HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

16 July 2008

**FORSTEO 20 µg/80 µl, solution for injection in pre-filled pen**
**Pack of 1 pre-filled 3 ml pen – CIP code: 362 216-2**

**Applicant: LILLY FRANCE SAS**

teriparatide

ATC code: H05AA02

List I

Marketing authorisation (MA) date: 10 June 2003 (centralised procedure)

Date of latest revision of Marketing Authorisation: 2 April 2008 (Extension of indication in the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture)

Exception drug status

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the new indication of treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

teriparatide

## 1.2. Therapeutic 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.

- **Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture."**

## 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. The 18-month course of FORSTEO should not be repeated over a patient's lifetime.

Patients should receive calcium and vitamin D supplements if dietary intake is inadequate.

Following cessation of FORSTEO therapy, patients may be continued on other osteoporosis therapies.

Use in renal impairment: FORSTEO should not be used in patients with severe renal impairment. In patients with moderate renal impairment, FORSTEO should be used with caution.

Use in hepatic impairment: No data are available in patients with impaired hepatic function.

Children: There is no experience in children. FORSTEO should not be used in children or young adults with open epiphyses.

Elderly patients: Dosage adjustment based on age is not required.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2008)

| | | |
|---|---|---|
| H | : | Systemic hormones |
| H05 | : | Calcium homeostasis |
| H05 A | : | Parathyroid hormones |
| H05 AA | : | Parathyroid hormones |
| H05AA02 | : | Teriparatide |

### 2.2. Medicines in the same therapeutic category

Teriparatide is the only bone formation agent indicated in the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy.

### 2.3. Medicines with a similar therapeutic aim

Bisphosphonates used in glucocorticoid-induced osteoporosis:
ACTONEL 5 mg: to maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses greater than or equal to 7.5 mg/day prednisone or equivalent.

DIDRONEL 400 mg and generics: to prevent bone loss in patients undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses greater than 7.5 mg/day prednisone or equivalent.

FOSAMAX 5 mg (not marketed): to prevent bone loss in patients undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses greater than 7.5 mg/day prednisone or equivalent.

## 3 ANALYSIS OF AVAILABLE DATA

One study (GHBZ) has been submitted by the manufacturer.

### 3.1. Efficacy

Principal study objective
To assess whether the increase in bone mineral density (lumbar spine BMD) observed after 18 months of treatment with FORSTEO is greater than that observed with alendronate 10 mg in patients at risk of fracture who have been under glucocorticoid therapy for at least 3 months.

Design
*Type of study:*
Phase III, 36-month, randomised, double-blind study comparing Forsteo 20 µg/day with alendronate 10 mg/day in fracture-risk patients who have been under glucocorticoid therapy equivalent to 5 mg/day or more of prednisone for at least 3 months.

*Duration:* The primary analysis was performed on the first 18 months of the study. Only these results are given below.

*Inclusion criteria:*
Patients (men or women) aged above 21 years who have been under corticoid therapy (mean prednisone equivalent dose ≥ 5 mg/day) for at least 3 months with a BMD T score ≤ -2 (or T score ≤ -1 in cases with a history of glucocorticoid-associated fracture) at the lumbar spine or femoral neck or total hip.

*Exclusion criteria:*

- bone metabolism disorder other than that induced by glucocorticoid therapy;
- episodes of urolithiasis during the two years prior to randomisation;
- history of treatment for osteoporosis:
    - oral bisphosphonate for 2 months or more during the 12 months prior to inclusion or for 2 weeks or more during the 6 months prior to inclusion;
    - intravenous bisphosphonate for any length of time during the 24 months prior to inclusion;
    - calcitonin during the two weeks prior to inclusion;
    - androgens or other anabolic steroids during the 6 months prior to inclusion;
    - fluoride during the 6 months prior to inclusion or for more than 6 months at any time prior to inclusion.

*Treatment*
Patients were randomised into two groups stratified by sex and history of bisphosphonate treatment.

