HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

13 December 2006

PREOTACT 100 µg
3761544: 2 glass, dual-chamber cartridges of 1.61 mg and 1.13 ml
3761550: 6 glass, dual-chamber cartridges of 1.61 mg and 1.13 ml

Applicant: NYCOMED FRANCE SAS

Marketing Authorization date: April 24, 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Recombinant human parathyroid hormone

1.2. Background

PREOTACT contains recombinant human parathyroid hormone, identical to endogenous human parathormone (PTH).

PTH stimulates bone formation through an indirect effect on osteoblasts by increasing the intestinal absorption of calcium and increasing tubular reabsorption of calcium and excretion of phosphate by the kidney.

1.3. Indication

Treatment of osteoporosis in postmenopausal women at high risk of fracture. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.

1.4. Dosage

The recommended dose of PREOTACT is 100 micrograms of parathyroid hormone administered once daily as a subcutaneous injection into the abdomen.

Patients must be trained to use the proper injection techniques. A user manual is available to instruct patients on the correct use of the PREOTACT pen. The pen is not included in the packs with cartridges.

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

A maximum treatment duration of 24 months is recommended.

Following treatment with PREOTACT, patients can be treated with a bisphosphonate to further increase bone mineral density.

Specific populations:

- Renal impairment:
No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 ml/min). No data is available in patients with severe renal impairment. PREOTACT should therefore not be used in patients with severe renal impairment.

- Hepatic impairment:
No dose adjustment is needed for patients with mild or moderate hepatic impairment (total score of 7 to 9 on the Child-Pugh scale). No data is available in patients with severe hepatic impairment. PREOTACT should therefore not be used in patients with severe hepatic impairment.

- Children and adolescents:
The safety and efficacy of PREOTACT in patients under 18 years have not been studied. PREOTACT should not be used in paediatric patients or young adults.

- Elderly:
Dose adjustment based upon age is not required.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

H: Systemic hormonal preparations
05: Medicinal product ensuring calcium homeostasis
A: Parathyroid hormones
A: Parathyroid hormone
03: Parathyroid hormone rhPTH (1-84)

2.2. Medicines in the same therapeutic category

Comparator drug

A single medicine product containing parathyroid hormone is currently indicated in the treatment of osteoporosis: FORSTEO – teriparatide.
FORSTEO is indicated in the treatment of overt osteoporosis and is reimbursed only in the event of complicated osteoporosis of at least two vertebral fractures.

2.3. Medicines with a similar therapeutic aim

These comprise all the medicines indicated in the treatment of postmenopausal osteoporosis. The following classes may be distinguished:

- Bisphosphonates
    - Oral route
      DIDRONEL 400 mg tablet and its generics (etidronate)
      ACTONEL 5 mg and 35 mg tablet (risedronate)
      FOSAMAX 10 mg, 70 mg tablet and other medicines containing alendronate 10 mg and 70 mg, FOSAVANCE tablet (alendronate or alendronate + vitamin D combination)
      BONVIVA 150 mg and 2.5 mg tablet (ibandronate)

    - IV route
      BONVIVA 3mg/3 months IV (ibandronate)

- EVISTA and OPTRUMA (raloxifen),
- PROTELOS (strontium ranelate)

Calcium and vitamin D are generally used for adjuvant treatment.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of PREOTACT in the treatment of postmenopausal osteoporosis is based on:

- An 18-month pivotal study versus placebo (TOP study) followed by an 18-month open-label follow-up study (OLES study).
- Two additional studies evaluating several dosing regimens: PaTH and POWER studies
- One published study Rittmaster which will not be described because of the small sample size of patients receiving PREOTACT at the dosage indicated in the Marketing Authorisation.

The laboratory also proposed an indirect comparison versus FORSTEO.

- **TOP Study (unpublished)**

Randomised, double-blind, placebo-controlled, 18-month study to evaluate the efficacy of PREOTACT on the incidence of new vertebral fractures in 2,532 patients with postmenopausal osteoporosis

The protocol planned a 36-month treatment period. However, because of the publication of data on osteosarcoma in the rat, the study was reduced to 18 months with an open-label follow-up period of 18 months (OLES study).

