HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

ACLASTA 5 mg, solution for infusion
Bottle of 100 ml (CIP code: 365 871-1)

Applicant: NOVARTIS PHARMA S.A.S.

zoledronic acid monohydrate
ATC code: M05BA08

List I

Medicine requiring special monitoring during treatment.

Date of initial Marketing Authorisation: 15 April 2005 (centralised procedure)

Date of latest revisions of Marketing Authorisation: 30 March 2010 (renewal for 5 years and not for an unlimited period because of the need for monitoring of tolerance)
18 May 2010: modification of sections 4.4 (Special warnings and precautions for use), 4.8 "Adverse effects" 4.2 "Posology and method of administration", and 4.5 "Interaction with other medicinal products" to include the risk of renal undesirable effects.

Reason for request: Renewal of inclusion on the list of medicines reimbursable by National Health Insurance at the same time as the renewal of inclusion of ZOMETA.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Zoledronic acid monohydrate

1.2. Indications

"Treatment of osteoporosis:
- in postmenopausal women
- in men

in patients with increased risk of fracture, including those with a recent low-trauma hip fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in postmenopausal women and in men at increased risk of fracture.

Treatment of Paget's disease."

1.3. Dosage

See SPC.

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION (21 October 2009)

2.1. Efficacy

Osteoporosis

No new efficacy data were provided for osteoporosis in postmenopausal women and in men and corticosteroid-induced osteoporosis.

Paget's disease

The company supplied the results[1,2] of the 18-month open-label extension phases of the two studies evaluated by the Committee at the time of inclusion. Continued efficacy in regard to bone remodelling was demonstrated for ACLASTA at 24 months.
The company also submitted the results of a study performed in 12 patients who were resistant to other bisphosphonates. This study will not be described, as only a summary was provided.

2.2. Tolerance

Analysis of the pharmacovigilance data covering the period April 2006 to the end of April 2009 showed 320 adverse effects, 148 of them serious. In 94 cases the adverse effect was not one mentioned in the SPC, and in most of these cases a connection with the treatment was considered doubtful. A connection was considered plausible in 3 cases (flu-like syndrome and extravasation) and probable in 5 cases (tachycardia, flu-like syndrome, vasovagal attack).

[1] Abelson et al. A review of Paget's disease of bone with a focus on the efficacy and safety of zoledronic acid 5 mg. Current Medical Research and Opinion 2008; 24(3): 695-705

[2] Hosking et al. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. JBMR 2007; 22(1).

Analysis of the last available pharmacovigilance report (exposure between April 2006 and the end of April 2009) showed 6 cases of atrial fibrillation, 5 of them serious, reported in France; all the patients had cardiovascular risk factors.
21 cases of osteonecrosis of the jaw (ONJ) were also reported. In 13 cases there was insufficient information to confirm the diagnosis of ONJ. Half of the cases involved patients with risk factors (corticosteroid therapy, dental treatment, poor dental hygiene, a history of bisphosphonate therapy). Only 6 of these cases meet the EMA definition of ONJ.

Zoledronic acid, in common with all bisphosphonates, has been the subject of three tolerance re-evaluations by the EMA:
- osteonecrosis of the jaw
- stress fracture
- atrial fibrillation

Osteonecrosis of the jaw[3] (mandibular and/or maxillary):
On 24.10.2006, following the first re-evaluation of the class of bisphosphonates in respect of ONJ by the EMA in 2005, the SPC of ACLASTA, in common with that of all medicinal products of this class, was revised on 24/10/2006 to include warnings and precautions for use in respect of the risk of ONJ in cases of infection or dental extraction.
Despite the changes to the SPCs of bisphosphonates, cases of ONJ have continued to be reported. The EMA consequently undertook a second re-evaluation in December 2007, the conclusions of which were published in September 2009[4].
This analysis revealed that the risk of ONJ is significantly greater in patients treated with IV bisphosphonates as cancer chemotherapy (incidence 0.8-12%) than in those treated orally for osteoporosis or Paget's disease (incidence 0.0004-0.06%). The risk of ONJ with oral bisphosphonates seems low.
Since the risk factors are many and not yet fully elucidated, the CHMP would like a more in-depth evaluation of the risk of ONJ through the creation of a European register and the performance of clinical studies.

