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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic Acid Hospira

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

Procedure No. **EMEA/H/C/002365**

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

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List of abbreviations

AEs	adverse events
ASMF	active substance master file
CLcr	creatinine clearance
CHMP or CPMP	Committee for Medicinal Products for Human Use
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
ICH	International Conference on Harmonisation
ICP	Inductive coupled plasma
IR	infra-red
MAH	Marketing Authorisation Holder
PK	pharmacokinetics
PP	polypropylene
PSUR	periodic safety update report
RH	relative humidity
RMP	Risk Management Plan
SAEs	serious adverse events
SmPC or SPC	Summary of Product Characteristics
TIH	tumour-induced hypercalcaemia
TSE	transmissible spongiform encephalopathy
UV	ultra violet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Ltd. submitted on 3 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic Acid Hospira, 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 for Zoledronic Acid Hospira 4 mg /5 ml and 4 mg/ 100 ml:

- 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).

For Zoledronic Acid Hospira 5 mg/ 100 ml:

- Treatment of osteoporosis
  - o in post-menopausal women
  - o in men

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

- Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
  - o in post-menopausal women
  - o 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 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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

ZOLEDRONIC ACID HOSPIRA 4 mg/5 ml CONCENTRATE FOR SOLUTION FOR INFUSION and

ZOLEDRONIC ACID HOSPIRA 5 mg/100 ml SOLUTION FOR INFUSION:

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/5 ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Limited
  - Date of authorisation: 20/03/2001
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/01/176/001-006

ZOLEDRONIC ACID HOSPIRA 4 mg/5 ml CONCENTRATE FOR SOLUTION FOR INFUSION:

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Zometa 4 mg/5 ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Limited
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/01/176/004-006

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
  - Not applicable

ZOLEDRONIC ACID HOSPIRA 5 mg/100 ml SOLUTION FOR INFUSION:

- 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/100 ml solution for infusion

- Marketing authorisation holder: Novartis Europharm Limited
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/05/308/001-002

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
  - Not applicable

ZOLEDRONIC ACID HOSPIRA 4 mg/100 ml SOLUTION FOR INFUSION:

- 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/5 ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Limited
  - 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 4 mg/5 ml concentrate for solution for infusion
  - Marketing authorisation holder: Novartis Europharm Limited
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/05/308/004-006

- Medicinal Product which is or has been authorised in accordance with Community provisions in force used for the demonstration of bioequivalence (if applicable) and/or in other studies:
  - Not applicable

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

An application was filed in the following countries: Australia (4 mg/ 5 ml), USA (4 mg/5 ml, 5 mg/ 100 ml).

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 Kristina Dunder

- The application was received by the EMA on 3 June 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 September 2011.
- During the meeting on 17-20 October 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 21 October2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 June 2012.
- During the CHMP meeting on 18-21 June 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 17 August 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 September 2012.
- During the meeting on 17-20 September 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 Hospira on 20 September 2012.

2. Scientific discussion

2.1. Introduction

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone by inhibiting osteoclast-mediated bone resorption.. It therefore 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. It is also used to treat osteoporosis in post-menopausal women and in men at increased risk of fracture, osteoporosis associated with long-term systemic

glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture, and Paget's disease of the bone.
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 Hospira is an application made according Generic application (Article 10(1) of Directive No 2001/83/EC) and hybrid application (Article 10(3) of Directive No 2001/83/EC). 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 4 mg/5 ml concentrate for solution for infusion, by Novartis Europharm Limited. Zometa 4 mg powder and solvent for solution for infusion was authorised in the EU on the 20 March 2001 (EU/1/01/176/001-003). Zometa 4 mg/5 ml concentrate for solution for infusion was authorised on the 24 March 2003 as a line extension to Zometa 4 mg powder and solvent for infusion (EU/1/01/176/004-006); this license belongs to the same global marketing authorisation. Zometa 4 mg/100 ml solution for infusion has been authorised as a line extension (EU/1/01/176/007-009) under the same global marketing authorisation on 24 August 2011, i.e. after the submission of the current application. Aclasta 5 mg/ 100 ml solution for infusion by Novartis Europharm Limited authorised on 15 April 2005 (EU/1/05/308/001-002) also belongs to the same global marketing authorisation.
Zoledronic Acid Hospira contains the same active substance as Zometa and Aclasta and is intended for parenteral administration; in view of this there is no requirement for bioequivalence testing (cf.CPMP/QWP/EWP/1401/98 Rev.1).
For Zoledronic Acid Hospira 4 mg /5 ml and 4 mg/ 100 ml, the applicant applied for all the indications of the reference product (Zometa) for:

- 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).

