EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2012
EMA/CHMP/271077/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic acid medac

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

Procedure No. **EMEA/H/C/002359**

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

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Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant medac Gesellschaft für klinische Spezialpräparate mbH submitted on 03 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid medac, 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 24 June 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and a hybrid application as defined in Article 10(3) 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 indication:

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).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC) and hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to 'The Guideline on the investigation of bioequivalence' (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

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, 4mg, powder and solvent for solution for infusion and ZOMETA 4 mg/ 5ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Ltd.
  - Date of authorisation: 20/03/2001
  - 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, powder and solvent for solution for infusion and Zometa 4 mg/ 5ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Ltd.
  - Marketing authorisation granted by: Community
    - Community Marketing authorisation number: EU/1/01/176/001- 006

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. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Alar Irs.

- The application was received by the EMA on 03 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011.
- During the meeting on 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 22 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 January 2012.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 February 2012.
- During the CHMP meeting on 15 March 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 April 2012.
- During the meeting on 21-24 May 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 medac on 24 May 2012.

2. Scientific discussion

2.1. Introduction

Zoledronic acid is a bisphosphonate. It stops the action of the osteoclasts, the cells in the body that are involved in breaking down the bone tissue. This leads to less bone loss. The reduction of bone loss helps to make bones less likely to break, which is useful in preventing fractures in cancer patients with bone metastases.

Patients with tumours 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.

Zoledronic acid medac 4mg/5ml concentrate for solution for infusion and 4mg/100ml solution for infusion is an application made according to Article 10 (1) generic application and Article 10(3) hybrid application of Directive 2001/83/EC, respectively. For this application, the reference medicinal product authorised in the Community not less than 6/10 years ago is Zometa 4 mg powder and solvent for solution for infusion and 4mg/5ml concentrate for solution for infusion, by Novartis Europharm Limited. Zometa 4mg powder and solvent for solution for infusion was authorised in the EU on the 20 March 2001 (EU/1/01/176/001-003). Zometa 4mg/5ml concentrate for solution for infusion was authorised on the 24 March 2003 as a line extension to Zometa 4mg powder and solvent for infusion (EU/1/01/176/004-006); this license belongs to the same global marketing authorisation. Zometa 4mg/100ml solution for infusion was also authorised as a line extension (EU/1/01/176/007-009) on the 24 August 2011 under the same global marketing authorisation.

The Applicant claims essential similarity for their product Zoledronic acid medac 4mg/5ml concentrate for solution for infusion and 4mg/100ml solution for infusion with the reference product.

The Zoledronic acid medac solutions are designed to be aqueous in nature, contain the same active substance as Zometa and are intended for parenteral administration; in view of this there is no requirement for bioequivalence testing (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

The applicant applied for all the indications of the reference product (Zometa):

- 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 medac 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.

In patients with renal impairment, the dosing instructions and monitoring of serum creatinine as detailed in SmPC section 4.2 should be followed.

Zoledronic acid medac 4 mg/5 ml concentrate for solution for infusion, further diluted in 100 ml should be given as a single intravenous infusion in no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of Zoledronic acid medac.

The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.

2.2. Quality aspects

2.2.1. Introduction

Zoledronic acid medac is available as a 4mg/5ml concentrate for solution for infusion contained in plastic vials with rubber stoppers and aluminium flip off cap and as a 4mg/100ml solution for infusion contained in glass bottles with a rubber stopper and a safety aluminium cap.

The full list of ingredients is defined in section 6.1 of the SmPC.

2.2.2. Active substance

Zoledronic acid is a white crystalline powder, sparingly soluble in sodium hydrochloride, slightly soluble in water and in hydrochloric acid, and practically insoluble in organic solvents. It has no chiral centers and shows polymorphism.

Manufacture

There are two different active substance manufacturers for the active substance used to prepare Zoledronic acid medac as concentrate for solution for infusion and another two manufacturers for the one used for Zoledronic acid medac as solution for infusion. The information on the active substance is presented in the form of an Active Substance Master File for all of them.