Inclusion criteria:
Women postmenopausal for at least 1 year, 45 years of age or older :
- If age between 45 and 54 years a lumbar T-score ≤ - 3 or ≤ - 2.5 with at least one prevalent vertebral fracture.
- If age ≥ 55 years a T score ≤ - 2.5 or ≤ - 2 with at least one prevalent fracture at baseline.

Primary endpoint: incidence of new and/or worsening of vertebral fractures as assessed by radiography at 18 months.

Secondary endpoints:
- Incidence of vertebral fractures at 12 months, incidence of non-vertebral fractures (hip and wrist and other clinical fractures)
- Change in height
- Change in bone mass density (BMD)

Patients injected themselves (subcutaneously) for 18 months with either 100 µg of PREOTACT (n = 1286) or a placebo (n = 1246) and received calcium (700 mg/day) and vitamin D (400 IU/day) supplements.

Results:

Baseline population characteristics (ITT population)

	Placebo (n = 1246)	**PREOTACT (n = 1286)**
Mean age ± SD	64.5± 7.92	64.4± 7.41
Duration of menopause	18.5 ± 9.64	18.6 ± 9.84
Previous history of vertebral fracture (n, %)	**235 (18.9)**	**236 (18.4)**
Mean lumbar T-score (L2-L4)	-2.96 ± 0.77	-3.02± 0.79
Femoral neck T-score	-2.21± 0.72	-2.25 ± 0.7
Total hip T-score	-1.89 ± 0.78	-1.92 ± 0.8

Source: clinical report of TOP study

Distribution of enrolled population according to number of vertebral fractures at baseline (n, %) (ITT)

Number of vertebrae fractured	**Placebo (n=1246)**	**PREOTACT (n=1286)**	**Total (N=2532)**
None	1008 (81.1)	1048 (81.6)	2056 (81.4)
1	184 (14.8)	165 (12.9)	349 (13.8)
≥2	51 (4.1)	71 (5.5)	122 (4.9)
Missing [c]	3	2	5

Primary endpoint (ITT population):

Incidence of new and/or worsened vertebral fractures at 18 months (n, %)

	Placebo (n=1246)	**PREOTACT (n=1286)**	**PREOTACT vs Placebo**	**p**
New fractures	42 (3.37)	17 (1.32)	RR = 0.39 (95% CI: 0.22-0.69)	0.001
Worsened	0	1 (0.08)	-	-
Total	42 (3.37)	18 (1.40)	RR = 0.42 (95% CI: 0.24-0.72)	0.001

The reduction in the relative risk of occurrence of a new vertebral fracture compared to the placebo group at 18 months was 61%.

According to the SPC, the most relevant fracture reduction was observed among patients at high risk of fractures such as patients with previous fractures and a lumbar spine T-score of < - 3.

Secondary endpoints (ITT population):

- Incidence of vertebral fractures at 12 months

	Placebo (n=1246)	PREOTACT (n=1286)	Difference
Patients with new vertebral fractures	23 (1.85)	17 (1.32)	NS

- Incidence of non-vertebral clinical fractures at 12 and 18 months

Visit	Number (%) of subjects		PREOTACT vs Placebo	
	Placebo (n = 1246)	PREOTACT (n = 1286)	Relative RR (95% CI)	p
12 months				
Non-vertebral fracture	4 (3.29)	54 (4.20)	1.28 (0.86. 1.90)	**NS**
Hip	3 (0.24)	1 (0.08)	0.32 (0.03. 3.10)	
Wrist	7 (0.56)	9 (0.70)	1.25 (0.47. 3.33)	
Other	31 (2.49)	44 (3.42)	1.38 (0.87. 2.16)	
18 months				**NS**
Non-vertebral fracture	73 (5.86)	71 (5.52)	0.94 (0.69. 1.29)	
Hip	3 (0.24)	3 (0.23)	0.97 (0.20. 4.79)	
Wrist	10 (0.80)	13 (1.01)	1.26 (0.55. 2.86)	
Other	61 (4.90)	56 (4.35)	0.89 (0.62. 1.27)	

No significant difference was observed in the incidence of non-vertebral clinical fractures at 1 year and 18 months.

