

15 March 2012 EMA/534119/2012

Assessment report

Zoledronic acid Teva Pharma

a authorised International non-proprietary name: zoledronic acid

Procedure No. EMEA/H/C/002437

Medicinal

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 Pharma, 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 26 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 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 indications:

Treatment of osteoporosis

- in post-menopausal women
- in men
- at increased risk of fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in men

at increased risk of fracture.

Treatment of Paget's disease of the bone in adults.

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 Pharma, bioequivalence study is not required.

Information on paediatric requirements

Not applicable

The chosen reference medicinal product is:

- Medicinal product which is or has been authorised in accordance with Community 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 4 mg/5ml concentrate for solution for infusion
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (dd-mm-yyyy) 20-03-2001
- Marketing authorisation granted by:
 - Community

- Community Marketing authorisation number: EU/1/01/176/001 EU/1/01/176/006
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: Aclasta, 5 mg solution for infusion
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (dd-mm-yyyy) 15-04-2005
- Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number:

EU/1/05/308/001 - EU/1/05/308/002

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Zoledronic acid Teva Pharma has been given a Marketing Authorisation in Mexico on 28 November 2008.

The product was not licensed in any EU/EEA country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: 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 2012, 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 Pharma on 15 March 2012.

2. Scientific discussion

2.1. Introduction

Zoledronic Acid Teva Pharma is a generic medicinal product containing the active substance zoledronic acid (as monohydrate). The reference medicinal product is Aclasta 5 mg solution for infusion. Both the qualitative and quantitative composition of the generic product is identical to the reference product. Both products are administered intravenously as an infusion.

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone. Zoledronic acid treatment rapidly reduces the rate of bone turnover.

The positive effect of zoledronic acid on various types of bone fractures, bone mineral density, bone histology, bone turnover markers, standing height and days of disability was demonstrated in patients with osteoporosis. In Paget's disease, bone of normal quality was found in responding patients after treatment with zoledronic acid.

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 Aclasta. 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 referring to the reference medicinal product Aclasta, a summary of the clinical data of zoledronic acid has been provided and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with Zoledronic acid Teva Pharma.

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 Pharma, a bioequivalence study is not required.

The proposed indications for the generic product are the same as for the reference product, with the exception of treatment of osteoporosis in patients at increased risk of fracture with recent low-trauma hip fracture. The applicant did not apply for this indication as they claim it is covered by a patent.

The proposed indications are:

Treatment of osteoporosis

- in post-menopausal women
- in men
- at increased risk of fracture

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in men

at increased risk of fracture.

Treatment of Paget's disease of the bone in adults.

2.2. Quality aspects

2.2.1. Introduction

Zoledronic Acid Teva Pharma is presented as 5 mg 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 bottles and in plastic bags.

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 active substance is manufactured on manufacturing sites in India and Israel.

The structure of zoledronic acid was confirmed by IR, MS, ¹³C-NMR and ¹H-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 aim of the development work was to develop a solution for infusion, equivalent to the originator product Aclasta.

Qualitative composition of the product is the same as composition of the reference product, with mannitol as a tonicity agent, sodium citrate as a buffering agent and water for injections as a solvent. All excipients are of compendial quality.

The formulation development focused on manufacturing conditions (effect of pH, oxygen and temperature sensitivity, order of addition of excipients), suitability of filters, sterilisation method, photostability, compatibility with the manufacturing equipment and compatibility with the primary packaging.

As the generic product is an aqueous intravenous solution containing the same active substance in the same concentration as the reference product, a bioequivalence study is not required.

Adventitious agents

No excipients of human or animal origin are used in the finished product.

Therefore, there is no risk of BSE/TSE transmission via this product.

Manufacture of the product

The manufacturing process of the finished product consists of 5 steps – preparation of the bulk solution, sterile filtration, end point filtration/filling, terminal sterilisation and inspection/packaging. The terminal sterilisation is done by autoclaving. The critical steps/parameters in the manufacturing process are environmental monitoring, bulk solution preparation, sterile filtration, end point filtration/filling and terminal sterilisation. Appropriate in-process controls are in place after each step.

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

Product specification

The specification of the finished product includes standard testing parameters typical for this kind of dosage form. The finished product is tested for description, identification, clarity and colour of solution, visible and subvisible particles, pH, osmolality, extractable volume, assay, related substances (any impurity, total impurities), sterility and bacterial endotoxins. A weight loss test is also introduced as the containers (plastic bottles and bags) are semi-permeable. The UPLC method used for identification, assay and related substances has been appropriately validated. All other test methods except the weight loss test are compendial.