The transparency Committee draws attention to the recommendations on the oral and dental care of patients treated with bisphosphonates[5]: "in patients who are to be treated with bisphosphonates for osteoporosis or Paget's disease, it is recommended that an initial oral and dental assessment, followed by any necessary dental treatment, be carried out. An annual oral and dental check-up is recommended. On the basis of the data currently available, use of bisphosphonates in osteoporosis cannot be considered a contraindication for the placement of a dental implant."

Concerning ACLASTA more particularly, the EMA concluded that the risk of ONJ posed by intravenous bisphosphonates used in osteoporosis was unknown but was lower than in cancer.
In a controlled double-blind study, 2 cases were reported, one in the zoledronic acid group (out of 3889 patients treated) and the other in the placebo group (out of 3876 patients treated). The postmarketing data showed 6 cases meeting the strict definition of ONJ.

[3] Osteonecrosis of the jaw is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a healthcare professional in a patient who is receiving or has received bisphosphonates and has not had radiation therapy to the craniofacial region.

[4] EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.
[5] AFSSAPS. Letter to healthcare professionals. Recommandations sur la prise en charge bucco-dentaire des patients traités par bisphosphonates [Recommendations on the oral and dental care of patients treated with bisphosphonates]. 18/12/2007

Additional data are needed to ascertain whether the risk of ONJ with zoledronic acid is lower in the osteoporosis population because of a lower dose and a different frequency of administration than that used in cancer.

Stress fracture (or fractures due to bone weakness)

The re-evaluation of bisphosphonates in respect of stress fracture was prompted by the publication of articles indicating a possible link between treatment with alendronic acid and the occurrence of stress fracture; this may be associated with an excessive increase in bone metabolism after long-term treatment with alendronic acid. Because of the mechanism mentioned, a "class effect" could not be ruled out. The EMA consequently carried out a re-evaluation of the class as a whole in 2008[6].

The EMA pharmacovigilance working group concluded that:

- stress fractures of the proximal extremity of the femoral shaft were associated with long-term treatment with alendronic acid. These fractures have occurred after minimal or no trauma;
- the available data did not show an increase in the risk of stress fractures with bisphosphonates other than alendronic acid;
- although analysis of the literature showed that the majority of the reported cases concerned alendronic acid, there is uncertainty about a possible "class effect", given that there are only limited long-term data for other bisphosphonates.

Concerning ACLASTA more particularly, the number of atypical femoral fractures reported in the clinical studies and in the pharmacovigilance reports is very small (4 cases in the clinical studies, 2 of these with ACLASTA and 2 with placebo).

Monitoring of the cases of stress fracture was recommended with the addition of a specific analysis in the PSURs* but no modification of the SPC was deemed necessary.

Atrial fibrillation (AF):

In June 2008, the EMA pharmacovigilance working group re-evaluated the benefit/risk ratio for bisphosphonates in respect of the risk of AF[7]. This re-evaluation of the class was prompted by the identification of an increase in the incidence of AF relative to placebo in patients treated with zoledronic acid in the HORIZON study and in those treated with alendronic acid in the FIT study.

The working group concluded that:

- the benefit/risk ratio remained favourable for the entire class;
- the risk of developing AF seemed higher with certain bisphosphonates, for biochemical reasons;
- the data obtained from the clinical studies indicated an increased risk with zoledronic acid and the data from the extension phases indicated an increased risk with alendronic acid and pamidronic acid.

As the risk of AF has already been identified and included in the SPC for ACLASTA, no additional modification was deemed necessary. Long-term tolerance studies have been planned to re-evaluate this risk.