- Height

No difference was demonstrated between the 2 groups for height of patients.

- Mean BMD at 18 months

Site	Placebo	Preotact®	p
lumbar spine	-0.32	6.53	<0.001
Total hip	-1.09	1.02	<0.001
Femoral neck	-0.69	1.78	<0.001
Trochanter	-0.56	1.04	<0.001
Forearm	-1.53	-4.99	<0.001

- **Open-label extension of TOP study (OLES)**

The primary objective of the open-label OLES study was to evaluate the safety of PREOTACT at 24 months in the 1,681 patients who completed the TOP study or who prematurely stopped treatment.

The secondary objectives were the evaluation of the effects of PREOTACT on BMD, Bone Mineral Content (BMC), and Bone Mineral Area (BMA) at different points of the skeleton, the incidence of vertebral and non-vertebral fractures, changes in height, markers of bone turnover and histomorphometric variables. The duration of the effect on BMD after discontinuation of PREOTACT was also measured.

Patients received PREOTACT by subcutaneous injection once daily with daily calcium (700 mg) and vitamin D (400 IU) supplementation.

Results:

Patients initially treated by placebo received PREOTACT for 18 months and those initially treated by PREOTACT continued to receive it for 6 months.

The incidence of adverse events was 95% in the placebo/PREOTACT group and 66% in the PREOTACT/PREOTACT group.

No statistical test was carried out.

The most frequent adverse events were: hypercalciuria, hypercalcaemia and nausea.

Incidence of adverse events (%)

	Placebo/PREOTACT (n = 900)	PREOTACT/PREOTACT (n = 781)
Hypercalciuria	48	15
Hypercalcaemia	34	9
Nausea	16	7

Efficacy:

No conclusions on the maintenance of the efficacy of PREOTACT could be made from this open-label extension study.

- **Complementary studies**

Three further studies based only on an intermediate criterion (BMD) were presented by the company and are described below.

PATH Study

Double-blind, placebo-controlled study randomised in 4 groups to evaluate the efficacy of PREOTACT and alendronate either as monotherapy or in combination for the treatment of postmenopausal osteoporosis.

Two hundred and thirty-eight (238) patients aged from 55 to 85 years, with a lumbar or hip T-score ≤ - 2.5 and with at least one risk factor for fractures were divided into four groups and received either:

		Treatments administered	
Group	Sample size	1st year	2nd year
1	59	PREOTACT + Placebo	alendronate 10 mg
2	59	PREOTACT + alendronate 10 mg	alendronate 10 mg
3	60	Placebo + alendronate 10 mg	alendronate 10 mg
4	60	PREOTACT + Placebo	Placebo

Patients also received calcium (400-500 mg/day) and vitamin D (400 IU) supplements.

The primary endpoint was the change in lumbar BMD compared to baseline at 24 months.

Results:

Increase in lumbar BMD relative to baseline at 1 year and 2 years

Group	Treatment Year 1	Treatment Year 2	Mean change in lumbar BMD relative to baseline at 1 year (%)	Mean change in lumbar BMD relative to baseline at 2 years (%)
1	PREOTACT	Alendronate	6.2 ± 6.9	12 ± 9
2	PREOTACT + Alendronate	Alendronate	6.1 ± 4.4	7.9 ± 4.6
3	Alendronate	Alendronate	4.7 ± 4.1	7.7 ± 5.2
4	PREOTACT	Placebo	6.2 ± 6.9	4.1 ± 5.1

The increase in lumbar BMD at 2 years in the group of patients treated by a daily subcutaneous injection of 100 µg of PREOTACT during the 1st year followed by 10 mg of alendronate/day during the 2nd year was statistically higher than that observed in the other groups, $p<0.05$.