Forsteo group: teriparatide 20 µg/day by subcutaneous injection + oral placebo
Alendronate group: alendronate 10 mg/day orally + placebo by subcutaneous injection

All patients were also given 1,000 mg calcium and 400-1,200 IU vitamin D supplements per day for at least 4 weeks before the beginning of the study and throughout its duration.

NB
The MA for Alendronate 10 mg does not cover this indication.
The GREES[1] recommendations, however, suggest it is an acceptable comparator.

*Primary endpoint:*
Variation in lumbar spine BMD.

NB
The clinical relevance of BMD is not ideal since the correlation between increased BMD (paraclinical criterion) and reduced fracture frequency (clinical criterion) has been poorly established in glucocorticoid-induced osteoporosis.

*Secondary endpoints:* The following in particular were examined:
Variation in BMD at the femoral neck or total hip
Vertebral or non-vertebral fractures.

Results:
The protocol included a primary analysis of the results on an ITT basis.
429 patients were randomised.
428 patients received treatment (214 patients per group).

[1] Abadie EC**,** Devogealer JP, Ringe JD, et al. Recommendations for the registration of agents to be used in the prevention and treatment of glucocorticoid-induced osteoporosis: updated recommendations from the Group for the Respect of Ethics and Excellence in Science. Seminars in Arthritis & Rheumatism. 2005 Aug;35(1):1-4.

*Patient characteristics (see Table 1)*
At baseline, 80% of patients were women, 80% of whom were postmenopausal.
The patients' mean lumbar T score was -2.5 in the alendronate 10 mg arm and -2.4 in the Forsteo arm. 27.6% of patients had a history of vertebral fracture and approximately 20% a history of non-vertebral fracture due to bone fragility.
The patients had been receiving a median prednisone equivalent dose ranging between 7.5 and 7.8 mg/day for at least one year.

Table 1: Baseline patient characteristics (ITT population)

| | **Alendronate 10 mg (n=214)** | **Forsteo 20 µg (n=214)** |
|---|---|---|
| Men (%) | 41 (19.2%) | 42 (19.6%) |
| Women (%) | 173 (80.8%) | 172 (80.4%) |
| postmenopausal (%) | 143 (82.7%) | 134 (78.4%) |
| premenopausal (%) | 30 (17.3%) | 38 (22.1%) |
| Age (years) (mean ± sd) | 59.1± 1.53 | 57.9 ± 1.52 |
| Glucocorticoid treatment: | | |
| Median prednisone equivalent dose (mg/day) | 7.8 | 7.5 |
| Median duration (years) | 1.2 (0.25 - 5.7) | 1.5 (0.25 - 5.2) |
| Underlying condition requiring glucocorticoid treatment | | |
| 1. Inflammatory rheumatism, including: | 161 (75.2%) | 161 (75.2%) |
| Rheumatoid arthritis | 111 (51.9%) | 98 (45.8%) |
| Systemic lupus erythematosus | 21 (9.8%) | 28 (13.1%) |
| Polymyalgia rheumatica | 8 (3.7%) | 10 (4.7%) |
| Vasculitis | 3 (1.4%) | 5 (2.3%) |
| Other | 18 (8.4%) | 20 (9.3%) |
| 2. Respiratory disease | 31 (14.5%) | 29 (13.6%) |
| 3. Inflammatory bowel diseases | 4 (1.9%) | 3 (1.4%) |
| 4. Others | 18 (8.4%) | 21 (9.8%) |
| **Previous bisphosphonate treatment for osteoporosis** | 20 (9.3%) | 20 (9.3%) |
| **History of vertebral fractures (%)** | 53 (25.4%) | 62 (30.0%) |
| **History of non-vertebral fractures due to fragility (%)** | 43 (20.1%) | 42 (19.6%) |
| **Lumbar spine BMD (g/cm$^2$) (mean ± sd)** | 0.867 ± 0.014 | 0.865 ± 0.014 |
| **T score (mean ± sd)** | | |
| Lumbar spine | -2.5 ± 0.1 | -2.4 ± 0.1 |
| Total hip | -2.0 ± 0.1 | -2.0 ± 0.1 |
| Femoral neck | -2.0 ± 0.1 | -2.2 ± 0.1 |

NB
Most patients in the trial population have another osteoporosis risk factor in addition to glucocorticoid therapy.