For Zoledronic Acid Hospira 5 mg/ 100 ml, the applicant applied for all the indications of the reference product (Aclasta) for:

- Treatment of osteoporosis
  - in post-menopausal women
  - in men

at increased risk of fracture, including those with a recent low-trauma hip 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 Hospira is presented as a 4 mg/5 ml concentrate for solution for infusion in glass or plastic vials, with rubber closure, an aluminium seal and flip-off top. It is also presented as a 4 mg/100 ml and 5 mg/ 100 ml solution for infusion in polypropylene bags with a twist-off port fitted with a cap, with an overwrap.
The full list of ingredients is defined in section 6.1 of the SmPC.

2.2.2. Active substance

Zoledronic acid is a white to off white powder, highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. It corresponds to the molecular formula $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and has a molecular mass 290.1 g/mol. The

pH of a 0.7% solution of zoledronic acid in water is approximately 2.0. It is hygroscopic and the anhydrous of zoledronic acid readily absorbs water to form a stable monohydrate. The zoledronic acid molecule has no chiral centres and is known to have two polymorphic forms (hydrates) and an amorphous form.

Manufacture

The information on the active substance is presented in an Active Substance Master File. The manufacture of zoledronic acid is performed in four steps including chemical synthesis, crystallisation, and filtration, which are described in sufficient detail. The starting materials are commercially available and well characterised. Critical steps and intermediates are presented in a satisfactory manner. Information regarding process validation has also been presented and considered acceptable. It has been confirmed by data that zoledronic acid manufactured by the active substance supplier is consistent with regard to the crystalline form.

Specification

The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), colour of solution (UV), solubility (visual), identification (FT-IR, HPLC), assay (potentiometric titration), impurities (HPLC), heavy metals (Ph.Eur.), residual solvents (HPLC), water content (Ph.Eur.), pH (Ph.Eur.), microbiological limits (Ph.Eur.), and bacterial endotoxins (Ph.Eur.).
The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.
Batch analysis data is presented for three production batches. All the results reported are all within the proposed specifications.

Stability

Stability studies have been performed on three batches of drug substance over 24 months at long term (25°C/60% RH) and six months accelerated (40°C/75% RH) conditions. Parameters studied were appearance, assay, related substance and water content. The data from both long-term and accelerated stability studies demonstrate that zoledronic acid is stable in the solid state. No significant shifts were observed and all results are within the specifications.
Stress studies under base hydrolysis, acid hydrolysis, heat degradation, photodegradation, and oxidation have been performed in order to identify potential degradation impurities. Zoledronic acid, like other biphosphonates, was found very stable once formed and most stress conditions actually reduce the level of impurities, leaving zoledronic acid intact.
One batch of zoledronic acid was exposed to UV light for 6 days. The study demonstrates that zoledronic acid is stable under the condition tested.
The proposed retest period and storage conditions are supported.

2.2.3. Finished medicinal product

Pharmaceutical development

Zoledronic Acid Hospira 4 mg/100 ml and 5 mg/100 ml solutions for infusion are simple sterile aqueous solutions for intravenous administration. The product is comprised of a clear, colourless solution, free from visible particulates, presented in 100 ml polypropylene (PP) infusion bags. The bags are closed with a PP twist-off closure and protected with a clear overwrap. Both are terminally sterilized containing no antimicrobial preservatives.
Zoledronic Acid Hospira 4 mg/5 ml concentrate solution for infusion is available also as a sterile aqueous solution. The drug product is comprised of a clear, colourless solution, free from visible particulates, presented in either clear plastic vials or clear Type I glass vials. The vial is filled with 5 ml of drug solution and closed with halo-butyl gray elastomeric stopper and aluminium seals with plastic flip-off tops. It is also terminally sterilized without any antimicrobial preservatives.
The active substance attributes that were considered during product development were the water of hydration in the drug substance and the drug substance solubility as a function of pH. The active substance is highly water soluble at the desired concentration.