POWER study

Double-blind, randomised, placebo-controlled study to evaluate the efficacy of a PREOTACT + hormone replacement therapy (HRT) combination versus HRT alone in 180 post-menopausal women with a low BMD (T score <-2).

Patients received daily calcium (1050 then 700 mg) and vitamin D (400 IU) supplements.

The primary endpoint was the change in lumbar BMD relative to baseline at12 months.

ITT* Analysis: at 12 months, the mean increase in the lumbar BMD relative to baseline was significantly greater in the PREOTACT + HRT (7.1%) group than in the HRT + placebo group (1.1%), p<0.001.

- **Indirect comparison:**

The company proposed an indirect comparison in terms of efficacy (reduction in the absolute risk of fractures) and safety of PREOTACT compared to FORSTEO based on the results of the NEERS and TOP studies. However, this indirect comparison cannot be taken into account by the committee because of the non-comparability of the populations included in these 2 studies.

In the NEERS study which evaluated FORSTEO, enrolled patients had at least one vertebral fracture (mean number of vertebral fractures per patient: 2.3 and more than 55% of patients had at least 2 fractures at baseline).

However in the TOP study, more than 80% of the included patients had no vertebral fracture at baseline.

3.2. Safety

During clinical trials, approximately 71% of the patients who received PREOTACT had at least one adverse event.

In the TOP study, the following adverse events were reported with a higher incidence with PREOTACT than with placebo:

- Nausea (22% with PREOTACT versus 7% with placebo)
- Dizziness (12% with PREOTACT versus 8% with placebo)
- Headaches (29% with PREOTACT versus 23% with placebo)
- Hypercalciuria (44% with PREOTACT versus 21% with placebo)
- Hypercalcaemia (27% with PREOTACT versus 4% with placebo)

In addition, Artralgia and back pain were reported with a similar incidence in the two groups.

Taking into account its action mechanism, hypercalcaemia and hypercalciuria are the expected adverse effects of PREOTACT. Hypercalcaemia was transient and was most frequently reported during the first 3 months of treatment.

Management and correction of the calcium imbalance mainly involved a reduction or discontinuation of oral calcium supplementation. However, approximately one third of patients on PREOTACT (459/1286) required adjustment of active treatment by administration of one injection every other day or even only once weekly.

* From clinical report CL1-11-03 , 2005

The SPC provides for a monitoring of serum and urinary calcium levels at 1, 3 and 6 months in patients receiving PREOTACT.

3.3. Conclusion

The efficacy of PREOTACT administered as a daily subcutaneous injection for 18 months in preventing vertebral fractures was demonstrated by comparison with placebo in the TOP pivot study.

Most of the patients enrolled in this study had no fracture at baseline: placebo (81.1%), PREOTACT (81.6%).

For the 2,532 patients studied (ITT population), 3.3% (42/1246) had at least one new vertebral fracture at 18 months in the placebo group versus 1.3% (17/1286) in the PREOTACT group i.e. a reduction in the relative risk of occurrence of a new vertebral fracture of 61% at 18 months.

However, no efficacy on the reduction in the incidence of non-vertebral fractures, including the hip was demonstrated with PREOTACT.

The committee regrets the lack of any direct comparison with FORSTEO or any other anti-osteoporosis drugs.

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 jeopardise the patient.

PREOTACT is a preventive treatment of vertebral osteoporotic fractures.

Its efficacy on hip fractures has not been established.

Public Health Benefit:

Because of the high incidence of postmenopausal osteoporosis and its serious consequences, this disease is a considerable public health burden.
There is an insufficiently covered public health need in osteoporosis.
In the absence of clinical study comparing PREOTACT with FORSTEO and/or with bisphosphonates, the expected impact of PREOTACT on the reduction in morbidity and mortality related to postmenopausal osteoporosis cannot be assessed.
No finding suggests that PREOTACT may provide an additional response to the above need compared to other anti-osteoporosis drugs.
Accordingly, in the current state of knowledge, PREOTACT is not expected to have an impact on public health.