Possible degradation products were discussed. During the development, manufacture of validation batches and the 6-months stability period (accelerated, intermediate and long-term conditions) these impurities were not detected. The forced degradation study for the analytical method also supports the assumption that these impurities are not likely to be present in the drug product and therefore are not specified.

Batch analysis data for six batches were provided. All results comply with specification.

Stability of the product

The stability studies were carried out in accordance with the current ICH/CHMP guidelines. All tests were conducted by validated, stability indicating analytical methods.

Stability results at long-term, intermediate and accelerated conditions were provided for the product in plastic bottles and plastic bags. Accelerated studies for plastic bags and bottles were performed at reduced relative humidity (25%) in order to assess possible weight loss due to use of semi-permeable containers. The stability studies are ongoing.

Photostability testing was performed according to the relevant ICH/CHMP guideline. The studies demonstrate that the product is not light sensitive in any of the proposed packaging types.

For the finished product in plastic bags and plastic bottles all stability results complied with specification and no trends/changes were observed.

The in-use shelf-life, supported by a study, is 24 hours at 2-8°C. Compatibility with the infusion sets was tested and found acceptable.

In general, the results support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 SmPC. 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

N/A

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 Pharma 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. yer authorit

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 solution for infusion containing 5 mg/100 ml zoledronic acid. The Applicant claims essential similarity for their product Zoledronic acid Teva Pharma 5 mg/100 ml solution for infusion with the reference product Aclasta 5 mg/ 100 ml solution for infusion.

GCP

Not applicable

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 (estimated based on Defined Daily Dose (DDD) of the main indication for zoledronic acid.

2.4.4. Discussion on clinical aspects

Not applicable

2.4.5. Conclusions on clinical aspects

Not applicable

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, which included a risk minimisation plan.

Safety issues	Agreed pharmacovigilance Activities	Agreed risk minimisation Activities
Important identified risks		
Osteonecrosis of the jaw	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Osteonecrosis of the jaw and related risk factors and precautions are included in [Sections 4.4 and 4.8] SPC and PL for 5 mg solution. ONJ has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates. 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. Cautions related to dental procedures are also given. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Medicil	al proor	Statement in [Section 4.8] SPC regarding the class effect: 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 (see section 4.4). In a large clinical trial in 7,736 patients, osteonecrosis of the jaw has been reported in one patient treated with zoledronic acid and one patient treated with placebo. Both cases resolved.
		ONJ is listed under SOC "Musculoskeletal and connective tissue disorders", with frequency not

Table 1. Summary of the risk management plan

Safety issues	Agreed pharmacovigilance Activities	Agreed risk minimisation Activities
		known.
Hypocalcaemia	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Drug is contraindicated in patients with hypocalcaemia. Precautions are stated in [Section 4.4] SPCs for 5 mg solution: Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy. Special precautions are given for treating patients with Paget's disease. Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum calcium before infusion of zoledronic acid is recommended for patients with Paget's disease.
	duct	Hypocalcaemia is stated as common undesirable effect in [Section 4.8] SPCs and in overdose [Section 4.9]. In addition it is stated [in Section 4.8] as class effect: "In clinical trials in osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87 mmol/l) following zoledronic acid administration. No symptomatic cases of hypocalcaemia were observed. In the Paget's disease trials, symptomatic hypocalcaemia was observed in approximately 1% of patients, in all of whom it resolved. Based on laboratory assessment, transient asymptomatic calcium levels below the normal reference range (less than 2.10 mmol/l) occurred in 2.3% of zoledronic acid-treated patients in a large clinical trial compared to 21% of zoledronic acid-treated patients in the Paget's disease trials. The frequency of hypocalcaemia was much lower following subsequent infusions.
• . (131910	Risk of zoledronate blood calcium lowering effect is stated in the PL for 5 mg solution, as well as need for calcium supplementation to prevent the risk and warning regarding patients with Paget's disease. Zoledronic acid use is contraindicated in patents with hypocalcaemia.
Renal dysfunction (renal impairment/ renal failure)	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Warnings are stated in [Section 4.4] SPCs for 5 mg solution:
Ner		Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after zoledronic acid administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above. Precautions related to renal failure are also stated.
		Renal impairment as class effects is listed in