*Results for the endpoints*

Sixty-nine per cent of patients completed the 18-month study. The reasons for dropping out are given in the table below:

| | **Alendronate 10 mg (n = 214)** | **Forsteo 20 µg (n = 214)** | **p** |
|---|---|---|---|
| Personal decision | 30 (14.0%) | 16 (7.5%) | 0.027 |
| Adverse events | 13 (6.1%) | 25 (11.7%) | 0.037 |
| Death | 12 (5.6%) | 7 (3.3%) | NS |
| Lost to follow-up | 8 (3.7%) | 3 (1.4%) | NS |
| Non-compliance | 3 (1.4%) | 3 (1.4%) | NS |
| Investigator's decision | 0 (0%) | 3 (1.4%) | NS |
| Sponsor's decision | 1 (0.5%) | 3 (1.4%) | NS |
| Other reasons | 1 (0.5%) | 3 (1.4%) | NS |
| Inclusion criteria not met | 2 (0.9%) | 1 (0.5%) | NS |
| **Total** | **70 (32.7%)** | **64 (29.9%)** | **NS** |

After 18 months, 103 patients had ceased glucocorticoid treatment (56 [26.2%] in the alendronate group and 47 [22.0%] in the FORSTEO group), which represents 24% of the total study population.

## Effect on BMD

Table 2: Increase in lumbar spine BMD at 18 months from baseline

| | **Alendronate 10 mg** | **Forsteo 20 µg** | **p** |
|---|---|---|---|
| ***Lumbar spine BMD*** *(primary endpoint)* | | | |
| n | 195 | 198 | |
| Mean baseline BMD (g/cm$^2$) | 0.869 ± 0.014 | 0.867 ± 0.015 | NS |
| Mean variation (g/cm$^2$) | 0.028 ± 0.006 | 0.059 ± 0.006 | <0.001 |
| **Mean percentage variation (%)** | **+3.4 ± 0.7%** | **+7.2 ± 0.7%** | **<0.001** |
| Men | +3.1 ± 1.8% | +5.7 ± 1.8% | NS |
| Premenopausal women | -1.9 ± 2% | +4.2 ± 1.6% | <0.001 |
| Postmenopausal women | +3.5 ± 0.8% | +7.4 ± 0.8% | <0.001 |
| ***Total hip BMD*** *(secondary endpoint)* | | | |
| n | 176 | 185 | |
| Mean baseline BMD (g/cm$^2$) | 0.786 ± 0.014 | 0.771 ± 0.014 | NS |
| Mean variation (g/cm$^2$) | 0.017 ± 0.004 | 0.026 ± 0.004 | 0.006 |
| **Mean percentage variation (%)** | **+2.2 ± 0.5%** | **+3.6 ± 0.5%** | **0.003** |
| Men | +2 ± 1.5% | +4.1 ± 1.6% | NS |
| Premenopausal women | +0.9 ± 1.4% | +3.8 ± 1.2% | 0.005 |
| Postmenopausal women | +2.5 ± 0.6% | +3.3 ± 0.6% | NS |
| ***Femoral neck BMD*** *(secondary endpoint)* | | | |
| n | 176 | 185 | |
| Mean baseline BMD (g/cm$^2$) | 0.729 ± 0.014 | 0.710 ± 0.014 | NS |
| Mean variation (g/cm$^2$) | 0.014 ± 0.005 | 0.024 ± 0.005 | 0.011 |
| **Mean percentage variation (%)** | **+2.1 ± 0.7%** | **+3.7 ± 0.8%** | **0.012** |
| Men | +3.1 ± 2.6% | +6.7 ± 2.8% | NS |
| Premenopausal women | +1.3 ± 1.8% | +2.4 ± 1.5% | NS |
| Postmenopausal women | +1.2 ± 0.7% | +2.3 ± 0.7% | NS |

At 18 months of treatment, the BMD increase in the Forsteo group was significantly greater than in the alendronate group, the mean difference between the groups being 3.8% at the lumbar spine, 1.4% at the total hip and 1.6% at the femoral neck.