The selected excipients are commonly used and are highly water soluble. They were chosen so that no pH adjustment is required during solution compounding and also match the reference product. Particularly for the 4 mg/ 100 ml strength, excipients also match the reference product in its admixed form as intended for administration. Appropriate comparative testing of the proposed drug product and reference product demonstrated equivalence between Hospira and the reference product and showed that the two products match key attributes such as potency, pH, osmolality, assay and impurities and are therefore considered comparable.
The product requires no headspace protection during manufacture or in the finished packaging.
Appropriate development studies were performed to assess the stability of zoledronic acid formulation in the proposed polypropylene flexible containers bags under exaggerated stress conditions.
Stress studies performed during method validation and stability testing at 55°C confirmed that zoledronic acid is a highly stable molecule with no evidence of degradation.
Particulate matter, were below the compendia limit of NMT 6000 particles per container even under elevated storage temperature.
All of the processes utilized in the manufacturing of Zoledronic Acid Hospira are routinely used in parenteral drug product manufacturing, including drug weighing and addition, mixing, pH adjustment, final dilution, filtration, fill volume, and sterilization. Therefore, there are no key critical process parameters that are unique for this drug product. Process validation studies were performed during the manufacture of the registration batches to investigate the critical manufacturing parameters. Suitable in-process testing is put in place to ensure the quality and the reproducibility of the process. The commercial batch sizes have been defined.
The process verification data demonstrates that the manufacturing process of Zoledronic Acid Hospira, 4 mg/100 ml and 5 mg/ 100 ml solution for infusion can repeatedly produce a finished product within predetermined specifications.
All the plastic packaging materials used for the product are of medical grade, contain additives that are considered safe for use in medical components and meet all the compendial requirements for physicochemical and biological safety attributes. Based on data from the developmental stability studies conducted, leachables will not be monitored routinely in accordance with ICH Q6A guideline. Stress stability studies were performed on the final product at 55°C for 30 days. No evidence of migration was noticed.
The container closure and package integrity have been demonstrated by appropriate studies.
As the solution for infusion is not reconstituted or admixed with other diluents or drug formulations, no compatibility studies were required or performed. Since the solution for infusion is packaged in a semi-permeable flexible plastic container and some moisture loss is expected over the shelf life, compounding has been properly determined to account for the potential potency gain and to guarantee product remains within the desired specifications throughout the entire shelf-life.
As far as the concentrate is concerned an admixture study was performed to demonstrate that Zoledronic Acid Hospira, 4 mg/ 5 ml, when diluted in either 5% Dextrose or 0.9% Sodium Chloride for appropriate dosing concentration, as stated in the package insert, is stable for up to 24 hours.
Particularly with regard to the 4 mg/ 5 ml concentrate, the product is filled in a glass vial as well as a plastic vial. The glass vial contains a thin layer of silicon dioxide that provides a barrier between the drug and the container surface thereby minimizing the drug interaction with the glass surface and eliminating particulate formation. It is noted that the reference product Zometa is packaged in a plastic vial. Hospira developed the product in a glass vial in addition to the plastic vial. It is known that bisphosphonates have the potential for chelation of residual metal ions, which may otherwise be present in glass containers. The metal chelation may manifest in the form of visible particulate formation. However, it has been shown that the product can be packaged in a glass container if the glass surface is appropriately treated by a thin layer of silicon dioxide that provides a barrier between the drug and the container and thereby minimizing the interaction of the product with the glass. The results obtained in the relevant feasibility study showed no difference between the two containers and indicate that the primary packaging components are appropriate for use.

Adventitious agents

There are no excipients of human or animal origin used in the formulation of Zoledronic Acid Hospira.

