HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 February 2008

FORSTEO 250 µg/ml, solution for injection in pre-filled pen
Pack of 1 pre-filled 3 ml pen – CIP code: 3622162

LILLY FRANCE SAS

teriparatide

Exception drug status

List I

Date of Marketing Authorisation: 10 June 2003 (centralised procedure)

Date of latest revision of Marketing Authorisation: 12 July 2007 (extension of indication to the treatment of osteoporosis in men at increased risk of fracture)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospitals use in the new indication: “treatment of osteoporosis in men at increased risk of fracture.”

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:
teriparatide

1.2. Indications
"Treatment of osteoporosis in postmenopausal women and **in men at increased risk of fracture**.
In postmenopausal women, a significant reduction in the incidence of vertebral and nonvertebral fractures but not hip fractures has been demonstrated."

N.B.:
Paragraph 5.1 (Pharmacodynamic properties) of the SPC states: "Independent risk factors, for example, low bone mineral density (BMD), age, the existence of previous fracture, family history of hip fractures, high bone turnover and low body mass index should be considered in order to identify women and men at increased risk of osteoporotic fractures who could benefit from treatment."

1.3. Dosage
The recommended dose of FORSTEO is 20 micrograms administered once daily by subcutaneous injection in the thigh or abdomen.
Patients must be trained to use the proper injection techniques.
A user manual is also available to instruct patients on the correct use of the pen.
The maximum total duration of treatment with FORSTEO should be 18 months.
Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.
Following cessation of FORSTEO therapy, patients may be continued on other osteoporosis therapies.
(Refer to SPC.)

2. SIMILAR MEDICINAL PRODUCTS

1. ATC Classification (2007)

H	:	Systemic hormones
H05	:	Calcium homeostasis
H05 A	:	Parathyroid hormones
H05 AA	:	Parathyroid hormones
H05 AA 02	:	Teriparatide

2. Medicines in the same therapeutic category

Comparator medicines

No medicine in the same therapeutic category has a marketing authorisation for the treatment of male osteoporosis.

3. Medicines with a similar therapeutic aim

- FOSAMAX 10 mg (alendronic acid) and generics are indicated in the “treatment of male osteoporosis”
- ACTONEL 35 mg (risedronate) is indicated for the "treatment of osteoporosis in men at increased risk of fracture".

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The extension of the indication for FORSTEO (teriparatide) in male osteoporosis is based on the results of the bone densitometry study GHAJ conducted between July 1997 and December 1998.

- Study GHAJ[1]

Objective: to demonstrate the superiority of FORSTEO 20 µg or 40 µg over placebo in increasing bone mineral density (BMD) in 437 men (mean age 58.7 years) with osteoporosis of either idiopathic or hypogonadal origin (hypogonadal defined as a low level of free testosterone or raised FSH or LH).

Methodology:
Double-blind, randomised, placebo-controlled study.

Inclusion criteria:
- Age 30-85 years
- primary osteoporosis of idiopathic or hypogonadal origin
- BMD at the lumbar spine or femoral neck or total hip ≤ -2.

Exclusion criteria:
- secondary forms of osteoporosis (endocrine diseases, malabsorption syndrome, glucocorticoid-induced osteoporosis) or osteoporosis due to bone metabolism disorders other than that classified as primary osteoporosis (Paget's disease, renal osteodystrophy, osteomalacia, or drug interactions);
- episodes of urolithiasis during the two years period prior to randomisation;
- history of treatment for osteoporosis:
    - either long-term treatment for 2 months or more during the 12 months period prior to inclusion (oral bisphosphonate), or for 2 months or more during the 24 months period prior to inclusion (fluoride), or for any length of time during the 24 months period prior to inclusion (intravenous bisphosphonate);
    - or treatment initiated shortly before inclusion: during the 2 months period before inclusion for calcitonin, the 3 months period before inclusion for bisphosphonates, or the 6 months period before inclusion for fluoride or any other hormonal therapy.

Treatments:
The patients were randomised into 3 groups receiving one of the following:
- FORSTEO 20 µg/day (n = 151)
- FORSTEO 40 µg/day (n = 139)
- Placebo (n=147)

All patients also received 1000 mg calcium and 400-1200 IU vitamin D supplements per day.

[1] Orwoll et al. The effect of teriparatide therapy on bone density in men with osteoporosis. Journal of Bone and Mineral Research 2003; 18 (1): 9-17.