The manufacture of Zoledronic acid is performed by different manufacturing processes by each of the active substance manufacturers. The syntheses are described in sufficient detail. Critical steps and intermediates are presented in a satisfactory manner. Information regarding process validation has also been presented and considered acceptable.

Specification

The specification applied by the finished medicinal product manufacturer of the concentrate for solution for infusion includes tests for description, solubility, identification by the Infrared (IR) and by High Performance Liquid Chromatography (HPLC), loss on drying, heavy metals, pH, clarity of solution, colour of solution, residual solvents by Gas Chromatography (GC), related substances by HPLC, assay by HPLC, microbial limits, phosphate and phosphite content, bacterial endotoxins and polymorphic purity (XRD).

The specification applied by the finished medicinal product manufacturer of the solution for infusion includes tests for appearance, identification by IR, pH, heavy metals, water content, phosphites by HPLC, residual solvents (GC), related substances by HPLC, assay by HPLC, microbial limits and bacterial endotoxins.

The finished product manufacturer of the solution for infusion has committed to test two more batches of the drug substance manufactured and to inform the Health Agency in case of deviation.

The in-house analytical procedures have been described and validated.

The CHMP recommended further validation of the GC method for residual solvents used by one of the active substance manufacturers for the active substance used for the concentrate for solution for infusion medicinal product.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Batch analysis results from 3 commercial batches were provided by each active substance manufacturer. Results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is capable and under control.

Stability

Satisfactory stability data of several batches of Zoledronic acid, stored from 12 to 60 months according to ICH conditions 25° ± 2°C/ 60 % ± 5 % RH and 6 months at 40° ± 2°C/ 75 % ± 5 % RH, has been provided by the different active substance manufacturers.

The parameters tested for the active substance used for the concentrate for solution for infusion presentation were description, water content, related substances, phosphates, assay and microbial limits.

The parameters tested for the active substance used for the solution for infusion presentation were description, water content, related substances, assay and microbial limits.

Forced degradation studies have also been performed by some of the active substance manufacturers demonstrating that degradation following exposure to high concentrations of acid and oxidising agent in combination with heat and under oxidative conditions occurs.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

2.2.3. Finished medicinal product

There are two different pharmaceutical presentations: concentrate for solution for infusion and solution for infusion.

Zoledronic acid medac 4mg/5ml concentrate for solution for infusion

Pharmaceutical development

Zoledronic acid medac 4mg/5ml concentrate for solution for infusion has been developed in accordance with the reference medicinal product as to have the same qualitative composition. This generic medicinal product was developed as a sterile product comparable in formulation, concentration and administration with the reference medicinal product. The physicochemical properties of the finished product and its components are based on the analysis of those of the reference product and the pharmaceutical form.

The excipients used in the manufacturing of the concentrate for solution for infusion medicinal product are the same as in the reference product and comply with the respective monograph in the Ph.Eur. Their choice and functions have been described. Mannitol, sodium citrate and water for injection are well accepted and commonly used in parenteral formulations. Mannitol is used as tonicity agent, sodium citrate for pH adjustment. The amount of excipients has been optimised to obtain an isotonic solution and a stable buffering system with zoledronic acid. Water for injection is purified by using resin filters and is deionized and dispensed through a 0.22 µm membrane filter.

The applicant has performed a specific compatibility study between the drug substance and the excipients at the accelerated conditions (50ºC) up to 4 weeks. No indication of incompatibility was seen.

The primary container for the final drug product is pre-sterilised clear, colourless cycloolefine copolymer with type I bromobutyl rubber stopper and sealed with aluminium polypropylene flip off seals corresponding to the monograph of Ph.Eur. 3.2.2.1 'plastic containers for aqueous solutions for infusion' and Ph.Eur.3.2.9 for 'rubber closures'.

Adventitious agents

A declaration from the finished medicinal product manufacturer confirm that the product contains no material of animal origin and is in line with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and medicinal products.