Safety issues	Agreed pharmacovigilance Activities	Agreed risk minimisation Activities
		[Section 4.8] SPCs. In addition, blood creatinine increased, pollakiuria, proteinuria are uncommon side effects; while frequency is unknown for renal impairment. Rare cases of renal failure 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 advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period.
		Additionally, SPCs state [in Section 4.2] that zoledronic acid is contraindicated in patients with creatinine clearance < 35 ml/min. No dose adjustment is necessary in patients with creatinine clearance \geq 35 ml/min.
		In PL zoledronic acid use is contraindicated in patents with severe kidney problems. Abnormal kidney test/kidney disorders are listed as uncommon side effects.
		Additional risk minimization activities: Communication and Educational Program (CEP) to emphasize to prescribers and patients risks related to renal dysfunction and the importance of monitoring renal function.
Hyper- sensitivity reactions (anaphylaxis)	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Drug is contraindicated in patients with hypersensitivity. Risk has been highlighted in the SPC section 4.8, frequency not known: hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock. were reported. PL states severe allergic reactions including dizziness and difficulty breathing as (additional) side effects. Drug must not be given in case of allergy to zoledronic acid, other bisphosphonates or any of the other ingredients of the medicine.
Ocular adverse events	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Risk has been highlighted in the product information for 5 mg solution; ocular undesirable effects are listed in [Section 4.8] SPC (common: ocular hyperaemia; uncommon: conjunctivitis, eye pain; rare: uveitis, episcleritis, iritis; not known: scleritis, orbital inflammation) and in PL.
Post-dose symptoms	Routine pharmacovigilance	Routine risk minimization activities: Labelling: SPC [in Section 4.4] states "The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic acid Teva Pharma can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic acid Teva Pharma administration." Effects are listed in Section 4.8 with unknown frequency: dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea. Acute phase reaction is listed as uncommon side

Safety issues	Agreed pharmacovigilance Activities	Agreed risk minimisation Activities
		effect; flu-like symptoms, chills, fatigue, malaise are common. Post-dose symptoms are stated in PL for 5 mg solution.
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 [Sections 4.4 and 4.8 as class effect]/ PL). Warnings are: 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 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.
	alprodule	Additionally, information is given in [Section 4.2] SPC for 5 mg solution concerning the optimal duration of bisphosphonate treatment for osteoporosis, which has not been established yet; the need for continued treatment should be re-evaluated periodically based on the benefits and potential risks on an individual patient basis, particularly after 5 or more years of use.
Atrial fibrillation	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.
AVN/fracture nonunion and /or delayed union	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Gastrointestinal AEs	Routine pharmacovigilance	Gastrointestinal disorders listed in section 4.8 are - common: nausea, vomiting, diarrhoea and uncommon: dyspepsia, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis. Currently available data do not support the need for risk minimization.

Safety issues	Agreed pharmacovigilance Activities	Agreed risk minimisation Activities
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).
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 5 mg solution.
		Precautions related to interactions with nephrotoxic drugs are also stated in other sections mentioning renal failure (see above Identified risk: Renal dysfunction). Additional risk minimization activities:
		Communication and Educational Program (CEP) to emphasize to prescribers and patients risks related to renal failure/impairment and the importance of monitoring renal function.
Important missing information		
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. Drug is contraindicated in pregnancy and breast-feeding in [Sections 4.3] SPC/PL for 5 mg solution.
Patients with severe renal impairment	Routine pharmacovigilance	Routine risk minimization activities: Labelling: Information and precautions are given in SPC/PL related to drug use in patients with severe renal impairment. Drug is contraindicated in patients with severe renal impairment with creatinine clearance < 35 ml/min. Additionally, precautions related to risks of renal failure are also given in [Section 4.4] SPC. The pharmacokinetics in patients with renal impairment is highlighted in [Section 5.2] SPC.
XIC'		Special care in case of kidney problems is stated in PL for 5 mg solution.
Medicil		Additional risk minimization activities: Communication and Educational Program (CEP) to emphasize to prescribers and patients risks related to renal failure/impairment and the importance of monitoring renal function.

The following additional risk minimisation activities were required:

The Marketing Authorisation Holder (MAH) shall provide an educational programme targeting all physicians who are expected to prescribe/use Zoledronic acid for the treatment of osteoporosis prior to the launch in Member States. The MAH must agree the content and format of the educational material,

together with a communication plan, with the national competent authorities in Member States prior to distribution of the educational programme.