The efficacy/adverse events ratio of PREOTACT is high.

PREOTACT is a medicinal product used for first or second-line therapy.

There are alternative treatments.

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit

PREOTACT does not provide an improvement in actual benefit (IAB V) in the management of vertebral postmenopausal osteoporosis.

4.3. Therapeutic use

Osteoporosis is defined by a T-score ≤ - 2.5 in the lack of any other cause of a disorder characterised by demineralization and bone fragility.

The aim of treating osteoporosis is to prevent fractures.

Before starting any anti-osteoporosis therapy, any calcium or vitamin D deficiency should be identified and treated. If necessary, calcium and vitamin supplements should be continued during anti-osteoporosis therapy.

According to the recommendations of AFSSAPS published in January 2006, treatment is systematically recommended in the event of osteoporosis complicated by a fracture. In the absence of fractures in post-menopausal women, the indication for treatment should be considered case by case, depending on the individual risk of fracture. This risk is evaluated from the value of the T-score and the possible presence of other risk factors for fractures. Treatment must therefore be considered in women with:

- A large reduction in bone mineral density (T score < - 3) or
- A T-score ≤ - 2.5 associated with risk factors for fractures, in particular: age > 60 years, current or past treatment with systemic corticosteroids at a dosage ≥ 7.5 mg/day prednisone equivalent, a body mass index < 19 kg/m², a history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 40 years).

As no direct comparison has been made between different anti-osteoporosis drugs (bisphosphonates, raloxifene, strontium ranelate, THR), the choice of treatment will depend on the risk of vertebral and/or non-vertebral fractures, age, number and site of fractures, as well as predisposing factors and any contraindications to any of these medicinal products.

Given the available data, PREOTACT may be proposed for the management of postmenopausal osteoporosis in women at high risk of vertebral.

PREOTACT was not shown to be effective for the prevention of peripheral fractures, including those of the hip.

Because of the risk of hypercalcaemia and hypercalciuria, it is recommended to conduct rigorous monitoring of serum and urinary calcium levels at 1, 3 and 6 months in patients receiving PREOTACT.

Available data support continuous treatment with PREOTACT for up to 24 months.

Another anti-osteoporosis drug and in particular a bisphosphonate may be proposed following treatment with PREOTACT.

4.4. Target population

The target population of PREOTACT is represented by women with vertebral postmenopausal osteoporosis with a low risk of hip fracture.

The population of women with osteoporosis may be estimated from the following data:

- Approximately 25% of women aged 65 years and 50% of women aged 80 years have osteoporosis (GTNDO*, 2003).
- According to INSEE (www.insee.fr), the populations of women aged over 50 years, 65 years, and 80 years were 11.5 million, 6 million and 1.9 million respectively on January 1, 2005.

According to this data, the population presenting postmenopausal osteoporosis may be estimated to be approximately 3 to 3.3 million women.

Given the population included in the study and the lack of any demonstration of efficacy on hip fractures, women over 80 years must be excluded from the target population of PREOTACT.

Consequently, the target population of PREOTACT is between 2 and 2.4 million.

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 in the Marketing Authorisation.

4.5.1. Scope of reimbursement

Treatment of vertebral postmenopausal osteoporosis:

- In female patients fracture caused by bone fragility,
- In the absence of a fracture, in women with substantially reduced bone mineral density (T-score < -3) or with a T-score ≤ - 2.5 associated with other risk factors for fractures and in particular, age > 60 years, current or previous systemic corticosteroid therapy at a dosage ≥ 7.5 mg/day prednisone equivalent, a body mass index < 19 kg/m², a history of femoral neck fracture in a first-degree relative (mother), early menopause (before the age of 50 years).

4.5.2. Packaging: Appropriate for the prescription conditions

4.5.3. Reimbursement rate: 65%

* National Technical Group for the Definition of Public Health Goals.