Manufacture of the product

The manufacturing process follows conventional pharmaceutical practices, which utilise a solution compounding step, filtration, filling into vials, and followed by standard Ph. Eur. terminal sterilisation.

The validation activities have been conducted in compliance with the European GMP and internal policies. The results of in-process controls and the analysis of the samples performed at each step guarantee the reproducibility of the process. All critical operating parameters associated with the manufacturing process were within the qualified parameters of the manufacturing equipment. Based on batch analysis data and adequacy of in-process controls, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product of consistent quality, complying with the designed specification.
Furthermore a validation scheme to support the manufacture of commercial scale Zoledronic Acid Hospira has been developed and provided. The applicant will conduct prospective process validation on the first three consecutive production-scale batches of the product which is acceptable since this is a terminal sterilisation process using standard Ph. Eur. conditions.

Product specification

The finished product (solution for infusion) release and shelf-life specifications includes tests and limits for clarity (Ph. Eur.), extractable volume (Ph. Eur.), pH (Ph. Eur.), identification (HPLC, visual colour), assay (HPLC), particulate matter (Ph. Eur.), impurities (HPLC), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).
For the concentrate for solution for infusion the finished product specifications includes in addition to the above tests and limits for appearance (visual), osmorality (Ph. Eur.) and fill volume (Ph. Eur.), instead of extractable volume.
Batch analyses data and Certificates of analysis were presented for one commercial and two smaller scale batches for each of the two strengths of the solution for infusion.
Furthermore batch analyses data and certificate of analysis were also provided for three commercial or smaller scale batches for each of the two proposed configurations i.e. glass and plastic vial for the concentrate.
For all parameters the obtained results were within the limits defined in the release specification.
The reported results indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the product

Solution for infusion 4 mg/ 100 ml and 5 mg/ 100 ml
Stability studies have been performed on three batches of each strength of the solution for infusion under long term 25 °C/40% RH and 30 °C/35% RH and accelerated 40 °C/<25% RH conditions. Results have been presented for up to 18 months and for six months under long term and accelerated conditions respectively.
All batches are of the same formulation and presented in the same container-closure system proposed for commercial production.
All attributes used to confirm the quality of the finished drug product on batch release are evaluated during stability testing, with the exception of identity.
The analytical methods used in the stability studies are the same as the methods used for the release testing. The assay and impurity methods are stability indicating and have been validated for their intended use.
No significant changes were observed in any of the monitored parameters and at any of storage conditions for up to six months compared to the initial values. All monitored parameters of the drug product are within the proposed stability specifications. As expected, an increasing time related trend can be observed in assay. This is due to the plastic container being semi-permeable, thus allowing some moisture loss. The assay results are within the proposed specification for the drug product.
In addition, the stability data gained on batches exposed to light and oxygen indicate that the drug product is not light or oxygen sensitive.
Stress Testing
Stress studies were performed by storing the drug product under freezer conditions for 3 cycles. Temperature cycling included storage at -20°C for 48 hours, 25°C for 24 hours, 40°C for 48 hours, and 25°C for 24 hours. Stability data presented confirm that the drug product is not adversely affected under these conditions.
Forced degradation studies performed during method validation also served to demonstrate the stability of Zoledronic Acid Hospira solution for infusion under various extreme conditions including acid, base, heat, oxidation and light. The data presented demonstrate that the product is stable and not susceptible to degradation. After first opening the product should be used immediately.

