.

The representativeness of cohort patients was studied in comparison with patients included in a registry established as part of the study. Details of patient characteristics were compared in different populations (patients in the registry, patients in the registry not included in the cohort, patients in the registry included in the cohort, patients in the registry treated with PROTELOS and included in the three-year follow-up period, and finally, patients in the PROTELOS cohort with at least one follow-up visit and/or at least one adverse effect reported since the initial consultation).
Data from patients in the follow-up cohort were similar in terms of age, BMI and age at menopause to those of the cohort without follow-up and the characteristics of patients in the cohort were similar to those in the registry.
Overall, the representativeness of patients in the cohort was acceptable.

The risk factors included in the study were: family history of osteoporosis, corticosteroid therapy for > 3 months, smoking > 10 cigarettes/day, alcohol > 2 units/day, low BMI < 20, early menopause < 40 years, history of primary or secondary amenorrhoea, inadequate calcium intake < 80 mg/day, frequent falls, visual disorders, use of sleeping pills, lack of physical exercise < 30 min/day, residence in a nursing home, prolonged immobility > 3 months. The conditions for reimbursement were defined by the Transparency Committee in its opinion of 05 July 2006, "Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures":
- in female patients who had had a fracture caused by bone fragility,
- in the absence of fractures, in women with substantially reduced bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly **age > 60 years, previous or current use of systemic corticosteroids at a daily dosage of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40).**

The definition used for risk factors was therefore broader in the cohort study.

III. RESULTS PRESENTED

Detailed report

On 08 January 2010, 32 890 female patients were included in the initial visit registry and 13 070 were included in the cohort.

Characteristics of DOCTORS

Three thousand and eighty-one (3 081) of the 37 004 doctors contacted agreed to take part in the study (8.3%) and 1 117 satisfied the regulatory and technical conditions to allow them to open their site and connect to the e-CRF. Eight hundred and fifty-two (852) of these doctors included patients treated with PROTELOS in the cohort.
The countries which recruited the largest number of patients were Germany (35.7% of inclusions in the cohort), Spain (25.7%), France (16.8%) and Italy (16.2%).

CHARACTERISTICS OF PATIENTS

Eleven thousand eight hundred and fifty-three (11 853; 90.7%) of the 13 070 women in the cohort had at least one follow-up visit and/or notification of a clinical event since the inclusion visit. Nearly half of these patients were followed up for between one and two years and more than a third were followed up for at least two years. Mean duration of follow-up after the initial visit was 20.6 months and mean duration of treatment was 17.1 months (i.e. 16 897 patient-years).
The mean age of patients in the cohort was 69 years (16.3% were aged 80 years or over), with a mean BMI of 25.6 (+/-4.3) kg/m2 and menopause at a mean age of 48 years.
In addition, 76.7% of patients had a medical history: most commonly arthritis (36.9%), arterial hypertension (29.8%) and dyslipidaemia (16%), and 2.3% had a history of deep vein thrombosis or pulmonary embolism.

Mean duration of osteoporosis in patients in the cohort was 3.1 years at the time of the initial visit.
Of the 13 070 patients in the cohort, 64.1% had a least one risk factor for osteoporosis and fractures (it should be pointed out that the definition used in this study for risk factors was very broad and exceeded the criteria used for reimbursement conditions for the medicine) and 45.3% had already had an osteoporotic fracture (30.1% a vertebral fracture, 22.2% a nonvertebral fracture).
More than half the patients (58.9%) were given calcium and/or vitamin D supplements.
Densitometry data were available for 37.5% of patients for lumbar score (median T score = -2.6 +/- 0.86 SD) and for 35.3% for femoral score (median T score = -2.1 +/-0.86 SD).

During follow-up so far, 662 of the 11 853 patients in the follow-up cohort (5.6%) have had a new fracture, 206 (1.7%) having a vertebral fracture and 301 (2.5%) a nonvertebral fracture. Also during follow-up, 72 patients have had a hip fracture (femoral neck and pelvic bone), and 69.4% of these patients had a history of fracture at inclusion.