**Effect on fracture rates** (secondary endpoint)

Analysis of fractures was conducted on only 165 of the 214 alendronate patients (77%) and on 171 of the 214 FORSTEO patients (80%).
The results should therefore be interpreted with the utmost caution given the number of patients (22%) for whom data are unavailable.

Table 3: Incidence of radiographic vertebral fractures by sub-group[2]

| Category | Fracture | Alendronate n (%) | FORSTEO n (%) | p |
|---|---|---|---|---|
| Overall | | 165 (100) | 171 (100) | |
| | None | 155 (93.9) | 170 (99.4) | |
| | Vertebral fracture | 10 (6.1) | 1 (0.6) | 0.004 |
| Postmenopausal women | | 111 (67.3) | 106 (62) | |
| | None | 105 (63.6) | 105 (61.4) | |
| | Vertebral fracture | 6 (3.6) | 1 (0.6) | 0.038 |
| Premenopausal women | | 23 (13.9) | 33 (19.3) | |
| | None | 23 (13.9) | 33 (19.3) | - |
| | Vertebral fracture | 0 (0) | 0 (0) | - |
| Men | | 31 (18.8) | 31 (18.1) | |
| | None | 27 (16.4) | 31 (18.1) | |
| | Vertebral fracture | 4 (2.4) | 0 (0) | 0.048 |

## 3.2. Adverse effects

Study data
No death was related to Forsteo exposure.
No case of cancer was related to Forsteo exposure.
The number of study withdrawals due to adverse events was 13 (6.1%) in the alendronate group compared with 25 (11.7%) in the Forsteo group.
No significant difference was observed between the two groups in terms of the frequency and severity of adverse events.
The non-serious adverse events most frequently observed with Forsteo were vertigo, headache and reactions at the injection site.
Episodes of hypercalcaemia were reported in 15% of Forsteo patients compared with 4.7% of alendronate patients.
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 covering surveillance of the risks of osteosarcoma, hypercalcaemia and orthostatic hypotension has been extended to introduce special monitoring for women of childbearing age.

SPC data
The following convention has been used for the classification of the adverse reactions: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

[2] Table taken from the EPAR

Table 4: SPC data regarding adverse reactions

| **Classification by organ system** | **Undesirable effects** |
|---|---|
| General disorders and administration site conditions | Rare: Possible allergic events soon after injection: acute dyspnoea, oro-facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral).<br><br>Common: Mild and transient injection site events, including pain, swelling, etythema. |
| Metabolism and nutrition disorders | Uncommon: Hypercalcaemia greater than 2.76 mmol/l (11 mg/dl)<br>Rare: Hypercalcaemia greater than 3.25 mmol/l (13 mg/dl) |
| Musculoskeletal and systemic disorders | Uncommon: Myalgia, arthralgia<br>Not known: Back cramp/pain* |
| Investigations | Uncommon: Alkaline phosphatase increase |

* Serious cases of back cramp or pain have been reported within minutes after the injection.

### 3.3. Conclusion

A comparator (alendronate 10 mg)-controlled study was conducted on patients with glucocorticoid-induced osteoporosis (N=428), the majority of whom were postmenopausal women (N=277). At baseline, the patients (mean age 59 years) had mean T scores of -2.5 at the lumbar spine and -2.1 at the femoral neck. In addition, 28% already had one or more vertebral fractures and 20% a non-vertebral fragility fracture.

Effect on lumbar spine BMD:
FORSTEO (teriparatide) was shown to significantly increase lumbar spine bone mass compared with alendronate 10 mg.

Effect on fracture rates:
Fracture data at 18 months were available for only 78% of the patients randomised. No conclusions can therefore be drawn on reductions in fracture rates (vertebral or non-vertebral).

