HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

ACLASTA 5 mg, powder for solution for infusion
1 transparent plastic (cycloolefinic polymer) bottle containing 100 ml (CIP: 365 871-1)

Applicant: NOVARTIS PHARMA SAS

Zoledronic acid monohydrate

ATC code: M05BA08

List I
This medicinal product requires specific monitoring during treatment.

Marketing authorisation (MA) date: 15 April 2005 (centralised procedure):

Date of last amendment to Marketing Authorisation: 3 October 2007 (extension of indication to treatment of osteoporosis in postmenopausal women at high risk of fracture.)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication: "**Treatment of osteoporosis in postmenopausal women at high risk of fracture**."

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Zoledronic acid monohydrate

1.2. Background

Bisphosphonate indicated in the treatment of postmenopausal osteoporosis administered by once yearly intravenous infusion.

1.3. Indication

"Treatment of Paget's disease of the bone.
Treatment of osteoporosis in postmenopausal women at high risk of fracture."

1.4. Dosage

For the treatment of postmenopausal osteoporosis, the recommended dose is a single intravenous infusion of 5 mg ACLASTA administered once a year: Cf. SPC for Paget's disease of the bone.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

M	: muscle and skeleton
M05	: medicinal products for the treatment of bone disorders
M05B	: drugs affecting bone structure and mineralisation
M05BA	: bisphosphonates
M05BA08	: zoledronic acid

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

A single bisphosphonate Injection has marketing authorisation in the treatment of postmenopausal osteoporosis: BONVIVA 3 mg solution for injection in pre-filled syringe (ibandronic acid)[1].

Oral bisphosphonates indicated in the treatment of postmenopausal osteoporosis:

- DIDRONEL 400 mg tablet and its generics (etidronate)
- ACTONEL 5 mg and 35 mg tablet (risedronate), ACTONELCOMBI tablet (risedronate 35 mg + calcium 1000 mg + vitamin D 880IU),

[1] BONVIVA 3 mg/IV is indicated in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures. The efficacy on femoral neck fractures has not been established.

- FOSAMAX 10 mg, 70 mg tablet and other proprietary medicines containing alendronate 10 mg and 70 mg, FOSAVANCE and ADROVANCE tablet (alendronate or alendronate + vitamin D combination)
- BONVIVA 150 mg and 2.5 mg tablet (ibandronate). The 2.5 mg dosage strength was not on the list of reimbursed medicinal products at the date of the opinion.

2.3. Medicines with a similar therapeutic aim

Other medicinal products indicated in the treatment of postmenopausal osteoporosis:

- EVISTA and OPTRUMA (raloxifene),
- PROTELOS (strontium ranelate),
- FORSTEO (teriparatide),
- PREOTACT (PTH 1-84), not included on the list of reimbursed medicinal products at the date of the opinion.

Calcium and vitamin D are generally used for adjuvant treatment.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. Efficacy compared with placebo

The efficacy of ACLASTA (zoledronic acid) in the treatment of postmenopausal osteoporosis was evaluated in a phase III pivot study versus placebo - (HORIZON study).
The company presented the results of the ZOL 2310 study which will not be discussed here as this also concerned male osteoporosis (outside the indication of the MA).

HORIZON Study[2]
Objective: to show the superiority of ACLASTA 5 mg in a single annual infusion over 15 minutes compared to placebo on the incidence of vertebral and hip fractures in 7,736 women with postmenopausal osteoporosis.

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

Inclusion criteria:
Postmenopausal women aged 65–89 years with

- a femoral T-score ≤ - 1.5 and at least 2 prevalent minor vertebral fractures or a moderate vertebral fracture or;
- a femoral T score ≤ - 2.5 with or without a prevalent vertebral fracture.

Exclusion criteria:

- concomitant use of bisphosphonates, fluorine, strontium, corticosteroids or parathormone (PTH)
- glomerular filtration rate (GFR) <30 ml, hyperparathyroidism, uveitis or iritis.