As at 08 January 2010, 27.9% of patients in the follow-up cohort had discontinued PROTELOS, 12.5% in the first six months of treatment (45.0% of treatment withdrawals), 19.2% in the first year (68.9% of treatment withdrawals), 7.2% in the second year (26.0% of treatment withdrawals) and 1.4% after two years (5.2% of treatment withdrawals).
Mean treatment duration between inclusion and withdrawal was 9 (+/-8) months with a median of 7 months, and the main reasons for discontinuing PROTELOS were patients being tired of the treatment (891 patients, 7.5%), adverse events (862 patients, 7.3%) and patient's request (633 patients, 5.3%).

At 12 months after the inclusion visit, 78% of patients were still taking their treatment; at 24 months, this figure was 69%.
In a study based on the Canadian Database of Osteoporosis and Osteopenia (Papaioannou, 2003), after one year 90.3% of patients were still taking etidronate, 77.6% were still taking alendronate and 80% were still taking hormone replacement therapy.

Compliance with treatment was measured by self-completed questionnaire at each follow-up visit (how often treatment had been forgotten during the month before the visit): approximately 10% of patients said that they had occasionally forgotten their treatment, about 25% had forgotten it rarely, and just

under 60% (visits at 18 months or later), very rarely. The proportion of patients who said that they had often or very often forgotten their treatment ranged from 3.7% to 18.8%, depending on the period.

Adverse effects
Tolerance data were analysed for 11 853 patients for whom information had been collected since the initial visit (at a follow-up visit or on notification of an adverse event).

General data

At least one emergent adverse event was reported in 1 938 patients (16.4% of the follow-up cohort), mainly diarrhoea (201 patients, 1.7%), nausea (115 patients, 1.0%), falls (80 patients; 0.7%) and vomiting (72 patients, 0.6%).
The most frequently reported disorders (≥1%) were gastrointestinal disorders (698 patients, 5.9%), muscle, connective and bone tissue disorders (271 patients, 2.3%), nervous system disorders (240 patients, 2.0%), infections/infestations (191 patients, 1.6%), skin and subcutaneous tissue disorders (169 patients, 1.4%), cardiac disorders (129 patients, 1.1%) and vascular disorders (122 patients, 1.0%).

Since the start of the study, 147 patients (1.2%) have reported an adverse event which had led to death and a total of 211 patients died during follow-up (1.8%).
The main causes of death were:

- cardiac (47 patients, 0.4%): coronary disease (20 patients, 0.2%), particularly myocardial infarction (16 patients, 0.14%) and heart failure (17 patients, 0.1%)
- benign, malignant and unspecified tumours (75 patients, 0.6%): malignant and unspecified breast tumours (26 patients, 0.2% including 22 cases of breast cancer) and malignant and unspecified gastrointestinal tumours (21 patients, 0.2%)
- nervous system disorders (13 patients, 0.1%): stroke (6 patients, 0.05%)
- respiratory, chest and mediastinal (10 patients, 0.1%): pulmonary embolism (5 patients, 0.04%).

The investigator did not consider any of these deaths to be related to PROTELOS therapy.

During follow-up, 502 patients reported 649 serious adverse events, i.e. 4.24% of patients in the follow-up cohort. These events account for 22.0% of all emergent events.
Most common serious events (≥ 0.5%) were:

- cardiac disorders (93 patients, 0.8%): coronary disease (33 patients, 0.3%), particularly myocardial infarction (18 patients, 0.15%), heart failure (32 patients, 0.3%) and arrhythmia (22 patients, 0.2%)
- benign or malignant tumours (24 patients, 0.2%): breast tumours (26 patients, 0.2% - including 22 breast cancers) and malignant and unspecified gastrointestinal tumours (21 patients, 0.2%)
- injuries, poisoning and convocations of surgery (70 patients, 0.6%), particularly falls (28 patients, 0.2%) and bone and joint injuries (34 patients, 0.3%)
- nervous system disorders (67 patients, 0.6%): stroke (21 patients, 0.2%).