Manufacture of the product

The manufacturing process consists of seven main steps: compounding, final mass adjustment, pre-filtration/solution first filtration, sterile filtration, sterilisation of the rubber closure and flip-off caps, filling-sealing and sterilisation by a standard autoclave cycle.

The manufacturing formula, flow chart and description of the manufacturing process are presented.

The manufacturing process has been satisfactorily validated.

Product specification

Adequate release and shelf-life specifications have been presented for the finished product and include: appearance, identification by Photo Diode Array detector (PDA) and HPLC, pH, particulate matter, extractable volume, water loss at shelf life only, assay (HPLC), related substances (HPLC), bacterial endotoxins and sterility.

The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and current guidelines. The analytical procedures are adequately described and validated.

The batch analysis results of five batches of the finished product manufactured at the smallest commercial size with active substance obtained by the two active substance manufacturers confirm consistency and uniformity of the product indicating that the process is under control.

Stability of the product

The conditions used in the stability studies are in accordance with the ICH stability guideline (25°C, 60% RH, 30°C, 65% RH and 40°C, 75% RH).

The results of the following tests were submitted: appearance, pH, particulate matter, extractable volume, water loss at shelf life only, assay, related substances, bacterial endotoxins and sterility.

Analysis of the stability samples has been performed by applying the validated and stability indicating test methods.

In-use stability at 25ºC and refrigerator conditions up to 24 hours has been confirmed.

Photostability studies according to ICH Q1B demonstrated that the product is not sensitive to light.

Forced degradation studies have been carried out as part of the assay and related substance analytical methods validation. No degradation is observed in case of elevated temperature, acid, base or light.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the Summary of Product Characteristics (SmPC) are acceptable.

Zoledronic acid medac 4mg/100ml solution for infusion

Pharmaceutical development

Zoledronic acid medac 4mg/100ml for solution for infusion has been developed in order to obtain a sterile ready-to-use solution for infusion containing the monohydrate of the biologically active zoledronic acid in a concentration of 4 mg/100 ml zoledronic acid. The formulation was developed based on the marketed reference product, as the reference product was not available as solution for infusion at that time. The similarity to the reference product after further dilution and zoledronic acid 4 mg/100 ml solution for infusion was investigated based on the comparison of testing of the physical and chemical characteristics between them. The amount of active ingredient and sodium citrate is similar, whereas the amount of Mannitol as isotonising agent was adjusted to take into account the ionic strength of the reconstitution solution of the reference product (i.e. 5% glucose or 0.9% sodium chloride solution).

The manufacturing process developed aims to manufacture an isotonic aqueous solution which is sterilised by terminal sterilisation. The excipients used in the manufacturing process are well known and the same as in the reference product and comply with the respective monographs in the Ph.Eur.

The risk of incompatibility was deemed considerably low as only well-known excipients are used and are identical to the reference product. Water for injection is used as unique solvent and no dilution with other solvents is envisaged. Stability studies did not reveal any incompatibility between active ingredient and excipients.

The primary container for the final drug product consists of a colourless glass type I infusion bottle, stoppered by a coated butyl rubber stopper and an aluminium flip-off cap. The container closure system complies with the requirements of Ph. Eur.

The suitability of the container closure system is confirmed by stability studies. Neither any incompatibilities nor any sorption of the active substance to the immediate container have been determined so far.

Adventitious agents

A declaration from the finished medicinal product manufacturer confirm that the product contains no ingredients of animal or human origin and that the product is in is in line with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and medicinal products.

Manufacture of the product

The manufacturing process consists of seven main steps: manufacture of the bulk solution, sterile filtration and filling, closure with sterile rubber stoppers and crimping with caps, visual inspection, sterilisation by a standard autoclave cycle, bulk packaging, final labeling and packaging of finished medicinal product.

The manufacturing formula, flow chart and description of the manufacturing process are adequately presented.

The manufacturing process is considered satisfactorily validated.

Product specification

Adequate release and shelf-life specifications have been presented for the finished product and include: appearance, identification (UV and HPLC), clarity, colour, osmolality, pH, particulate matter, subdivisible particles, extractable volume, assay (HPLC), related substances (HPLC), bacterial endotoxins and sterility.

