23 January 2014
EMA/179093/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic acid Teva Generics

International non-proprietary name: ZOLEDRONIC ACID

Procedure No. EMEA/H/C/002805

Note

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

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List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
BSE	Bovine spongiform encephalopathy
CEP	Communication and Education Program
CHMP	Committee for Medicinal Products for Human use
COP	Cyclic Olefin Polymer
DDD	Defined Daily Dose
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
EURD	European Union Reference Date
FTIR	Fourier Transform Infra-Red spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
ICH	International Conference on Harmonization (of technical requirements for registration of pharmaceuticals for human use)
IR	Infra-Red spectroscopy
HPLC	High Performance Liquid Chromatography
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
NMR	Nuclear Magnetic resonance spectroscopy
NMT	Not More Than
ONJ	Osteo-Necrosis of the Jaw
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PRAC	Pharmacovigilence Risk Assessment Committee
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SEB	Styrene-Ethylene-Buylene
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UPLC	Ultra-high Performance Liquid Chromatography
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Generics B.V submitted on 7 June 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid Teva Generics, 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 18 October 2012.

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 adult men

at increased risk of fracture, including those with recent low-trauma hip fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in adult 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 No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data.

This application is submitted as a duplicate of Zoledronic acid Teva Pharma authorised on 16 August 2012 in accordance with Article 82.1 of Regulation (EC) No 726/2004. The EC considers that the requirements of Article 82(1) and Regulation (EC) 726/2004 are met.

The current application applies for the full indication of the reference product Aclasta, and thus also includes the indications that were excluded from its duplicate Zoledronic acid Teva Pharma (as covered by patent law).

Information on paediatric requirements

Not applicable

The chosen reference 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 4 mg/5ml concentrate for solution for infusion
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 20 March 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: Aclasta, 5 mg solution for infusion
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 15 April 2005
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/05/308/001-002

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2. Manufacturers

Manufacturers responsible for batch release

Pharmachemie B.V.
Swensweg 5
Haarlem 2031 GA
The Netherlands

Teva Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
2100 Gödöllő
Hungary

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bengt Ljungberg

- The application was received by the EMA on 7 June 2013.
- The procedure started on 26 June 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2013.
- During the PRAC meeting on 10 October 2013, the PRAC adopted an RMP Advice.
- During the meeting on 24 October 2013, 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 24 October 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 November 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 December 2013.
- During the PRAC meeting on 08 January 2014, the PRAC adopted an RMP Advice.
- During the meeting on 23 January 2014, 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 Generics.

2. Scientific discussion

2.1. Introduction

Zoledronic Acid Teva Generics 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 Generics.

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 Generics, a bioequivalence study is not required.

The proposed indications are:

Treatment of osteoporosis

- in post-menopausal women
- in adult men

at increased risk of fracture including those with recent low-trauma hip fracture

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in adult men

at increased risk of fracture.

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

2.2. Quality aspects

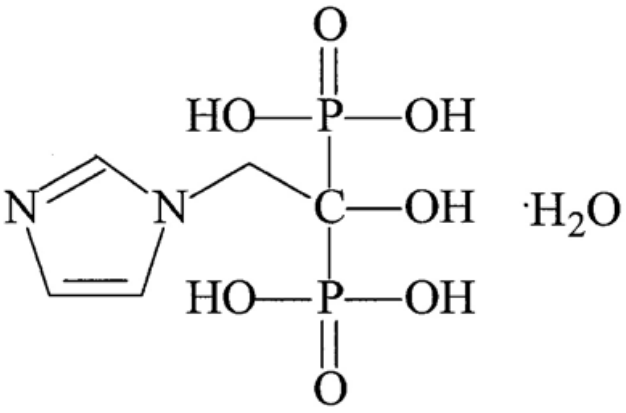
2.2.1. Introduction

Zoledronic Acid Teva Generics is presented as a solution for infusion for intravenous use containing 5 mg of zoledronic acid as active substance. Other ingredients are mannitol, sodium citrate and water for injections.