Concentrate for solution for infusion 4 mg/ 5 ml
Stability studies have been performed on six batches of the concentrate for solution for infusion under 25 °C/40% RH and 30 °C/35% RH for up to 24 months and under 40 °C/<25% RH for six months. Three batches were packaged in the in plastic containers and the remaining three batches were packaged in glass vials.
All attributes used to confirm the quality of the finished drug product on batch release are evaluated during stability testing, with the exception of identity and fill volume as they are not expected to change over time. The acceptance limits for these attributes remain the same as those used to confirm the quality of the finished drug product on batch release.
The analytical methods used in the stability studies are the same as the methods used for the release testing. In addition the assay and impurity methods are stability indicating and have been validated for their intended use.
No significant changes were observed in any of the monitored parameters and at any of storage conditions compared to the initial values. All monitored parameters of the drug product are within the proposed stability specifications.
Zoledronic Acid Hospira concentrate for solution for infusion was stress tested with acid, base, heat, oxidant (peroxide) and light during the method validation. Photostability testing was performed according to ICH guideline Q1B.
The effects of light stress was evaluated by physical and chemical testing. The
results indicates that Zoledronic Acid Hospira 4 mg/5 ml is not light sensitive, therefore, no special instructions need to be added to the package insert regarding the light sensitivity.
Adequate information demonstrating the compatibility of the concentrate when diluted in 0.9% w/v sodium chloride solution and 5% w/v dextrose solution was provided. After aseptic dilution, the diluted product should be used immediately.

The proposed shelf-life and storage conditions based on the available data are accepted for both the solution and the concentrate for solution for infusion.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the 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 Hospira manufactured by Hospira UK Ltd. 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 a concentrate for solution for infusion containing 4mg/5ml zoledronic acid, and for solutions for infusion containing 4mg/100ml and 5mg/100ml zoledronic acid. Zoledronic Acid Hospira contains the same active substance as Zometa and Aclasta and is intended for parenteral administration; in view of this there is no requirement for bioequivalence testing (cf.CHMP/QWP/EWP/1401/98 Rev.1).

GCP

Not applicable

Exemption

Zoledronic Acid Hospira 4 mg/5 ml
The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product Zometa 4 mg/5 ml concentrate for solution for infusion. The applied product also contains the same excipients as Zometa 4mg/5ml concentrate for solution for infusion. 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.

Zoledronic Acid Hospira 4 mg/100 ml solution for infusion
According to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) no bioequivalence studies are required if the applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product and if no excipients interact with the active substance. Zoledronic Acid Hospira 4 mg/ 100 ml solution for infusion is intended for intravenous use and contains the same active substance as the Zometa 4 mg/5ml which was authorised at the time of submission. Zoledonic Acid Hospira 4mg/100ml also contains the same active substance as Zometa 4mg/100 ml which was authorised during the Zoledronic Acid Hospira procedure. In addition, the applied product contains the same excipients as Zometa concentrate except for the addition of sodium chloride corresponding to 0.9% w/v. Zometa concentrate for solution for infusion is recommended to be diluted with 0.9% w/v sodium chloride or 5% w/v glucose solution. Thus, no bioequivalence studies are necessary for the applied product and the applicant has submitted none.

Zoledronic Acid Hospira 5 mg/100 ml solution for infusion
The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product Aclasta 5 mg solution for infusion. The applied product also contains the same excipients as the reference product Aclasta. 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. Pharmacodynamics

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

2.4.3. 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

Hospira Zoledronic acid 4mg/5ml and 4mg/ 100ml (reference product Zometa):

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Identified risk		
Renal function impairment/ dysfunction	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC.
Osteonecrosis of the jaw	* Routine Pharmacovigilance * Targeted follow up questionnaire * Periodic class effect review. * Special 15 day expedited reporting of events regardless of seriousness/ listedness.	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC.
Acute phase reaction	* Routine Pharmacovigilance	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Hypocalcemia	* Routine Pharmacovigilance	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC.
Ocular adverse events	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within 4.8 of the Hospira Zoledronic Acid SPC.
Atrial fibrillation	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Anaphylaxis	* Routine Pharmacovigilance	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Atypical subrochanteric/ femoral fractures	* Routine Pharmacovigilance. * Periodic class effect review (incorporating CHMP stress fracture definition recommendation). * Targeted questionnaire. * Special 15-day expedited reporting of events relating to the above safety concerns regardless of seriousness/ listedness.	Currently the Hospira Zoledronic acid SPC and PIL, which is based upon the reference product, does not include any specific warnings regarding stress fractures. The CHMP assessment report was received whilst the original dossier was being compiled. During the assessment process the SPC and PIL has been updated accordingly to ensure prescribers and patients are aware of this class effect. For fracture healing impairment, no additional risk minimisation steps are currently considered necessary.
Potential risk		