Treatments:
Patients were randomised after stratification according to receiving or not concomitant treatment with anti-osteoporosis treatments (hormone replacement therapy, raloxifene, tamoxifen, calcitonins or tibolone) to receive either a single annual infusion over 15 minutes of zoledronic acid 5 mg or placebo for 3 years. Bisphosphonates were not authorised. Patients also received 1 to 1.5 g calcium per day and 400 to 1200 IU of vitamin D per day.

Primary efficacy endpoint:

- Incidence of morphometric vertebral fractures[3] at 3 years (this endpoint was evaluated in women not receiving concomitant treatment, n=5,675).
- Incidence of hip fractures at 3 years (evaluated on the total study population, n = 7,736).

Results:
The characteristics of patients at baseline are described in table 1.
Patients had an average age of 73 years, approximately 30% had no prevalent vertebral fractures and 85% had never received bisphosphonates.
The results were analysed for all randomised women (ITT population) and on the population evaluable for morphometric vertebral fractures who had received at least one dose of treatment (mITT population).

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[2] Black DM et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809-22.
[3] Diagnosed by radiography of thoracic or lumbar spine.

Table 1: Baseline population characteristics (ITT population)

	Zoledronic acid	Placebo
n	**3,875**	**3,861**
Average age (years)	73.1	73.0
Number of years since menopause. n (%)		
≤ 5	1 (0.03)	3 (0.08)
>5 - 30	3,005 (77.55)	3,011 (77.98)
> 30	858 (22.14)	833 (21.57)
Previous treatments n (%)		
Bisphosphonates	565 (14.58)	557 (14.43)
MHT	825 (21.3)	813 (21.1)
Calcitonins	444 (11.5)	425 (11)
SERMs	434 (11.2)	412 (10.7)
Others	43 (1.1)	43 (1.1)
Femoral neck T-score n (%)		
≤ -2.5	2,814 (72.62)	2,734 (70.81)
(Between - 2.5 and - 1.5)	1,002 (25.86)	1,073 (27.79)
> -1.5	35 (0.90)	38 (0.98)
Mean BMD* en g/cm^2 (DS)		
Total femur	0.668 (0.0015)	0.669 (0.0015)
Lumbar	0.822 (0.0081)	0.814 (0.0089)
Femoral neck	0.580 (0.0014)	0.581 (0.0014)
Number of prevalent vertebral fractures. n (%)		
0	1,457 (37.60)	1,383 (35.82)
1	1,093 (28.21)	1,076 (27.87)
≥ 2	1,323 (34.14)	1,401 (36.29)

*Bone Mineral Density

Table 2. Concomitant treatments (ITT Population) during study in addition to calcium/vitamin D

	Group 1*		**Group 2****	
	Zoledronic acid (N = 3,045) n (%)	**Placebo (N = 3,039) n (%)**	**Zoledronic acid (N = 830) n (%)**	**Placebo (N = 822) n (%)**
Total number of patients	248 (8.1%)	348 (11.5%)	672 (81.0%)	672 (81.8%)
Raloxifene (hydrochloride)	45 (1.5%)	72 (2.4%)	345 (41.6%)	346 (42.1%)
Salmon Calcitonins	44 (1.4%)	65 (2.1%)	137 (16.5%)	144 (17.5%)
Alendronate	**38 (1.2%)**	**91 (3.0%)**	**19 (2.3%)**	**30 (3.6%)**
Oestriol	38 (1.2%)	38 (1.3%)	34 (4.1%)	19 (2.3%)
Oestradiol	26 (0.9%)	19 (0.6%)	68 (8.2%)	69 (8.4%)
Conjugated oestrogens	22 (0.7%)	18 (0.6%)	109 (13.1%)	101 (12.3%)
Risedronate	**21 (0.7%)**	**48 (1.6%)**	**11 (1.3%)**	**26 (3.2%)**
Calcitonin	15 (0.5%)	18 (0.6%)	39 (4.7%)	34 (4.1%)
Tamoxifen	6 (0.2%)	5 (0.2%)	4 (0.5%)	10 (1.2%)
Raloxifene	4 (0.1%)	10 (0.3%)	24 (2.9%)	28 (3.4%)
Medroxyprogesterone (acetate)	1 (0.0%)	2 (0.1%)	23 (2.8%)	20 (2.4%)

Source: Study report.