The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and current guidelines. Analytical procedures are described and validated.

The batch analysis results of three batches of the finished product manufactured with active substance obtained by the two active substance manufacturers confirm consistency and uniformity of the product indicating that the process is capable and under control.

Stability of the product

The conditions used in the stability studies are in accordance with the ICH stability guideline at long term (5°C ± 3° C & 25 °C ± 2 °C/ 60 % RH ± 5 % RH), Intermediate (30 °C ± 2 °C/ 65 % RH ± 5 % RH) and accelerated stability testing (40 °C ± 2 °C/ 75 % RH ± 5 % RH).

The results of the following tests were submitted: appearance, clarity, colour, osmolality, pH, particulate matter, subvisible particles, extractable volume, assay, related substances (HPLC), bacterial endotoxins and sterility, visual closure appearance and container closure integrity.

Analysis of the stability samples has been performed by applying the validated and stability indicating test methods. Forced degradation studies have been carried out to demonstrate that the methods were stability-indicating.

In-use stability at 25ºC and refrigerator conditions up to 96 hours has been confirmed.

Photostability studies according to ICH Q1B demonstrated that the product is not sensitive to light.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the Summary of Product Characteristics (SmPC) are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished medicinal 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.

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. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation for future quality development

The CHMP recommended that the GC method for analysis for all residual solvents applied by one of the active substance manufacturers used to obtain Zoledronic acid medac 4mg/5ml concentrate for solution for infusion should be fully validated.

The finished product manufacturer of the solution for infusion committed to test two more batches of the drug substance manufactured and to inform the EMA in case of deviation.

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 medac manufactured by medac 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 concentrate for solution for infusion containing 4 mg/5 ml zoledronic acid, and solution for infusion containing 4 mg/100 ml zoledronic acid. The Applicant claims essential similarity for their product Zoledronic acid medac 4mg/5ml concentrate for solution for infusion and 4mg/100ml solution for infusion with the reference product Zometa 4mg/5ml concentrate for solution for infusion and Zometa 4mg/100ml solution for infusion.

No formal scientific advice by the CHMP was given for this medicinal product.

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 medac 4mg/5ml concentrate for solution for infusion and 4mg/100ml solution for infusion is the same as of the reference product.

The claim of essential similarity can be accepted. There are no objections to the approval of Zoledronic acid medac 4mg/5ml concentrate for solution for infusion and 4mg/100ml solution for infusion from a clinical point of view.

Clinical studies

Not applicable.

2.4.2. Pharmacokinetics

Not applicable.

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

No post-marketing data are available. The medicinal product has not been marketed in any country.