The product is available in plastic bottles and 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 and has the following structure:



It exists in several crystalline forms; this application uses a hydrate. The molecule does not contain any chiral centres.

It is a white crystalline non-hygroscopic powder, sparingly soluble in 0.1N sodium hydroxide solution, slightly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents.

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.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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 on 10 batches of the active substance up to 60 months of storage at 25 °C / 60% relative humidity (RH) and on 6 batches for 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 aluminium 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 reference medicinal 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.

The primary packaging is either a 100 ml multilayer polyolefin/styrene-ethylene-butylene (SEB) bag with SFC polypropylene infusion port closed with rubber stopper and snap cap or a 100 ml Cyclic Olefin Polymer (COP) plastic bottle, fitted with a chlorobutyl/butyl rubber stopper and aluminium cap fitted with violet plastic flip off disc. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

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 sub-visible 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

Stability data on 2 commercial scale batches of finished product from the proposed manufacturer stored under long term conditions for up to 24 months at 25 ºC / 40% RH, for up to 12 months under intermediate conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 25% RH according to the ICH guidelines were provided. 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 batches of finished product were identical to those proposed for marketing and were packed in both types of primary packaging proposed for marketing, as well as in glass vials. During the stability studies, increase in sub-visible particles was observed in the glass vials which were therefore withdrawn from the application.

Samples were tested for appearance, clarity of solution, visible particles, colour of solution, osmolality, extractable volume, pH, assay, related substances, sterility, bacterial endotoxins and particulate contamination. Tests were performed according to the specification and using the analytical procedures presented in the dossier. In addition, a test for weight loss (NMT 5% of filling mass) was performed for the plastic vials and bags.

For the finished product in plastic bags, all stability results complied with specification and no trends/changes were observed. For the plastic bottles however, an out of specification result after 24 months stored under long-term conditions was noted. Therefore, the shelf-life was reduced to 18 months, and the SmPC updated accordingly. This product is a duplicate of Zoledronic acid Teva Pharma EMEA/H/C/002437 for which stability studies were on-going. The company therefore provided a commitment to reduce its shelf-life from 24 to 18 months within 3 months of this opinion.

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

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

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 to be 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 clinical use.

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

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. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Zoledronic acid Teva Generics manufactured by Teva Generic 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.

2.4. Clinical aspects

2.4.1. Introduction

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

GCP

Not applicable

Exemption

The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. The applied product also contains the same excipients as the reference product. For this type of product, no bioequivalence studies are required

according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) and the applicant has submitted none.

2.4.2. Pharmacokinetics

Not applicable (See above - exemption).

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. 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.

2.4.5. Conclusions on clinical aspects

The application contains an adequate review of published clinical data. No bioequivalence studies are required for this type of products (CHMP/QWP/EWP/1401/98 Rev. 1).

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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1, the PRAC considers by consensus that the risk management system for zoledronic acid monohydrate (Zoledronic acid Teva Generics) in the treatment of osteoporosis in post-menopausal women and in men is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw (ONJ) • Hypocalcaemia • Renal dysfunction (renal impairment/renal failure) • Hypersensitivity reactions (anaphylaxis) • Ocular adverse events • Post-dose symptoms
Important potential risks	• Atypical femoral fractures (subtrochanteric) • Atrial fibrillation • Cerebrovascular adverse events • AVN/fracture nonunion and /or delayed union, • Gastrointestinal AEs • Medication errors • Potential interaction with nephrotoxic drugs (products that can significantly affect renal function, paracetamol/ acetaminophen)
Missing information	• Use during pregnancy and lactation • Patients with severe renal impairment

The PRAC agreed.