In all, 796 patients (6.7% of the follow-up cohort) reported 958 adverse events which the investigator considered to be possibly treatment-related. These events accounted for 32.5% of all events (958 / 2 951).
The most common events concerned:

- gastrointestinal disorders (528 patients, 4.45%): diarrhoea (1.49%), nausea (0.90%), vomiting (0.52%)
- skin disorders (94 patients, 0.8%): allergic dermatitis (0.29%), pruritus (0.14%), allergic pruritus (0.13%)
- nervous system disorders (67 patients, 0.57%): headache (0.25%), amnesia (0.11%).

Eight of these disorders were considered to be serious: one ulcerative colitis, one haemorrhoids, two allergic dermatitis, one generalised rash, one disorder of consciousness, one amnesia and one vasovagal syncope.

And during follow-up, 775 patients reported 897 adverse events which led to treatment withdrawal. The type of disorders in question were similar to the events possibly related to PROTELOS therapy.

Venous thromboembolic events

Cohort data

In the follow-up cohort, 51 thromboembolisms were reported in 44 patients (0.37%): deep vein thrombosis (33 patients, 0.28%), pulmonary embolism (16 patients, 0.14%) which accounted for a third of thromboembolisms, and retinal vein occlusion (2 patients, 0.02%). Seven of these patients experienced pulmonary embolism combined with deep vein thrombosis.
Global incidence of these events was 2.5 [1.8; 3.3] per 1 000 patient-years.
The investigator considered that 15 (29.4%) of these events were possibly treatment-related: ten deep vein thromboses, four pulmonary embolisms including three combined with deep vein thrombosis, and one retinal vein occlusion.

Mean time to onset of these events was 371 days (+/-237), range 22-989 days, with a median time of 296 days.
Mean patient age at the time of these events was 76 years (+/- 5 years), range 64-86 years. Patients who had thromboembolic events were older than patients in the follow-up cohort (68.9 years +/- 10.3), with ten of them aged 80 years or over (incidence of thromboembolism for patients aged 80 years or over was 3.4 [1.63; 6.26] per 1 000 patient-years, 2.28 [1.58; 3.18] per 1 000 patient-years in patients aged under 80 years).

The main potential risk factors found were a previous history of VTE and/or thrombosis (ten patients) or prolonged immobilisation (eleven patients).
The outcome of these events was:
- recovery: 24 cases, 47.1%
- recovering: 13 cases, 25.5%
- not recovered: 4 cases, 7.8%
- recovered with sequelae: 3 cases (5.9%)
- death: 7 cases (13.7%)

Other epidemiological data on thromboembolic events

Overall Safety Set

OSS 2007 groups patients from both phase II trials and the five phase III trials carried out with PROTELOS 2 g versus placebo. This database includes a total of 7 572 patients, 3 803 of whom were treated with PROTELOS and 3 769 with placebo. Mean duration of exposure to treatment was just under three years.
In this database, the annual incidence of thromboembolic events was 7.9 per 1 000 patient-years in the PROTELOS group and 5.8 per 1 000 patient-years in the placebo group, with a difference between the two groups at the threshold of significance (OR = 1.37 [0.99; 1.89], p = 0.057).

General Practice Research Database

The study period was extended from 02 December 2004 (the date when PROTELOS was placed on the market in the United Kingdom) to 21 January 2008 (the date when data were extracted). The study was published (Bréart, 2009) in the journal 'Osteoporosis International'.
Three cohorts of women aged over 50 years formed from this cohort were followed up:
- reference cohort of non-osteoporotic women (115 009)
- a reference cohort of untreated osteoporotic women (11 546)
- cohorts of women who had taken PROTELOS (2 408) or alendronate (20 084).