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
AVN/ fracture non or delayed union Fracture healing impairment	* Routine Pharmacovigilance. * Periodic class effect review (incorporating CHMP stress fracture definition recommendation). * Targeted questionnaire. * Special 15-day expedited reporting of events relating to the above safety concerns regardless of seriousness/ listedness.	Currently the Hospira Zoledronic acid SPC and PIL, which is based upon the reference product, does not include any specific warnings regarding stress fractures. The CHMP assessment report was received whilst the original dossier was being compiled. During the assessment process the SPC and PIL has been updated accordingly to ensure prescribers and patients are aware of this class effect. For fracture healing impairment, no additional risk minimisation steps are currently considered necessary.
Cardiac arrhythmias	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Cerebrovascular AEs	* Routine Pharmacovigilance * Targeted follow up questionnaire	No additional risk minimisation steps are currently considered necessary.
Interstitial lung disease	* Routine Pharmacovigilance	No additional risk minimisation steps are currently considered necessary.
Focal segmental glomerulosclerosis	* Routine Pharmacovigilance	No additional risk minimisation steps are currently considered necessary.
Interaction with products which can significantly affect renal function (including paracetamol/ acetaminophen)	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Interaction with aminoglycosides	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Medication errors	* Routine Pharmacovigilance	Clear labelling. Clear dosage instructions (in SPC/ CMI). Clearly identifiable packaging.
Interactions with nephrotoxics	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Missing information		
Use in pediatric patients with or without renal impairment	* Routine Pharmacovigilance	Not a licensed indication and therefore not referenced in the SPC. No additional risk minimisation steps are currently considered necessary.
Use in pregnancy/ lactation	* Routine Pharmacovigilance	Contraindicated within section 4.6 of the Hospira Zoledronic Acid SPC.
Use in non causcasian patients	* Routine Pharmacovigilance	No additional risk minimisation steps are currently considered necessary.
Use in patients with renal impairment	* Routine Pharmacovigilance	Included in section 4.4 and 4.8 of the zoledronic acid SPC.
Use in patients with hepatic impairment	* Routine Pharmacovigilance	Included in section 4.4 of the zoledronic acid SPC.

Hospira Zoledronic Acid 5mg/100ml (reference product Aclasta):

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Identified risk		
Renal function impairment/ dysfunction	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC. Educational materials target to physicians and patients.
Osteonecrosis of the jaw	* Routine Pharmacovigilance * Targeted follow up questionnaire * Periodic class effect review.	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC.

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
	* Special 15 day expedited reporting of events regardless of seriousness/ listedness.	
Post dose symptoms	* Routine Pharmacovigilance	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Hypocalcemia	* Routine Pharmacovigilance	Included within section 4.4 and 4.8 of the Hospira Zoledronic Acid SPC.
Ocular adverse events	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within 4.8 of the Hospira Zoledronic Acid SPC.
Anaphylaxis	* Routine Pharmacovigilance	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Potential risk		
Atrial fibrillation	* Routine Pharmacovigilance * Targeted follow up questionnaire	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Atypical subrochanteric/ femoral fractures	* Routine Pharmacovigilance. * Periodic class effect review (incorporating CHMP stress fracture definition recommendation). * Targeted questionnaire. * Special 15-day expedited reporting of events relating to the above safety concerns regardless of seriousness/ listedness.	Currently available data do not support the need for risk minimisation.
Gastrointestinal disorders	* Routine Pharmacovigilance	Included within section 4.8 of the Hospira Zoledronic Acid SPC.
Cerebrovascular AEs	* Routine Pharmacovigilance * Targeted follow up questionnaire	No additional risk minimisation steps are currently considered necessary.
Interaction with products which can significantly affect renal function (including paracetamol/ acetaminophen)	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Interaction with aminoglycosides	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Medication errors	* Routine Pharmacovigilance	Clear labelling. Clear dosage instructions (in SPC/ CMI). Clearly identifiable packaging.
Interactions with nephrotoxics	* Routine Pharmacovigilance	Included within section 4.5 of the Hospira Zoledronic Acid SPC.
Missing information		
Use in pregnancy/ lactation	* Routine Pharmacovigilance	Contraindicated within section 4.6 of the Hospira Zoledronic Acid SPC.
Use in patients with renal impairment	* Routine Pharmacovigilance	Included in section 4.4 and 4.8 of the zoledronic acid SPC.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.
The CHMP, having considered the data submitted, was of the opinion that the following additional risk minimisation activities were required:
The MAH shall provide an educational pack targeting all physicians who are expected to prescribe Zoledronic Acid Hospira 5 mg/ 100 ml in 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.
The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution prior to the launch in the Member State.