***** patients not receiving concomitant treatment

** patients receiving concomitant treatment

- Effects on morphometric vertebral fractures (primary endpoint)

Table 3: Incidence of morphometric vertebral fractures at 3 years - mITT population (group 1 – women with no concomitant anti-osteoporosis treatment)

	Zoledronic acid N = 2,822	Placebo N = 2,853	Absolute reduction in the incidence of fractures in % (CI)
Women with at least one morphometric vertebral fracture after 3 years of treatment (n, %)	92 (3.26%)	310 (10.87%)	7.6 (6.3-9)

In the population of women not receiving concomitant anti-osteoporosis treatment (mITT), ACLASTA was superior to placebo for the reduction in incidence of new morphometric vertebral fractures. The reduction in relative risk of morphometric vertebral fractures compared to placebo was 70%; 95% CI [62%; 76%], $p < 0.0001$, which corresponds to an absolute reduction in the vertebral fracture risk of 7.6% compared to placebo.

- Effects on hip fractures (primary endpoint)

Table 4: Incidence of hip fractures at 3 years (ITT population)

	Zoledronic acid N = 3,875	Placebo N = 3,861	Absolute reduction in fracture incidence %
Number of women with at least one new hip fracture after 3 years of treatment	52 (1.44)	88 (2.49)	1.05

In the whole study population including women concomitantly receiving an anti-osteoporosis treatment, ACLASTA was better than placebo for the reduction in the incidence of new hip fractures. The relative risk reduction in hip fracture incidence compared to placebo was 41%; 95% CI [17%; 58%], p = 0.0024, which corresponds to an absolute reduction in hip fracture risk of 1.05% compared to placebo.

- Effects on all clinical fractures (secondary endpoints)

ACLASTA reduced the absolute risk of clinical fractures by 4.41%, clinical vertebral fractures by 2.06%, and clinical nonvertebral fractures including the hip by 2.74%, compared to placebo (cf. table 5).

Table 5: Incidence of clinical fractures at 3 years in the total study population (ITT population)

	Treatment	N	n	Incidence (%)	ARR (absolute reduction) %	RRR (relative reduction) %	p [6]
Clinical fractures [1]	**Zoledronic acid**	3,875	308	8.42	4.41	33% [23%, 42%]	<0.001
	Placebo	3,861	456	12.83			
Clinical vertebral fractures[2]	**Zoledronic acid**	3,875	19	0.53	2.06	77% [63%, 86%]	<0.001
	Placebo	3,861	84	2.59			
Non-clinical vertebral fractures[1]	**Zoledronic acid**	3,875	292	7.97	2.74	25% [13%, 36%]	<0.001
	Placebo	3,861	388	10.71			
Hip	**Zoledronic acid**	3,875	52	1.44	1.05	41% [17%, 58%]	0.0024
	Placebo	3,861	88	2.49			
Wrist	**Zoledronic acid**	3,875	97	2.68	0.64	19%	NS
	Placebo	3,861	120	3.32			
Humerus	**Zoledronic acid**	3,875	41	1.13	0.82	42% [15%, 61%]	0.0047
	Placebo	3,861	71	1.95			
Ribs	**Zoledronic acid**	3,875	35	0.93	0.02		NS
	Placebo	3,861	33	0.95			
Others	**Zoledronic acid**	3,875	92	2.53	0.83	24% [1%, 42%]	0.0424
	Placebo	3,861	122	3.36			

[1] Excluding finger, toe and facial fractures (these are considered as not due to osteoporosis).

[2] Clinical vertebral fractures include symptomatic (i.e. painful) dorsal and lumbar fractures.