The risk of venous thromboembolism (VTE) increased by approximately 40% (HR = 1.38 [1.03; 1.86][12]) in untreated osteoporotic women (annual incidence (AI) = 5.6 / 1 000 patient-years) compared with non-osteoporotic patients (AI = 3.2/1000 patient-years).
In comparison with untreated osteoporotic patients, there was no statistically significant increase in the risk of events for treated patients:
- for patients treated with PROTELOS, the annual incidence was 7.0 / 1 000 patient-years with a hazards ratio of 1.15 [0.63; 2.10] (p = 0.656);
- for patients treated with alendronate, the annual incidence was = 7.2 / 1 000 patient-years with a hazards ratio of 1.10 [0.81; 1.50] (p = 0.646);
- for untreated patients, the annual incidence was 5.6 / 1000 patient-years.

A further analysis was carried out with data collected on 04 January 2009 concerning 3 202 patients in the PROTELOS cohort, 27 780 patients treated with alendronate and 14 599 untreated osteoporotic women.

[12] By adjusting for age, history of thromboembolism, BMI and corticosteroids

The results of this further analysis, which supported the early results, were:

- for patients treated with PROTELOS, annual incidence was 8.3 / 1 000 patient-years with a hazards ratio of 0.96 [0.60; 1.52] ;
- for patients treated with alendronate, annual incidence was = 7.5 / 1 000 patient-years with a hazards ratio of 0.83 [0.65; 1.06];
- for untreated patients, annual incidence was 6.2 / 1000 patient-years.

Drug Safety Research Unit cohort

Patients were identified from UK National Health Service prescriptions, and prescribing doctors received a questionnaire a year after the first prescription, asking them to provide data on the patient's age, treatment duration and the main clinical events observed since the start of prescription. Cases of thromboembolism reported were subsequently the subject of a specific asessment.
Analysis of cases was limited to treatment-emergent events or those appearing within 30 days of treatment discontinuation.
The study began in December 2005 (12 months after prescription of PROTELOS) and was published (Osborn, 2010) in the journal 'Drug Safety'.
Questionnaires were sent for 23 832 patients with a response rate of 52.8%; 13.3% of these responses could not be used. The cohort analysed therefore consisted of 10 782 patients.
Forty-eight (48) thromboembolic events were reported for the first year of treatment (31 deep vein thromboses and 17 pulmonary embolisms) for an exposure of 7 697 patient-years. Annual incidence was 6.24 [4.60; 8.27] per 1 000 patient-years.

Patients aged 80 years or over

In the follow-up cohort, 1 948 (16.4%) of patients were aged 80 years or over. Ninety three percent (93.0%) were aged between 80 and 90 years, and 7% were aged 90 years or over.
Mean age at menopause was 49 years (+/-4.7 years). BMI at inclusion was 25.2 (+/-4.2) kg/m2 (data comparable with the whole follow-up cohort).
Of these patients, 69.4% had at least one risk factor for osteoporosis and fracture. This percentage was higher than for the whole cohort (63.6%). The three most common risk factors were lack of exercise (35%), frequent falls during the preceding year (24.6%) and inadequate calcium intake (20.7%).
In the follow-up cohort, 69.7% of patients aged 80 years or over had at least one fracture at inclusion; 48.9% fractures were vertebral and 35.5% nonvertebral.
Densitometry data were available for 27.6% (538/1948) of patients for femoral bone density and for 25.8% (503/1948) of patients for vertebral bone density. Mean femoral T-score at inclusion was -2.57 (+/-0.78) SD and lumbar T-score was -2.48 (+/-1.07) SD.
Of the patients aged 80 years or over, 4.2% had a history of thromboembolism (3.2% deep vein thrombosis and 1.5% pulmonary embolism).
Mean duration of their PROTELOS therapy after inclusion (17.1 +/- 9.8 months) was similar to that of all patients in the follow-up cohort.

Of the 1 948 patients aged 80 years or over, 416 (21.4%) reported 713 adverse events. These events accounted for 24.2% of all events reported (these patients representing 16.4% of all patients in the follow-up cohort).
During follow-up, 76 patients had a fatal adverse event. The main causes of death were cardiac disease (1.44%), particularly myocardial infarction (0.4%).
In addition, a further 30 patients died, bringing the number of deaths in patients aged 80 years or over to 106 (5.4%).