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

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Glucocorticoid-induced osteoporosis is the most common type of secondary osteoporosis. It is characterised by bone loss and changes in bone microarchitecture, resulting in increased bone fragility and fracture risk.
Bone loss occurs soon after the initiation of treatment and is particularly severe in the first few months.
Osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck may affect life expectancy.

FORSTEO is a curative treatment.
FORSTEO increases lumbar spine bone mass; its efficacy in diminishing fracture rates has not been formally demonstrated.
The efficacy/safety ratio for this medicinal product is high.
FORSTEO is a medicinal product used for first or second-line therapy.
There are alternative treatments.

Public health benefit:
Because of the frequency of glucocorticoid-induced osteoporosis and the severity of its consequences, this disease may be considered as a moderate public health burden.

Improved management of osteoporosis is a public health need within the scope of identified priorities (a GTNDO[3] priority).

In view of the available data from a comparative study with FOSAMAX 10 mg (beneficial effect on lumbar spine BMD, poorly predictive value on fracture risk in cases of glucocorticoid-induced osteoporosis, and beneficial effect on fracture rates not formally demonstrated), FORSTEO is not expected to have any additional impact on morbidity and quality of life.
In addition, there is no guarantee that these study results can be transposed into real practice since the profile of patients in real life is likely to be different (in terms of the severity of their osteoporosis, menopausal status, underlying diseases and duration of glucocorticoid treatment).

Overall, the available evidence does not suggest that FORSTEO will provide an additional response to the identified need.

Consequently, FORSTEO is not expected to provide any public health benefit in this indication.

The actual benefit of this proprietary drug is substantial.

### 4.2. Improvement in actual benefit

In view of the available data, the Committee considers that FORSTEO will provide a minor improvement in actual benefit (IAB IV) in the treatment of glucocorticoid-induced osteoporosis in women and men at high risk of fracture with at least two vertebral fractures.

[3] National Technical Group for Defining Public Health Objectives (DGS-2003).

### 4.3. Therapeutic use

Prevention of glucocorticoid-induced osteoporosis should be considered for patients receiving long-term (more than 3 months), systemic corticosteroid treatment at doses greater than or equal to 7.5 mg/day prednisone or equivalent.
Treatment should be routinely introduced for patients with a history of osteoporotic fracture. For those without a history of osteoporotic fracture, treatment should be considered if the spinal or femoral T score is < -1.5.

The bisphosphonates DIDRONEL 400 mg and generics, ACTONEL 5 mg and FOSAMAX 5 mg (not marketed) can be used to prevent bone loss from the start of glucocorticoid therapy.

FORSTEO may be proposed in the management of glucocorticoid-induced osteoporosis in men or women at high risk of fracture (i.e. with at least 2 vertebral fractures), provided the contraindications are observed.
It should be given once daily by subcutaneous injection in the thigh or abdomen.
The maximum total duration of treatment with FORSTEO should be 18 months. It should then be replaced with a different medicinal product, particularly a bisphosphonate.

### 4.4. Target population

The target population for FORSTEO includes patients with glucocorticoid-induced osteoporosis (receiving more than 3 months of corticosteroid treatment at doses greater than or equal to 7.5 mg/day prednisone or equivalent) with a high risk of fracture (history of at least 2 vertebral fractures). A precise estimate of this population cannot be made due to the lack of available data.

Given that long-term systemic corticosteroid therapy is one of the risk factors for osteoporosis and fragility fractures in both men and postmenopausal women, the extension of the indication for FORSTEO to severe glucocorticoid-induced osteoporosis will not greatly increase the target population corresponding to its previous two indications (approximately 160,000 patients). The indication extension is likely to add no more than 1,000 to 2,000 patients to that total. These are patients with purely glucocorticoid-induced osteoporosis at high risk of fracture (with at least 2 vertebral fractures).

### 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 use by hospitals and various public services.

4.5.1. Scope of reimbursement

Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture (with a history of at least two vertebral fractures).

4.5.2. Packaging: Appropriate to prescription requirements.

4.5.3. Reimbursement rate: 65%

4.5.4. Exception drug status