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product

Risk minimisation measures

The applicant identified the following risk minimisation measures in the RMP:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Osteonecrosis of the jaw (ONJ)	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.	Not applicable
Hypocalcaemia	Drug is contraindicated in patients with hypocalcaemia. Precautions are stated in [Section 4.4] SPCs for 5 mg solution. 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. Risk of zoledronate blood calcium lowering effect is stated in the PL for 5 mg solution, as well as need for calcium	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	supplementation to prevent the risk and warning regarding patients with Paget's disease.	
Renal dysfunction (renal impairment/ renal failure)	Warnings are stated in [Section 4.4] SPCs. Renal impairment as class effects is listed in [Section 4.8] SPCs. 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 ≥ 35 ml/min. In PL zoledronic acid use is contraindicated in patients with severe kidney problems. Abnormal kidney test/kidney disorders are listed as uncommon side effects.	**Communication and Educational Program (CEP)** to emphasize to prescribers and patients risks related to renal dysfunction and the importance of monitoring renal function.
Hypersensitivity reactions (anaphylaxis)	Drug is contraindicated in patients with hypersensitivity. Risk has been highlighted in the SPC [section 4.8] and in the PL, frequency not known.	Not applicable
Ocular adverse events	Risk has been highlighted in the product information; ocular undesirable effects are listed in [Section 4.8] SPC and in PL.	Not applicable
Post-dose symptoms	PL and SPC [in Section 4.4] states that the incidence of post-dose symptoms occurring within the first three days after administration. Effects are listed in Section 4.8 with unknown frequency.	Not applicable
Important potential risks		
Atypical femoral fractures	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).	Not applicable
Atrial fibrillation	Risk of atrial fibrillation has been highlighted in [Section 4.8] the SPC/PL as post-marketing experience. A questionnaire for atypical femoral fracture as a supplement to the SAE form is available.	Not applicable
Cerebrovascular AEs	Currently available data do not support the need for risk minimization.	Not applicable
AVN/fracture nonunion and /or delayed union	Currently available data do not support the need for risk minimization.	Not applicable
Gastrointestinal AEs	Gastrointestinal disorders have been highlighted in [Section 4.8] the SPC/PL.	Not applicable
Medication errors	Clear difference in appearance and labelling of the cartons and vials or bottles/bags for each	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	strength (4 mg/5 ml concentrate (vials) and 5 mg solution (bottles/bags, 100 ml). Different sizes of containers (5 ml vs. 100 ml). Clear indications and posology are stated in sections 4.1 and 4.2 of the SPC and PL.	
Potential interaction with nephrotoxic drugs	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.	**CEP** to emphasize to prescribers and patients risks related to renal failure/impairment and the importance of monitoring renal function
Missing information		
Use during pregnancy and lactation	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.	Not applicable
Patients with severe renal impairment	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. Special care in case of kidney problems is stated in PL.	**CEP** to emphasize to prescribers and patients risks related to renal failure/impairment and the importance of monitoring renal function.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

A PIL User test report has been completed for the product "Zoledronic acid Teva Pharma 5 mg solution for infusion". Since this is an application for a duplicate Marketing Authorisation of the same product the PIL User Test performed for Zoledronic acid Teva Pharma also applies for this procedure.

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 positive benefit/risk balance, comparable to the reference product can therefore be concluded.

4. Recommendation

Outcome

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 Generics for the treatment of:

osteoporosis

- in post-menopausal women
- in adult men

at increased risk of fracture, including those with recent low-trauma hip fracture;
treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in adult 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

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that the educational programme implemented for the authorised indications of 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 treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture is updated. The educational programme contains the following:

- Physician educational material
- Patient information pack

The physician educational material should contain the following key elements:

- The Summary of Product Characteristics
- Reminder card with the following key messages:
    - Need to calculate creatinine clearance based on actual body weight using the Cockcroft-Gault formula before each treatment with Zoledronic acid Teva Generics
    - 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 especially those at an advanced age and those receiving diuretic therapy
    - Need to infuse Zoledronic acid Teva Generics slowly over a period of no less than 15 minutes
    - Once-yearly dosing regime
    - Adequate calcium and vitamin D intake are recommended in association with Aclasta administration
    - Need for appropriate physical activity, non-smoking and healthy diet
- Patient information pack

The patient information pack should be provided and contain the following key messages:

- Package leaflet
- Contraindication in patients with severe kidney problems
- Contraindication in pregnancy and in breast-feeding women
- 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.