The physician educational pack should contain:

- The Summary of Product Characteristics.
- Reminder card
- Patient information pack

The Reminder card should contain the following key messages:

- Need to measure serum creatinine before treatment with Zoledronic Acid Hospira 5 mg/ 100 ml.
- 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 Hospira 5 mg/ 100 ml slowly over a period of no less than 15 minutes.
- One-yearly dosing regime.
- Adequate calcium and vitamin D intake are recommended in association with Zoledronic Acid Hospira 5 mg/ 100 ml administration.
- Need for appropriate physical activity, non-smoking and healthy diet.

The patient information pack should contain:

- Package leaflet.
- Patient educational material with the following key messages:
  - Contraindication in patients with severe kidney problems.
  - Contraindication in pregnancy and in breast-feeding women.
  - Need for adequate calcium & 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.

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 2013?.

User consultation

Overall, the test methodology used to perform the User consultation follows the Readability Guideline. Both the first and the second test round met the success criteria of 90 % of the subjects being able to locate the requested information, and of those, 90 % being able to give the correct answer, to indicate

that they understood the information presented. The general impression of the package leaflet (content, language and layout) was mostly positive.

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 4 mg/ 5 ml concentrate for solution for infusion and 5 mg/ 100 ml solution for infusion and a hybrid application for zoledronic acid 4 mg/100 ml solution for infusion. During the course of the evaluation of the present application the pharmaceutical form 4mg/100ml solution for infusion has been authorised as an extension to the marketing authorisation of Zometa.
The reference products are Zometa and Aclasta.

Zometa is indicated for:

- 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).

Aclasta is indicated for:

- Treatment of osteoporosis
  - in post-menopausal women
  - in men

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

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.

Zoledronic Acid Hospira contains the same active substance as Zometa and Aclasta and is intended for parenteral administration; in view of this there is no requirement for bioequivalence testing (cf.CHMP/QWP/EWP/1401/98 Rev.1).

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 additional risk minimisation activities are required beyond those included in the product information for Zoledronic Acid Hospira 5 mg/ 100 ml indicated in the:

- Treatment of osteoporosis
  - in post-menopausal women
  - in men

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

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 Hospira 4 mg /5 ml and 4 mg/ 100 ml in the:

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

and Zoledronic Acid Hospira 5 mg/ 100 ml in the:

- Treatment of osteoporosis
  - in post-menopausal women
  - in men

  at increased risk of fracture, including those with a recent low-trauma hip 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 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 MAH shall provide an educational pack targeting all physicians who are expected to prescribe Zoledronic Acid Hospira 5 mg/ 100 ml in 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.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution prior to the launch in the Member State.

The physician educational pack should contain:

- The Summary of Product Characteristics.
- Reminder card
- Patient information pack

The reminder card should contain the following key elements:

- Need to measure serum creatinine before treatment with Zoledronic Acid Hospira 5 mg/ 100 ml.
- 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 Hospira 5 mg/ 100 ml slowly over a period of no less than 15 minutes.
- One-yearly dosing regime.
- Adequate calcium and vitamin D intake are recommended in association with Zoledronic Acid Hospira 5 mg/ 100 ml administration.
- Need for appropriate physical activity, non-smoking and healthy diet.

The patient information pack should contain:

- Package leaflet.
- Patient educational material with the following key messages:
    - Contraindication in patients with severe kidney problems.
    - Contraindication in pregnancy and in breast-feeding women.
    - Need for adequate calcium & 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.