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 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 issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks		
Renal function impairment	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.2 Posology and Method of Administration:* Infusion time ≥ 15 minutes. Hypercalcaemia: evaluate benefit/risk in severe renal impairment. Prevention of SREs: dose reduction guidance by baseline CrCl. Monitor prior to each dose. Withhold treatment until resolution if pre-defined Serum creatinine increases occur. *SPC Section 4.4 Special Warnings and Precautions for Use:* Renal function impairment and failure have been seen after one dose. Use of zoledronate is not recommended in severe renal impairment (CrCl < 30 mL/min) *SPC Section 4.5 Interactions:* Caution advised when zoledronate is administered with aminoglycosides, nephrotoxic drugs. Increased risk of renal dysfunction in myeloma patients treated with thalidomide. *SPC Section 4.8 Undesirable effects:* Acute renal failure, renal impairment, serum creatinine and BUN increased.
Osteonecrosis of the jaws (ONJ)	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.4 Special Warnings and Precautions for Use:* General information on ONJ. Dental examination and if necessary preventive dentistry recommended prior to treatment. Dental procedures to be avoided during treatment. Unknown effect of treatment discontinuation if ONJ occurs: in such case assess individual benefit/risk. *SPC Section 4.8 Undesirable effects:* ONJ and risk factors described.
Atypical femoral fractures	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.4 Special Warnings and Precautions for Use:* General information on atypical femoral fractures. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femoral fracture. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		evaluated for an incomplete femoral fracture. *SPC Section 4.8 Undesirable effects:* Atypical subtrochanteric and diaphyseal femoral fractures
Acute phase reaction	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* IV administration has been most commonly associated with a flu-like syndrome in about 9% of patients, incl. bone pain (9.1%), fever (7.2%), fatigue (4.1%) and rigors (2.9%).
Hypocalcaemia	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.2 Posology and Method of Administration:* Prevention of SREs: Patients should also be administered 500 mg oral calcium supplement and 400 IU vitamin D daily. *SPC Section 4.4 Special Warnings and Precautions for Use:* Standard hypercalcaemia-related metabolic parameters, such as seruim levels of calcium, phosphate and magnesium should be carefully monitored after initiating zoledronate theraopy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. *SPC Section 4.8 Undesirable effects:* Hypocalcaemia is included in the ADRs.
Ocular adverse events	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* Conjunctivitis, uveitis, episcleritis, scleritis, and orbital inflammation are included in the ADRs.
Atrial fibrillation	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* Atrial fibrillation is included in the ADRs.
Anaphylaxis	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* Nausea, vomiting, anorexia, diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth are included in the ADRs.
GI disorders in paediatric OI patients	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* Nausea, vomiting, anorexia, diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth are included in the ADRs.
Important potential risks		
Cardiac arrhythmias	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.8 Undesirable effects:* Atrial fibrillation is included in the ADRs.
Cerebrovascular AEs	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Focal segmental glomerulosclerosis	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Fracture healing	Routine pharmacovigilance	Currently available data do not support the

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
impairment		need for risk minimisation.
Interstitial lung disease	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Bone growth impairment in paediatric OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Progressive hearing loss in paediatric OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Increased risk of fractures in paediatric type I OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Potential interactions		
Products that can significantly affect renal function	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.4 Special Warnings and Precautions for Use:* Use of nephrotoxic drugs may increase the potential for deterioration in renal function. *SPC Section 4.5 Interaction with other medicinal products and other forms of interaction:* Caution is indicated when zoledronate is used with other potentially nephrotoxic drugs.
Important missing information		
Paediatric patients	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.2 Posology and method for admistration and 4.4 Special warnings and precautions for use :* Zoledronate should not be used in the paediatric population because safety and efficacy in children have not been established.
Races other than Caucasian	Routine pharmacovigilance	Currently available data do not support the need for risk minimisation.
Fertility, pregnancy and lactation	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.3 Contraindications:* Zoledronate is contraindicated in breast-feeding women. *SPC Section 4.6 Pregnancy and lactation:* Zoledronate should not be used during pregnancy. It is not known whether zoledro-nate is excreted into human milk. Zoledro-nate should not be used by breast-feeding women.
Patients with severe renal impairment	Routine pharmacovigilance	**Routine risk minimisation activities:** Detailed information in SPC sections 4.2, 4.4, 4.5, 4.8 (see renal function impairment above)
Paediatric patients with renal impairment	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.4 Special warnings and precautions for use:* The safety of zoledronate in paediatric patients with renal impairment has not been established.
Patients with hepatic insufficiency	Routine pharmacovigilance	**Routine risk minimisation activities:** *SPC Section 4.4 Special warnings and precautions for use:* As only limited clinical data are available in patients with severe hepatic insufficiency, no specific

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		recommendations can be given for this patient population.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

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

User consultation

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

Zoledronic acid medac is a generic of Zometa for which the reference product information has been adopted entirely including the format.

3. Benefit-risk balance

This application concerns a generic version of zoledronic acid 4mg/5ml concentrate for solution for infusion and a hybrid application for zoledronic acid 4mg/100ml solution for infusion. 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 decision that the benefit-risk balance of Zoledronic acid medac 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, and in the treatment of adult patients with tumour-induced hypercalcaemia (TIH) is favourable and therefore recommends the granting of the marketing authorisation.

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 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 European Medicines Agency.

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.