The educational programme contains the following:

- Physician educational material
- Patient educational material

The physician educational material should contain the following key messages:

- Need to measure serum creatinine before treatment with Zoledronic acid Teva Pharma
- Contraindication in patients with creatinine clearance < 35 ml/min
- Contraindication in pregnancy and in breast-feeding women due to potential teratogenicity
- Need to ensure appropriate hydration of the patient
- Need to infuse Zoledronic acid Teva Pharma slowly over a period of no less than 15 minutes
- One-yearly dosing regime
- That all patients should be provided with the educational material and be counselled about:
 - Need for adequate calcium and vitamin D supplementation, appropriate physical activity, non-smoking and healthy diet
 - Key signs and symptoms of serious adverse events
 - When to seek attention from the health care provider

The patient educational material should contain the following key messages:

- Contraindication in pregnancy and in breast-feeding women
- Need for adequate calcium and vitamin D supplementation, appropriate physical activity, nonsmoking and healthy diet
- Key signs and symptoms of serious adverse events
- · When to seek attention from the health care provider

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference medicinal product, which currently is on a 1-yearly cycle. The next data lock point for the reference medicinal product is 30 April 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 solution for infusion (5 mg / 100 ml). The reference product Aclasta is indicated for treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture, including those with a recent low-trauma hip fracture and for treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture, as well as for treatment of Paget's disease of the bone in adults.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 which is acceptable according to 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 balance comparable to the reference product can therefore be concluded.

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 Pharma in the

Treatment of osteoporosis

- in post-menopausal women
- in men

at increased risk of fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in men

at increased risk of fracture.

Treatment of Paget's disease of the bone in adults.

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

The Marketing Authorisation Holder (MAH) shall provide an educational programme targeting all physicians who are expected to prescribe/use Zoledronic acid Teva Pharma for the treatment of osteoporosis prior to the launch in Member States. The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authorities in Member States prior to distribution of the educational programme.

The educational programme contains the following:

- Physician educational material
- Patient educational material

The physician educational material should contain the following key messages:

- Need to measure serum creatinine before treatment with Zoledronic acid Teva Pharma
- Contraindication in patients with creatinine clearance < 35 ml/min
- Contraindication in pregnancy and in breast-feeding women due to potential teratogenicity
- Need to ensure appropriate hydration of the patient
- Need to infuse Zoledronic acid Teva Pharma slowly over a period of no less than 15 minutes
- One-yearly dosing regime
- That all patients should be provided with the educational material and be counselled about:
 - Need for adequate calcium and vitamin D supplementation, appropriate physical activity, non-smoking and healthy diet
 - Key signs and symptoms of serious adverse events
 - When to seek attention from the health care provider

The patient educational material should contain the following key messages:

- Contraindication in pregnancy and in breast-feeding women
- Need for adequate calcium and vitamin D supplementation, appropriate physical activity, nonsmoking and healthy diet
- Key signs and symptoms of serious adverse events
- When to seek attention from the health care provider

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented.

The Marketing Authorisation Holder (MAH) shall provide an educational programme targeting all physicians who are expected to prescribe/use Zoledronic acid Teva Pharma for the treatment of osteoporosis prior to the launch in Member States. The MAH must agree the content and format of the

educational material, together with a communication plan, with the national competent authorities in Member States prior to distribution of the educational programme.

The educational programme contains the following:

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The physician educational material should contain the following key messages:

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- · Contraindication in pregnancy and in breast-feeding women due to potential teratogenicity
- Need to ensure appropriate hydration of the patient
- Need to infuse Zoledronic acid Teva Pharma slowly over a period of no less than 15 minutes
- One-yearly dosing regime
- That all patients should be provided with the educational material and be counselled about:
 - Need for adequate calcium and vitamin D supplementation, appropriate physical activity, non-smoking and healthy diet
 - o Key signs and symptoms of serious adverse events
 - o When to seek attention from the health care provider

The patient educational material should contain the following key messages:

- Contraindication in pregnancy and in breast-feeding women
- Need for adequate calcium and vitamin D supplementation, appropriate physical activity, nonsmoking and healthy diet
- Key signs and symptoms of serious adverse events
- When to seek attention from the health care provider