SKELID 200 mg, tablets  
B/28 (CIP code: 338 553-2)

Applicant: SANOFI-AVENTIS FRANCE

disodium tiludronate  
ATC code: M05BA05

List I

Date of Marketing Authorisation: 29 May 1995

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
disodium tiludronate

1.2. Indications
Treatment of Paget's disease.

1.3. Dosage
See SPC

2 UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION
(18 October 2006)

2.1. Efficacy
Since the most recent opinion regarding renewal of listing (18 October 2006), an open-label study\(^1\) compared the use of tiludronic acid 400 mg/d (n =28) with risedronic acid 30 mg/d (n=21) for 2 months in patients suffering from Paget's disease. No difference between these two treatments was observed in respect of reduction in bone remodelling and bone scintigraphy markers.

2.2. Tolerance
Like all bisphosphonates, tiludronic acid has been reviewed by the EMA for tolerance in three indications:
- osteonecrosis of the jaw (ONJ)
- stress fracture
- atrial fibrillation

Osteonecrosis of the jaw\(^2\) (mandible and/or maxilla):
Following the first re-assessment of the class of bisphosphonates in respect of ONJ by the EMA in 2005, the SPC of SKELID, in common with that of all proprietary drugs of this class, was revised in 2007 to include under “Special warnings and precautions for use” the risk of ONJ secondary to infections or dental extractions. Despite the changes to the SPCs of bisphosphonates, cases of ONJ have continued to be reported. The EMA consequently undertook a second re-assessment in December 2007, the conclusions of which were published in September 2009\(^3\).
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.

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\(^2\) Osteonecrosis of the jaw is defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to bisphosphonates and had not had radiation therapy to the craniofacial region.

\(^3\) EMA. CHMP Assessment report on bisphosphonates and osteonecrosis of the jaw. 24/09/2009.
Since the risk factors are many and not yet fully elucidated, the CHMP would like a more in-depth assessment of the risk of ONJ through the creation of a European register and the performance of clinical studies.

No cases of ONJ have been reported or published in the literature for patients treated with tiludronic acid. No new change has been made to the SPC of SKELID.

The Transparency Committee draws attention to the recommendations on the oral and dental care of patients treated with bisphosphonates: “in patients who are to be treated with bisphosphonates for osteoporosis or Paget's disease, it is recommended to carry out an initial oral and dental assessment, followed by any necessary dental treatment. An annual oral and dental checkup is recommended. Based on the currently available data, use of bisphosphonates in osteoporosis cannot be considered a contraindication for the placement of a dental implant.”

Stress fracture (or fractures due to bone weakness)
The class re-assessment 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 proposed mechanism, a class effect could not be ruled out. The EMA consequently carried out a re-assessment of the class as a whole in 2008. 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 have not demonstrated an increase in the risk of stress fractures with bisphosphonates other than alendronic acid;
- although analysis of the literature had shown that the majority of cases concerned alendronic acid, there is uncertainty about a possible “class effect”, given that there are only limited long-term data for other bisphosphonates.

No cases of stress fracture have been reported or published in the literature for patients treated with tiludronic acid. It has been recommended that cases of stress fracture should be monitored, with an additional specific analysis having been added to the PSURs, but the SPC has not been amended.

Atrial fibrillation (AF):
In June 2008, the EMA pharmacovigilance working group re-evaluated the risk/benefit ratio of bisphosphonates in respect of the risk of AF. This re-assessment 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.

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4 Afssaps. Letter to healthcare professionals. Recommendations on the oral and dental care of patients treated with bisphosphonates. 18/12/2007
6 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
The working group concluded that:
- the risk/benefit ratio remained favourable for the entire class;
- the risk of developing AF seemed higher with certain bisphosphonates, for biochemical reasons;
- the data obtained from clinical studies indicated increased risk for zoledronic acid and, in the case of data from extension phases, for alendronic acid and pamidronic acid.

No cases of AF have been observed with tiludronic acid.

### 3 USAGE DATA

Between February 2006 and February 2010, 1,337,112 SKELID 200 mg tablets were sold in France.

### 4 TRANSPARENCY COMMITTEE CONCLUSIONS

Paget’s disease is a localised, monoostotic or polyostotic bone condition. It is generally benign and progresses slowly. It is frequently asymptomatic, with only 5 to 10% of patients experiencing bone pain. However, complications of varying degrees of severity and involving varying levels of handicap can arise at some sites. These complications can be irreversible (hypoacusis). In exceptional cases, Paget’s disease is life-threatening (sarcoma degeneration).

In the light of the tolerance data, the Transparency Committee considers that the efficacy/adverse effects ratio of SKELID, like that of all proprietary drugs of the bisphosphonates class, is moderate.

This proprietary drug is a first-line therapy.

There are treatment alternatives.

The actual benefit of SKELID remains substantial.