EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Zoledronic acid Teva

International non-proprietary name: **zoledronic acid**

Procedure No. **EMEA/H/C/002439**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 6 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid Teva, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 October 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference medicinal product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: prevention of skeletal related events and treatment of tumour-induced hypercalcaemia (TIH).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. According to the Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), bioequivalence studies are not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. As this is the case with Zoledronic Acid Teva, bioequivalence study is not required.

Information on paediatric requirements

Not applicable

Information on the reference medicinal product

The chosen reference medicinal product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Zometa 4 mg powder and solvent for solution for infusion and 4mg/5ml concentrate for solution for infusion.
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 22-03-2001
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/01/176/001-006

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Zometa 4mg/5ml concentrate for solution for infusion
- Marketing authorisation holder: Novartis Europharm Ltd
- Date of authorisation: 22-03-2001
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/01/176/0014-006

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

At the time of submission of the application, Teva Group had not licensed the product in any country of the European Union and outside the European Union Teva Group had registered the product in Mexico only.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

- The application was received by the EMA on 6 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 August 2011.
- During the meeting on 19-22 September 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 January 2012.
- During the CHMP meeting on 16-19 January, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 13 February 2012.
- During the meeting on 12-15 March 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zoledronic Acid Teva on 15 March 2012.

2. Scientific discussion

2.1. Introduction

The marketing authorisation application for Zoledronic acid Teva 4mg/5ml concentrate for solution for infusion is a generic application submitted to the centralised procedure according to regulation (EC) No 726/2004, Article 3(3). The reference product is the centrally authorised medicinal product Zometa 4mg/5ml concentrate for solution for infusion, authorised to Novartis Europharm Limited on 20 March 2001.

The active substance of this generic medical product is zoledronic acid, a bisphosphonate that acts primarily on bone. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease.

Patients with tumors can have high levels of calcium in their blood, released from the bones. By preventing the breakdown of bones, Zoledronic acid also helps to reduce the amount of calcium released into the blood.

The safety and efficacy profile of zoledronic acid has been demonstrated in several clinical trials, details of which can be found in the EPAR of the reference product Zometa. In addition, there is long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application, a summary of the clinical data has been provided and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with Zoledronic acid Teva.

The applicant applied for all the indications of the reference product:

- prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone
- treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Zoledronic acid Teva must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks ; patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

The recommended dose in hypercalcaemia is a single dose of 4 mg zoledronic acid.

Since Zoledronic acid Teva contains the same active substance as the currently approved product and is to be administered as an aqueous intravenous solution, bioequivalence studies are not required.

2.2. Quality aspects

2.2.1. Introduction

Zoledronic Acid Teva is presented as 4ml/5mg concentrate for solution for infusion for intravenous use. It is a clear and colourless solution, free from visible particles. It contains zoledronic acid as the active substance and excipients as described in the section 6.1 of the SmPC.

The product is available in plastic vials and glass vials.

2.2.2. Active substance

The active substance is zoledronic acid, chemical name [1-hydroxy-2-(1H-imidazol-1) ethylidene] bisphosphonic acid or 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid. It exists in several crystalline forms; this application uses a hydrate. The corresponding molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$, molecular weight of the monohydrate is 290.11. The molecule does not contain any chiral centres.

It is a white crystalline powder, containing plate-shape particles, non-hygroscopic, sparingly soluble in 0.1N sodium hydroxide solution, slightly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Manufacture

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The structure of zoledronic acid was confirmed by IR, MS, ^{13}C-NMR and ^{1}H-NMR.

Specification

As there is no monograph of zoledronic acid in the Ph.Eur., the applicant developed their own specifications and test methods for the quality control. Control tests include description, identity by FTIR and HPLC, assay and impurities by HPLC, residual solvents by GC, polymorphism by XRD, pH of the solution, heavy metals, loss on drying, microbial purity and endotoxins.