A total of eleven thromboembolic events occurred in ten of these patients, made up of six deep vein thromboses, four pulmonary embolisms and one retinal vein occlusion.
The incidence of these events was 3.4 [1.63; 6.26] per 1 000 patient-years. In the investigator's opinion, none of these cases was treatment-related.
The incidence of these events in patients aged under 80 years was 2.3 [1.58; 3.18] per 1 000 patient-years (40 events reported).

French patients

In France, 6 097 women were included in the registry (18.5% of all women in the registry) and 2 200 in the cohort (16.8% of all women in the cohort). A total of 1 958 women were followed up (89.0% in the French cohort).

12.2% of these women were followed up for less than a year, 48.6% were followed up for one to two years and 39.3% were followed up for at least two years. Mean duration of follow-up was 21.7 (+/-7.5) months. These data were similar to those for all patients.
Mean duration of treatment after the initial visit was 19.0 (+/-8.7 months), corresponding to 3 098 patient-years.
The characteristics of the French cohort were similar to those for the general cohort in terms of, mean age, BMI and mean age at menopause. However, there are more women aged over 80 years in France (19.4%) than in the global cohort (16.3%) and the percentage of patients receiving calcium and vitamin D supplements is lower in France (47.1% vs. 58.9%).
Bone mineral density (BMD) data are only available for fewer than half the patients (48.4% for lumbar BMD and 47.5% for femoral BMD): mean T score was -2.5 for lumbar BMD and -2.2 for femoral BMD (similar results to the global cohort).
The number of patients with at least one risk factor was higher in the French cohort (79.3% vs. 64.1%), as was the number of women with a history of osteoporotic fracture (51.0% vs. 45.3%), particularly vertebral fracture (33.1% vs. 22.2%).

Over the follow-up period, a new fracture was reported in 104 of the 1 958 patients who made up the follow-up cohort in France: 38 patients (1.9%) reported a vertebral fracture and 70 (3.6%) a nonvertebral fracture (a higher percentage than that of the general cohort, i.e. 2.5%).

Data from the Thales database were used to compare prescribing doctors and patients treated with PROTELOS.
The distribution of prescribing doctors in France in terms of sex, specialty and practice region was globally similar between the Thales data and the French cohort. However, the proportion of specialist doctors was higher in the cohort than in the Thales database (12.7% vs. 2.6%).
Patient characteristics were globally similar between the cohort and the Thales database, in terms of mean age, BMI and history of fracture. However, it should be noted that the percentage of patients aged 80 years or over was 19.4% in the cohort compared with 25.4% in the Thales database.

In France, 21.9% of patients in the follow-up cohort discontinued treatment with PROTELOS (this percentage is higher in the global cohort, i.e. 27.9%): 7.7% in the first six months of treatment (35.2% of discontinuations), 14.1% in the first year (64.3% of discontinuations), 6.8% in the second year (30.8% of discontinuations) and 1.1% after two years (4.9% of discontinuations).
Mean treatment duration was 10.4 (+/- 7.7) months and the most common reasons for withdrawal were adverse events (143 patients, 7.3%) and patients being tired of treatment (131 patients, 6.7%).

Conclusion

These new data concerning PROTELOS tend overall to show a higher risk of thromboembolism in patients treated with PROTELOS, particularly in women aged 80 years or over (incidence levels are similar in the various epidemiological studies submitted). However, this risk estimated in everyday conditions of use remained similar to that found in the trials.

Concerning data on the use PROTELOS, particularly in France, the data submitted were not sufficient for an accurate assessment of compliance with the conditions for reimbursement as defined by the Transparency Committee, in particular because results for bone mineral density (BMD) were available at inclusion for fewer than half of patients, and because of the use in this study of a much broader definition of risk factors than that used for reimbursement.

These intermediate results need to be confirmed by full follow-up of the cohort.