Treatment duration:
The study design had a 24-month treatment period. However, it was prematurely terminated in December 1988 because of osteosarcoma observed in rats. As a result, the median observation time was 10.8 months in the placebo group and 10.3 months in the FORSTEO 20 µg group.

NB: The CHMP considered this duration of treatment to be acceptable.

Primary endpoint: Variation in lumbar spine BMD

Results:
The protocol included a primary analysis of the results on an ITT basis. Since the dosage specified in the marketing authorisation for this indication is 20 µg/day, only the results for the group receiving this dose will be presented.
At baseline, 35% of the patients had a history of vertebral fracture and 59% a history of non-vertebral fracture. Less than 15% of the patients had been treated previously for osteoporosis.

Table 1: Baseline patient characteristics (ITT population)

Parameters	**Placebo n = 147**	**FORSTEO 20 µg n = 151**
Mean age (years)	59± 13	59± 13
Mean BMI (kg/m^2)	25± 4	25± 4
Low free testosterone level (%)	50	48
Lumbar spine T score	-2.4 ± 1.2	-2.0 ± 1.3
Femoral neck T-score	-2.7 ± 0.8	-2.6 ± 0.8
Total hip T-score	-1.9 ± 0.8	-1.8 ± 0.8
History of treatment for osteoporosis	12%	15%
History of vertebral fractures (%)	57 (38.8%)	50 (33.1%)
History of non-vertebral fractures (%)	79 (53.7%)	100 (66.2%)
Overall history of fractures (%)	103 (70.1%)	114 (75.5%)

Table 2: Variation in lumbar spine BMD (primary endpoint) and total hip BMD (secondary endpoint) at 12 months relative to baseline (%)

	Placebo (n=147)	**FORSTEO 20 µg (n = 151)**	**p**
Lumbar spine BMD			
n	143	141	
Mean baseline BMD (g/cm^2)	0.85 ± 0.14	0.89 ± 0.15	NS
Mean variation (g/cm^2)	0.01 ± 0.03	0.05 ± 0 .04	<0.001
Mean variation (%)	0.54 ± 4.19	5.73 ± 4.46	<0.001
Total hip			
n	137	135	
Mean baseline BMD (g/cm^2)	0.83 ± 0.11	0.84 ± 0.10	NS
Mean variation (g/cm^2)	0.00 ± 0.02	0.01 ± 0.02	0.017
Mean variation (%)	0.41 ± 2.77	1.14 ± 2.89	0.040
Femoral neck			
n	137	135	
Mean baseline BMD (g/cm^2)	0.70 ± 0.11	0.71 ± 0.10	NS
Mean variation (g/cm^2)	0.00 ± 0.03	0.01 ± 0.03	0.013
Mean variation (%)	0.36 ±3.95	1.44 ± 3.61	0.038

After 12 months of treatment, BMD increased at the lumbar spine by 5.3% and at the total hip by 0.7% compared with placebo. The difference was 1.1% at the femoral neck.

- Other data:

Study GHBJ[2]

Three hundred and fifty-five (355) patients from study GHAJ who had been treated with teriparatide 20 µg or 40 µg or placebo during study GHAJ were enrolled in an open-label follow-up study. Patients were allowed to receive other osteoporosis therapies (bisphosphonates or testosterone) during this phase. The primary objective of this follow-up study was safety surveillance.

In view of the objective, methodology and analysis of this study, the results are only considered indicative.

Out of the 355 patients included in the follow-up, data on the incidence of vertebral fractures after 30 months were only available for 248 patients who had initially been treated with teriparatide 20 µg or placebo.

No statistically significant difference in the incidence of fractures of any severity was found between placebo and teriparatide 20 µg (marketing authorisation dosage) or 40µg dosages.

Comparisons with active comparator drugs

No comparative study is available versus standard of care (SOC) alendronate (FOSAMAX) or risedronate (ACTONEL) in the treatment of male osteoporosis.

3.2. Safety

Safety data for FORSTEO (teriparatide) in the extended indication of male osteoporosis come from the pivotal study GHAJ and the cohort observational study GHBJ. The safety profile of FORSTEO in men was the same as that observed in women. No new undesirable effect was identified.

The most commonly reported adverse events in patients treated with FORSTEO are: nausea, pain in the limbs, headache and vertigo.

The European risk management plan covers surveillance of the risks of osteosarcoma, hypercalcaemia and orthostatic hypotension.