The acceptance criteria for impurities, including limits for organic impurities, inorganic impurities and residual solvents, are defined. The limits were evaluated and found to be acceptable from the point of view of safety. No genotoxic impurities were detected in the batches of the active substance. No solvents are carried over from early steps of the synthesis.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP/ICH guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP/ICH requirements.

Results of analysis of three batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

Stability data of six batches of the active substance up to 60 months of storage at 25°C/60% relative humidity (RH) and 6 months at 40°C/75% RH were provided. Compliance with specification has been confirmed at both conditions. Following parameters were tested during stability studies: description, identity, impurities and assay by HPLC, polymorphism by XRD, loss on drying and microbial purity. No negative trends were observed.

The stability data support the proposed retest period 60 months when stored in amber glass container with teflon liner and a white polypropylene cap as immediate packaging, inserted into an aluminum laminated bag.

2.2.3. Finished medicinal product

Pharmaceutical development

The development of the Zoledronic acid Teva 4mg/5ml concentrate for solution for infusion was aiming to manufacture a medicinal product essentially similar to Zometa, the reference product, which contains the same active substance and the same excipients. The excipients used are sodium citrate (buffer), mannitol (tonicity system) and water for injection; all of them are described in the European Pharmacopoeia.

Since the formulation is an aqueous intravenous solution containing the same active substance at the same concentration as the reference product no bioequivalence studies are required.

The finished product is terminally sterilised, this is the most suitable sterilisation method given the nature of the active substance.

Adventitious agents

Not applicable

Manufacture of the product

The manufacturing process is a standard process for parenteral formulations. The manufacturing process consists of four main steps: dissolution, filtration, filling and terminal moist heat sterilisation. The required manufacturing parameters and ranges were determined during manufacturing process development and process validation.

The critical steps in the manufacture are environmental monitoring, bulk solution preparation, sterile filtration, filling and terminal sterilisation.

Validation of the manufacturing process has been performed on commercial scale batches. Holding times at each manufacturing step were defined and validated.

The batch analysis data show that this medicinal product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this parenteral preparation.

Product specification

The release and shelf life specification includes tests and limits for description (visual), clarity of solution (Ph.Eur), visible particles (Ph.Eur), colour of solution (Ph.Eur), osmolality (Ph.Eur), extractable volume (Ph.Eur), pH value (Ph.Eur), identification (In-house), assay and related substances (In-house), sub-visible particles (Ph.Eur), bacterial endotoxins (Ph.Eur) and sterility (Ph.Eur).

Batch analysis results from validation batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Commercial scale batches of Zoledronic Acid 4 mg/5 ml concentrate for solution for infusion for both glass and plastic vials were manufactured and introduced in stability program for the testing periods

and conditions: 6 months under accelerated conditions (40°C ± 2°C/75% RH ± 5°C), 12 months on long term conditions (25°C ± 2°C/60% RH ± 5°C) and 12 months on intermediate conditions (30°C ± 2°C/75% RH ± 5°C).

A photostability testing was performed on both glass and plastic in accordance with the requirements of ICH Q1B.

For the parameters appearance, colour, clarity, pH, visible particles, sub-visible particles, bacterial endotoxin and sterility no significant changes were noticed for the available period of study, as compared to the initial testing point, and there are no differences regardless of the storage conditions.

The in-use shelf-life, supported by a study, is 24 hours at 2-8°C.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Zoledronic acid Teva from Teva Pharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all zoledronic acid containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Pharmacokinetics

Not applicable

2.3.4. Toxicology

Not applicable

2.4. Clinical aspects

2.4.1. Introduction

This is an application for concentrate for solution for infusion containing 4 mg/5 ml zoledronic acid. The Applicant claims essential similarity for their product Zoledronic acid Teva 4 mg/5 ml concentrate for solution for infusion with the reference product Zometa 4 mg/5 ml concentrate for solution for infusion.

GCP

Not applicable

Exemption

There are no bioequivalence studies submitted with this application. Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1):

"Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".

The pharmaceutical form and mode of administration as well as the qualitative and quantitative composition of Zoledronic acid Teva 4 mg/5 ml concentrate for solution for infusion is the same as of the reference product Zometa 4 mg/5 ml concentrate for solution for infusion.