[6] MHRA. Bisphosphonates and stress fractures. January 2009.

[7] EMA post-authorisation evaluation of medicines for human use. Updated overall assessment report of responses to agency request for information on bisphosphonates and the potential risk of atrial fibrillation-zoledronic acid-2008

Other adverse effects: renal tolerance
Cases of increased blood creatinine have also been shown and have been the subject of a letter to prescribers[8] informing them that:
"Cases of renal impairment and kidney failure have been observed following administration of ACLASTA, particularly in patients with pre-existing renal impairment or other risk factors such as advanced age, concomitant administration of nephrotoxic medicines or of diuretics, or dehydration following administration of ACLASTA. Renal impairment can occur after the first administration, as observed in certain patients. Cases of kidney failure necessitating dialysis or even resulting in death have been reported. ACLASTA should not be used in patients with creatinine clearance < 35 ml/min. Monitoring of blood creatinine must be considered in patients at risk. Patients must be properly hydrated before administration of ACLASTA".

The SPC was modified on 18 May 2010 to take account of this risk of renal adverse effects (see appended Table).

3 USAGE DATA

ACLASTA does not appear in the available prescription panels (EPPM IMS DOREMA).

The table below shows the number of packs of ACLASTA sold in the community and in hospital according to GERS:

	2005	2006	2007	2008	2009
° In hospital	0	103	480	2022	4459
° In the community	0	737	1598	18,189	45,380

[8] Information importante de pharmacovigilance: cas d'altération de la fonction rénale et d'insuffisance rénale survenus avec ACLASTA® (Acide zolédronique 5 mg, solution pour perfusion) [Important pharmacovigilance information: cases of renal impairment and kidney failure with ACLASTA® (zoledronic acid 5 mg, solution for infusion) - Letter to healthcare professionals 06/04/2010

4 TRANSPARENCY COMMITTEE CONCLUSIONS

Re-evaluation of actual benefit:

Paget's disease is a generally benign, slow-progressing, localised bone disorder affecting one or more bones. It is frequently asymptomatic, bone pain being demonstrated in only 5 to 10% of patients. At some sites, however, it can lead to complications of varying severity and which cause varying degrees of disability and which are sometimes irreversible (hypoacusia). Paget's disease is in very rare instances life-threatening (sarcomatous degeneration).

Osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck can be life-threatening.

In the light of the new tolerance data, the efficacy/adverse effects ratio of ACLASTA, like that of all medicinal products of the bisphosphonates class, is moderate.

This medicinal product is a first-line therapy for Paget's disease and osteoporosis. Its efficacy in the prevention of vertebral and peripheral fractures, including femoral neck fractures, has been demonstrated.

Alternative medicinal products exist.

The transparency Committee considers that actual benefit of ACLASTA remains substantial in all of these indications.

Transparency Committee recommendations

The transparency Committee recommends continued inclusion on the list of medicines reimbursed by National Health Insurance at the dosage in the Marketing Authorisation and only in the therapeutic indications qualifying for reimbursement:

- Treatment of osteoporosis in men at increased risk of fracture, in particular those with a recent low-trauma proximal-femoral-extremity (PFE) fracture,
- Treatment of osteoporosis in postmenopausal women at increased risk of fracture, in particular those with a recent low-trauma PFE fracture:
    - in patients with a fracture caused by bone fragility,
    - in the absence of a fracture, in women with substantially decreased bone density (T-score < -3) or with a T-score ≤ -2.5 associated with other risk factors for fractures, 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 extremity fracture in a first-degree relative (mother), early menopause (before the age of 40 years)."

- Treatment of osteoporosis associated with long-term systemic corticosteroid therapy in postmenopausal women and men at increased risk of fracture.

- Treatment of Paget's disease.

Packaging: appropriate for the prescription conditions

Reimbursement rate: 65%

APPENDIX 1: Changes to the SPC for ACLASTA, of 18 May 2010.