3.3. Conclusion

A placebo-controlled study demonstrated that FORSTEO (teriparatide) increased lumbar spine bone mass significantly more than placebo in men with a mean age of 59 years and a mean T score of -2.2 at the lumbar spine and -2.7 at the femoral neck, 36% of whom had had a vertebral fracture at baseline. The efficacy of FORSTEO in diminishing fracture rates has not been demonstrated in men. Moreover, no controlled comparative study versus a standard of car (SOC) is available.

The undesirable effects observed were in line with this product's known safety profile.

[2] Kaufman. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 2005;16: 510-516.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck may affect life expectancy.
In men, FORSTEO increases lumbar spine bone mass; its efficacy in diminishing fracture rates has not been demonstrated.
FORSTEO treatment may be used to prevent osteoporotic fractures in patients with idiopathic or hypogonadal osteoporosis when aetiological treatment for this condition has proved to be inadequate or inappropriate.

Public health benefit:

It is difficult to quantify the public health burden of osteoporosis in men. Improving prevention of femoral neck fractures in the elderly is a public health need within the scope of the priorities identified by the GTNDO.
The impact that this product may be expected to have on morbi-mortality and quality of life cannot be quantified from the available data (particularly because of the lack of any comparison with existing treatments and the failure of a placebo-controlled study to demonstrate an effect on fracture risk).
In addition, there is no guarantee that the results of the study can be transposed into real practice (particularly, the profile of patients treated in real practice is likely to be different from that of the study, and there is the concern of patients' compliance with this daily injection treatment).
Nothing suggests, therefore, that FORSTEO will provide an additional answer to the identified need
Accordingly, in the current state of knowledge, FORSTEO is not expected to provide any public health benefit.

The efficacy/safety ratio for this medicinal product is high.
FORSTEO is used in first or second-line therapy.
There are alternative treatments.
The actual benefit of this drug is substantial.

4.2. Improvement in actual benefit

In the absence of comparative data with bisphosphonates indicated in the treatment of male osteoporosis, the Transparency Committee considers that FORSTEO provides no improvement in actual benefit (level V) over the bisphosphonates indicated in the treatment of osteoporosis in men at increased risk of fracture.

4.3. Therapeutic use

Since male osteoporosis is "secondary" in more than 50% of cases, it is important to treat the associated causes (mainly endocrine disorders) and to discontinue the use of "toxic factors" (such as tobacco and alcohol). Regular load-bearing exercise and the correction of any dietary deficiencies in calcium and vitamin D are also recommended.
In addition to aetiological treatment and calcium and vitamin D supplementations, bisphosphonates (alendronate – FOSAMAX® 10 mg taken daily – and risedronate – ACTONEL® 35 mg taken weekly) and teriparatide (FORSTEO) are indicated in the treatment of osteoporosis in men.
In men, FORSTEO and bisphosphonates have been shown to increase bone mass, but their efficacy in diminishing fracture rates has not been demonstrated.

As it is the case in women, FORSTEO should be reserved for severe osteoporosis, i.e. cases that are complicated by at least two vertebral fractures.

4.4. Target population

The target population for FORSTEO in the extended indication of male osteoporosis comprises all men with severe osteoporosis, i.e. cases that are complicated by at least two vertebral fractures

For indicative purposes, in the absence of epidemiological data from France, the prevalence of densitometrically diagnosed osteoporosis (T score < -2.5) may be estimated from a US study. It is likely to 3-6% in men over 50.[3] Extrapolating these figures to the French population (INSEE, 1 January 2007, n = 9,750,000) gives that between 300,000 and 585,000 men are affected by osteoporosis in France.

No epidemiological data are available for the number of osteoporotic men with vertebral fractures in France.
For indicative purposes, however, European studies (EVOS 1999 and Salmelson 2006) suggest that 12% of osteoporotic men have a radiological vertebral fracture.
The population of osteoporotic men in France who have one radiological vertebral fracture must therefore be between 36,000 and 72,000 patients.
There are, however, no available data from which the population of osteoporotic men with at least two vertebral fractures can be estimated.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services.

4.5.1 Scope of reimbursement
Treatment of osteoporosis in men who have at least two vertebral fractures.

4.5.2 Packaging: A pack contains 1 pre-filled 3 ml pen containing 750 µg teriparatide, suitable for 28 days' treatment.

4.5.3 Reimbursement rate: 65%

4.5.4 Exception drug status

[3] Looker AC et al. Prevalence of low femoral bone density in older US adults from NHAES III. J Bone Mineral Res 1997;12: 1761-8.