The claim of essential similarity can be accepted. There are no objections to the approval of Zoledronic acid Teva 4 mg/5 ml concentrate for solution for infusion from a clinical point of view.

2.4.2. Pharmacokinetics

Not applicable

2.4.3. Post-marketing experience

The products containing zoledronic acid are registered by Teva Group only in Mexico. Based on the sales data, from the date of first registration on 28 November 2008 until the Data Lock Point (31 July 2011), it was estimated that patient exposure to Teva's zoledronic acid was 38, 469 patient-days. Exposure has been estimated based on Defined Daily Dose (DDD) of 4 mg for parenteral use (based on

WHO Collaborating Centre for Drug Statistic Methodology, ATC/DDD Index, 2011). In the indication of bone metastases a dose is given in a 15-minute intravenous infusion; the dose could be repeated every 3 to 4 weeks.

2.4.4. Discussion on clinical aspects

No new data are requested or provided. The indications are in accordance with the reference medicinal product.

2.4.5. Conclusions on clinical aspects

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. The clinical aspects of the SmPC are in line with the SmPC of the reference medicinal product.

Therefore, the CHMP agreed that no further clinical studies are required.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan.

Safety concern	**Proposed pharmacovigilance Activities (routine and additional)**	**Proposed risk minimisation Activities (routine and additional)**
Important identified risks		
Osteonecrosis of the jaw	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Information on osteonecrosis of the jaw is included in SPC and PL for 4 mg/5 ml concentrate. SPC [Section 4.4] states that osteonecrosis of the jaw has been reported in patients, predominantly those with cancer, receiving treatment with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy,

Safety concern	Proposed pharmacovigilance Activities (routine and additional)	Proposed risk minimisation Activities (routine and additional)
		corticosteroids, poor oral hygiene). For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. Statement in [Section 4.8] SPC: Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported, predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged. Precautions are also stated in PL: pateint should tell doctor if has or has had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth (that could be signs of bone damage in the jaw, osteonecrosis) are listed as uncommon side effects.
Hypocalcaemia	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Risk of hypocalcaemia is included in SPC for 4 mg/5 ml concentrate. SPC states [Section 4.4] that standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zoledronic Acid Teva therapy. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered. [In Section 4.8] Hypocalcaemia is listed as common undesirable effect. In overdose section [Section 4.9] it is stated that patients who have received doses higher than those recommended should be carefully monitored, since (among others) serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated. Possible interaction with aminoglycosides resulting

Safety concern	Proposed pharmacovigilance Activities (routine and additional)	Proposed risk minimisation Activities (routine and additional)
		in a lower serum calcium level for prolonged period is also stated in [Section 4.5] SPC for 4 mg/5 ml concentrate. Risk of zoledronate blood calcium lowering effect is stated in the PLs for 4 mg/5 ml concentrate, as well as need for calcium supplementation to prevent the risk.
Renal impairment/ renal failure	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Warnings and precautions are stated in [Section 4.4] SPC for 4 mg/5 ml concentrate on renal insufficiency. Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of Zoledronic Acid Teva are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic Acid Teva should be withheld. Zoledronic Acid Teva should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic Acid Teva treatment should be resumed at the same dose as that given prior to treatment interruption. The use of Zoledronic Acid Teva is not recommended in patients with severe renal impairment. Renal and urinary disorders are also listed in [Section 4.8] SPC. In addition, renal failure is also listed in overdose [Section 4.9] for 4 mg/5 ml concentrate. Additionally, SPC state [in Section 4.2] dose adjustments in patients with renal impairment. Treatment precautions with 4 mg/5 ml concentrate are given separately for TIH patients and patients with bone metastases with mild to moderate renal impairment. In PL zoledronic acid use is contraindicated in patents with kidney problems. Blood tests changes (such as higher levels of creatinine), including severe kidney impairment are