<table>
<tr><th colspan="2">Dosage and method of administration</th></tr>
<tr><th>Old SPC (10 March 2010)</th><th>New SPC (18 May 2010°</th></tr>
<tr><td><u>Patients with renal impairment</u>
Use of ACLASTA in patients with creatinine clearance < 35 ml/min is not recommended due to limited clinical experience in this population.
No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.</td><td><u>Patients with renal impairment</u>
ACLASTA should not be used in patients with creatinine clearance < 35 ml/min (see section 4.4).

No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.</td></tr>
<tr><th colspan="2">Special warnings and precautions for use</th></tr>
<tr><th>Old SPC</th><th>New SPC</th></tr>
<tr><td>The dose of 5 mg zoledronic acid must be administered over at least 15 minutes.

ACLASTA is not recommended in patients with severe renal impairment (creatinine clearance < 35 ml/min) due to limited clinical experience in this population. Patients should have their blood creatinine level measured before receiving ACLASTA.

Patients must be appropriately hydrated prior to administration of ACLASTA. This is especially important in the elderly and for patients receiving diuretic therapy. Caution is indicated when ACLASTA is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see Interaction with other medicinal products and other forms of interaction).</td><td>Renal impairment has been observed following the administration of ACLASTA (see section 4.8), especially in patients with pre-existing renal dysfunction or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section 4.5), or dehydration occurring after ACLASTA administration. Renal impairment requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal dysfunction or with any of the risk factors described above.

The following precautions should be taken into account to minimise the risk of renal adverse effects.
• Creatinine clearance should be measured before each ACLASTA dose.
• ACLASTA should not be used in patients with creatinine clearance < 35 ml/min (see section 5.2).
• Transient increase in blood creatinine may be greater in patients with pre-existing renal dysfunction.
• Monitoring of blood creatinine should be considered in at-risk patients.
• ACLASTA should be used with caution when concomitantly used with medicinal products that could impact renal function (see section 4.5).
• Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of ACLASTA.
• A single dose of ACLASTA should not exceed 5 mg and the duration of the infusion should be at least 15 minutes (see section 4.2).</td></tr>
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<tr><th colspan="2">Interaction with other medicinal products and other forms of interaction</th></tr>
<tr><th>Previous SPC</th><th>New SPC</th></tr>
<tr><td>Zoledronic acid is eliminated by renal excretion. Caution is indicated when ACLASTA is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).</td><td>Zoledronic acid is eliminated by renal excretion. Caution is indicated when ACLASTA is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

In patients with renal dysfunction, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.</td></tr>
<tr><th colspan="2">Adverse effects</th></tr>
<tr><th>Previous SPC</th><th>New SPC</th></tr>
<tr><td>
<table>
<tr><td>Renal and urinary disorders</td><td>Uncommon</td><td>Blood creatinine increased, pollakiuria, proteinuria</td></tr>
</table>

Class effects:
Renal dysfunction
Zoledronic acid has been associated with renal dysfunction manifested as deterioration in renal function (i.e. increased blood creatinine) and in rare cases acute renal impairment. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal dysfunction or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration), the majority of whom received a 4 mg dose every 3–4 weeks, but it has been observed in patients after a single administration.
</td><td>
<table>
<tr><td>Renal and urinary disorders</td><td>Uncommon</td><td>Blood creatinine increased, pollakiuria, proteinuria</td></tr>
<tr><td></td><td>Not known**</td><td>Renal dysfunction. Cases of renal dysfunction requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post-infusion period (see sections 4.4 and 4.8 Class effects)</td></tr>
</table>
**Based on post-marketing reports. Frequency cannot be estimated from available data.

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Renal dysfunction
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	advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medicinal products, **concomitant diuretic therapy**, severe dehydration), the majority of whom received a 4 mg dose every 3–4 weeks, but it has also been observed in patients after a single administration.