- Effects on BMD (secondary endpoints)

Over a 3-year period, ACLASTA significantly increased BMD in the lumbar spine, femur (femoral neck and total femur) and distal radius compared to placebo (cf. table 6).

Table 6: Change in femoral BMD (total femur and femoral neck) and lumbar BMD at 3 years relative to baseline.

Site	Treatment	n[1]	Adjusted mean change	Difference between 2 groups 95 % CI
Total femur	**Zoledronic acid**	3.061	4.15%	6.02
	Placebo	3.077	-1.87%	[5.77; 6.28]***
Femoral neck	**Zoledronic acid**	3.067	3.92%	5,06
	Placebo	3.083	-1.13%	[4.76; 5.36]***
Lumbar spine	**Zoledronic acid**	228	6.95%	6,71
	Placebo	212	0.24%	[5.69; 7.74]***

[1] number of women with measurable values both at baseline and at 3 years, *** p<0.0001

3.1.2. Efficacy data versus active comparator

Two clinical studies ZOL 2313[4] and ZOL 2315[5] compared ACLASTA 5 mg in a single annual infusion over at least 15 minutes, with FOSAMAX 70 mg/week (alendronate) on the intermediate endpoints: BMD and bone remodelling markers (telopeptides N (NTX) and C (CTX)). The populations studied included women not covered by the MA indication of these medicinal products i.e. osteopenic women. Consequently, no details about these studies are given here.

The Committee regretted the absence of comparative data on the reduction in fracture incidence.

3.2. Adverse events

The most commonly observed side effects with zoledronic acid (ACLASTA) were infusion reactions and in particular: fever, myalgia, flu-like syndrome, arthralgia and headache. These reactions were twice as frequent with ACLASTA than with placebo and occurred during the first three days of administration of ACLASTA. Their incidence was reduced by the administration of paracetamol or ibuprofen shortly after the administration of ACLASTA.

The global incidence of atrial fibrillation was 2.5% (96 out of 3,862) with ACLASTA versus 1.9% (75 out of 3,852) with placebo. The event rate of atrial fibrillation considered serious by the investigator was 1.3% (51 out of 3,862) with ACLASTA versus 0.6% (22 out of 3,852) with placebo. The mechanism of the increased incidence of atrial fibrillation is not known. This is a new adverse reaction which was not observed during the pre-clinical, clinical or post-MA studies. Transient increases in serum creatinine concentrations were observed with zoledronic acid (1.8% vs 0.81%) and this is a class effect. Two cases of osteonecrosis of the jaw with a positive outcome were observed during the HORIZON study, one with ACLASTA and the other with placebo.

3.3. Conclusion

The anti-fracture efficacy of zoledronic acid 5 mg (ACLASTA) administered in a single annual infusion over not less than 15 minutes for 3 years was established in a clinical study (HORIZON) conducted in 7,736 women with postmenopausal osteoporosis.

ACLASTA was superior to placebo on the reduction in risk of morphometric vertebral and hip fractures (primary endpoints).

The absolute reduction in the vertebral fracture risk compared to placebo, evaluated in the population of patients not receiving concomitant anti-osteoporosis treatment, was 7.6%.

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4 Mcclung et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 2007; 41: 122-128.

5 Saag et al. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone 2007; 40: 1238-1243.

The absolute reduction in the risk of hip fracture compared to placebo evaluated in the total study population including women receiving concomitant anti-osteoporosis treatment or not was 1.05%.
The committee regrets the absence of studies comparing the anti-fracture efficacy of ACLASTA with that of other anti-osteoporosis drugs.

The most commonly observed side effects with ACLASTA were infusion reactions and their incidence could be reduced by administration of paracetamol or ibuprofen.
Renal adverse reactions (increased serum creatinine concentrations) have been observed with zoledronic acid. These are class effects. Two cases of osteonecrosis of the jaw with a positive outcome were observed during the HORIZON study, one with ACLASTA and the other with placebo. However, atrial fibrillation (2.5% vs 1.9%), an adverse reaction not reported in Paget's disease, was observed. The mechanism of the increased incidence of atrial fibrillation is not known. The SPC is currently being changed to include this undesirable effect.

A European Risk Management Plan is currently being evaluated by the EMEA.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Postmenopausal osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck may be life-threatening for the patient.
ACLASTA is used for the prevention of osteoporotic fractures.
Its efficacy/adverse effects ratio is high.

Public health benefit:

Because of the high incidence of postmenopausal osteoporosis and its serious consequences, this disease has a high public health burden.
The improved management of postmenopausal osteoporosis is a public health need coming within the scope of identified priorities (GTNDO priority*).
The available clinical data (demonstrated benefit on the incidence of femoral neck fractures and vertebral fractures in a placebo-controlled study) suggest that an additional impact on morbidity and quality of life is possible but not proven. Moreover, the probable improvement in compliance with a prolonged treatment in which adherence plays a paramount role, is a major element in favour of an impact on morbidity.
To conclude, the available evidence suggests that the medicinal product ACLASTA may provide an additional response to an identified need.
Consequently, in the current state of knowledge, ACLASTA is expected to have a public health benefit. This benefit is low.

This medicinal product is for first-line therapy.
There are alternative treatments and in particular other parenteral or oral bisphosphonates.
The actual benefit of this proprietary drug is substantial.

4.2. Improvement in actual benefit

ACLASTA (zoledronic acid) provides a minor improvement in actual benefit (IAB IV) in the management of postmenopausal osteoporosis in women at high risk of fracture.

* National Technical Group for Definition of Public Health Goals (DGS-2003)

4.3. Therapeutic use

Osteoporosis is defined by a T-score ≤ - 2.5 in the absence of any other cause of a demineralising bone disease or bone fragility.
The purpose of treatment of osteoporosis is to prevent fractures.
Calcium and vitamin D deficiencies must be sought and corrected before the institution of any anti-osteoporosis treatment. Vitamin and calcium supplementation must be continued where necessary throughout anti-osteoporosis treatment.

According to the AFSSAPS recommendations published in January 2006, treatment is systematically recommended in women with osteoporosis complicated by a fracture. In postmenopausal women without fracture, 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 fracture. 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 fracture, in particular: age > 60 years, current or past 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 40 years).

In the absence of direct comparison between different anti-osteoporosis drugs (bisphosphonates, raloxifene, teriparatide and strontium ranelate), 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.

Among the bisphosphonates indicated in the treatment of postmenopausal osteoporosis, zoledronic acid (ACLASTA®) decreases the risk of vertebral and nonvertebral fractures including hip fracture in women with postmenopausal osteoporosis.
Because of its safety profile, the use of ACLASTA requires monitoring for atrial fibrillation and maxillary osteonecrosis.

As with all other anti-osteoporosis drugs, treatment should be reconsidered if a fracture occurs after the first year of treatment, despite satisfactory compliance. Another medicinal product may be proposed including in the same pharmacological class.

4.4. Target Population

The target population of ACLASTA in this indication is represented by women with postmenopausal osteoporosis at a high risk of fracture.
The population of women with postmenopausal 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 female population aged over 50 years was 11.5 million on 1 January 2005, that over 65 years was 6 million and that over 80 years, 1.9 million.

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

Medication is only justified for part of this population.

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

As osteodensitometry has only recently become reimbursable in France, no data are available to estimate the subpopulation of women with osteoporosis without a fracture and a T score < -3 or a T score ≤ -2.5 associated with several others risk factors for 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 in the marketing authorisation's new indication and dosage under the following conditions:

Treatment of osteoporosis in postmenopausal women at high risk of fracture:

- In women with a fracture caused by bone fragility,
- In women without fracture with a large reduction in bone mineral density (T-score < -3) or with a T-score ≤ - 2.5 associated with other risk factors for fracture and in particular, age > 60 years, current or past 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).

4.5.1 Packaging: appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%