Safety concern	Proposed pharmacovigilance Activities (routine and additional)	Proposed risk minimisation Activities (routine and additional)
		listed as common side effects.
Hypersensiti-vity reactions	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients is contraindication for use of Zoledronic Acid Teva [in Section 4.3]. In addition, hypersensitivity reaction and angioneurotic oedema are listed in [Section 4.8] SPC. PL also states known allergy as contraindication and severe allergic reaction: shortness of breath, swelling mainly of the face and throat, as uncommon side effects.
Ocular adverse events	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Risk has been highlighted in the product information for 4 mg/5 ml concentrate; ocular undesirable effects are listed in [Section 4.8] SPC (common: conjunctivitis, uncommon: blurred vision, scleritis and orbital inflammation, very rare: uveitis, episcleritis) and in PL (tearing of the eye, eye sensitivity to light, painful redness and/or swelling of the eye).
Acute phase reaction	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Acute phase reaction has been highlighted in [Section 4.8] SPC/PL as common undesirable effects (Flu-like syndrome, consisting of fatigue, weakness, chills and bone, joint and/or muscle ache). Flu-like syndrome, consisting of fatigue, weakness, chills and bone, joint and/or muscle ache, is stated as common side effect in PL.
Atrial fibrillation	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Atrial fibrillation (from studies and as post-marketing experience) is listed as side effect in [Section 4.8] SPC. It is listed in PL for 4 mg/5 ml concentrate as very rare side effect.
Important potential risks		
Atypical femoral fractures	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Potential risk identified with zoledronic acid and other bisphosphonates has been highlighted in the product literature. SPC states [in Section 4.4] atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have

Safety concern	Proposed pharmacovigilance Activities (routine and additional)	Proposed risk minimisation Activities (routine and additional)
		sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture. Information in [Section 4.8] SPCs with regard to rare frequency of reported atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) during post-marketing experience. Risk is stated in PL: unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely.
Cardiac arrhythmias	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Risk of atrial fibrillation has been highlighted in [Section 4.8] the SPC/PL as post-marketing experience.
Cerebrovascular AEs	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Fracture healing impairment	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Focal segmental glomerulo-sclerosis	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Interstitial lung disease	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Potential interaction with nephrotoxic drugs	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Caution when zoledronic acid is administered in conjunction with medicinal products that can significantly impact renal function is stated in the [Section 4.5] SCP/PL for 4 mg/5 ml concentrate. See also above under identified risk "Renal impairment/ renal failure".
Medication errors	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Clear difference in appearance and labelling of the cartons and vials or bottles/bags for each strength (4 mg/5 ml concentrate (vials) and 5 mg solution (bottles/bags, 100 ml). Different sizes of containers (5 ml vs. 100 ml).
Important missing information		
Races other than	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.

Safety concern	Proposed pharmacovigilance Activities (routine and additional)	Proposed risk minimisation Activities (routine and additional)
Caucasians		
Use during pregnancy and lactation	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** It is stated in [Section 4.6] SPC/PL that zoledronic acid should not be used during pregnancy or lactation.
Use in patients below 18 years of age	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Information is given in [Section 4.2] SPC/PL: drug use is not recommended in children below the age of 18 years.
Patients with severe renal impairment	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Information and precautions are given in [Sections 4.2 and 5.2] SPC/PL related to drug use in patients with severe renal impairment. In Sections 4.2 it is stated: The use of Zoledronic Acid Teva is not recommended in patients with severe renal impairment.
Patients with hepatic insufficiency	Routine pharmacovigilance	**Routine risk minimization activities:** **Labelling:** Information is given in [Sections 4.4 and 5.2] SPC for 4 mg/5 ml concentrate: As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 1-yearly cycle. The next data lock point for the reference medicinal product is 31 August 2012.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of zoledronic acid concentrate for solution for infusion (4mg/ 5 ml). The reference product Zometa is indicated for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone, and for treatment of tumour-induced hypercalcaemia (TIH).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and

pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

There are no bioequivalence studies submitted with this application, and this is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1), as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zoledronic acid Teva in the

- prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone
- treatment of adult patients with tumour-induced hypercalcaemia (TIH).

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable