21 November 2013
EMA/806574/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic Acid Accord

International non-proprietary name: Zoledronic acid

Procedure No. EMEA/H/C/002667

Note

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 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on the 1st of May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic Acid Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 December 2011.

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 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, and 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).

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

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Not applicable

The chosen reference product is:

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

- Product name, strength, pharmaceutical form Zometa, 4mg/5ml, powder and solvent for solution for infusion and Zometa 4 mg/ 5ml 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/1/01/176/001-009

■ 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
- Date of authorisation: 20-03-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/01/176/004-006

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. Manufacturers

Manufacturer(s) responsible for batch release

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
HA1 4HF
United Kingdom

1.3. 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 1 May 2012.
- The procedure started on 23 May 2012.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 13 August 2012
- During the meeting on 20 September 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 20 September 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the consolidated List of Questions to all CHMP members on 19 February 2013
- During the CHMP meeting on 21 February 2013, 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 List of Outstanding Issues on 25 April 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 May 2013
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a revised List of Outstanding Issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP revised List of Outstanding Issues on 19 August 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the revised List of Outstanding Issues to all CHMP members on 02 September 2013
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a revised List of Outstanding Issues to be addressed in writing or in an oral explanation by the applicant
- The applicant submitted the responses to the CHMP revised List of Outstanding Issues on 22 October 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the revised List of Outstanding Issues to all CHMP members on 29 October 2013
- During the meeting on 21 November 2013, 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 Accord.

2. Scientific discussion

2.1. Introduction

Zoledronic Acid Accord is a generic medicinal product containing the active substance zoledronic acid (as monohydrate). The reference medicinal product is Zometa 4 mg/5 ml, Concentrate for solution for infusion. The qualitative composition of the generic product is identical to the reference product. Both products are administered intravenously as an infusion.

Zoledronic acid is a nitrogen containing biphosphonate and it binds to hydroxyapatite in the bone mineral matrix and strongly inhibits bone resorption. The ability of bisphosphonates to persist in bone matrix and to reduce osteoclast activity depends on their affinity for the bone matrix and potency of the inhibition of farnesyl pyrophosphate synthase. Zoledronic acid has the highest affinity for bone, followed by alendronate, ibandronate, risedronate, etidronate and clodronate and it also alters mineral-surface properties, allowing greater adsorption. Zoledronic acid at 4 mg reduced skeletal related events in prostate cancer patients with bone metastases. Zoledronic acid 4 mg is recommended for initial treatment of hypercalcaemia and zoledronic acid 8 mg for relapsed or refractory hypercalcaemia.

The proposed indications for the generic product are the same as those of the reference product:

- 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.
- Treatment of tumour-induced hypercalcaemia (TIH).

Zoledronic acid 4 mg/5 ml, Concentrate for solution for infusion is subject to medical prescription.

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 Accord, a bioequivalence study is not required.

2.2. Quality aspects

2.2.1. Introduction

Zoledronic Acid Accord is presented as a concentrate for solution for infusion for intravenous use containing 4 mg/ 5mLof zoledronic acid as the active substance.

Other ingredients are: mannitol, sodium citrate and water for injections.

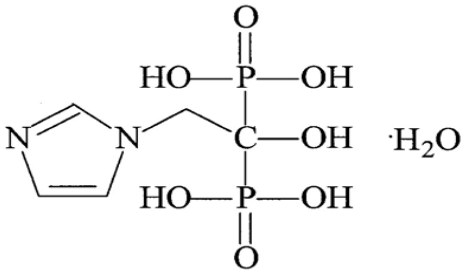
The product is available in cyclo olefin copolymer vial with chlorobutyl rubber stoppers and aluminium seals with flip off cap.

The pack sizes are consistent with those of the reference product.

2.2.2. Active substance

The active substance is not described in the European Pharmacopoeia, pharmacopoeias of the member states.

The chemical name of zoledronic acid is [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, therefore it does not exhibit stereoisomerism.

Polymorphism is not relevant as the active substance is present in solution in the finished product.

The active substance is a white to off-white crystalline powder, non-hygroscopic, slightly soluble in water and insoluble in methanol.

The active is present in the drug product dissolved in water, hence the polymorphic form and particle size distribution are not considered as critical quality aspects. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

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

The active substance is manufactured in 2 steps of chemical synthesis (I and II) and 1 acidification/purification stage starting from imidazole 1-acetic acid (III).

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

The active substance specification contains tests for description, solubility, identity by IR and HPLC, assay by titration, chromatographic purity anions, impurities by HPLC, pH of the solution, Clarity of solution, heavy metals, loss on drying, microbial purity and endotoxins.

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 satisfactorily validated in line with the CHMP/ICH requirements.

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

Stability

Stability data of 3 batches of the active substance were provided for up to 60 months of storage at 30 °C/65 % relative humidity (RH) and 6 months at 40 °C/75 % RH (ICH compliant) stored in double polythene bags and kept in polyethylene drums, same as the commercial container closure system. Compliance with specification has been confirmed at both conditions. Following parameters were tested during stability studies: description and solubility, identification, impurities, assay, loss on drying, X-ray diffraction pattern, microbial purity and endotoxins.

Forced degradation studies were performed, where zoledronic acid was subjected to high humidity, UV, heat, acid, base and hydrogen peroxide hydrolysis. No significant changes are seen during acid or alkaline forced degradation studies. Exposure to an oxidizing agent significantly increased the level of 1-Imidazole acetic acid content. No changes are seen after UV exposure, high humidity and heat treatment.

The stability data support the proposed retest.

2.2.3. Finished medicinal product

Pharmaceutical development

Zoledronic Acid Accord is presented as a clear, colourless solution in a clear cyclo olefin copolymer vial with chlorobutyl rubber stopper and aluminum cap with flip-off seal. This medicinal product is supplied in vials as a sterile, concentrate for solution for infusion containing 4 mg/5 ml of zoledronic acid.

The qualitative composition of Zoledronic Acid Accord is the same as the 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.

Pre-formulation and formulation development studies were performed. A comparison of impurity profile, description, assay and pH of Zoledronic Acid Accord (batch no ASZLEP1005B) and Zometa (batch no S0235B) were presented and showed no significant difference.

Since the medicinal product is administered to patients as an aqueous intravenous solution containing the same active substance in the same concentration as the reference product it is not required to submit a bioequivalence study.

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 preparation of the bulk solution, sterile filtration, filling, terminal sterilisation and inspection/packaging. The terminal sterilisation is done by autoclaving. The critical steps/parameters in the manufacturing process are bulk solution preparation, sterile filtration, sterilisation/depyrogenation of the container closure system, filling and terminal sterilisation. Appropriate in-process controls are in place after each step.

Validation of the manufacturing process has been performed on three pilot batches. Holding times at each manufacturing step were defined and validated. All results comply with specification. A commitment for prospective process validation on the first three consecutive production-scale batches of additional batch size of the drug product was provided.

Product specification

The specification of the finished product includes standard testing parameters typical for this kind of dosage form such as tests for description, identification, clarity and colour of solution, particulate contamination, pH, extractable volume, assay, related substances, sterility and bacterial endotoxins. The limits proposed are justified according to relevant EU/ICH guidelines, Ph. Eur and batch data. All analytical methods have been appropriately validated.

Batch analysis has been performed on 3 pilot scale batches and the results show that the finished product meets the proposed specifications.

Stability of the product

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

Stability results were submitted at long-term and accelerated ICH conditions for up to 18 months and 6 months, respectively. The product was stored in 5 ml/20 mm ready to use cyclo olefin copolymer vials with 20 mm chlorobutyl plus stopper and 20 mm aluminium flip off

violet seal, the proposed commercial container closure system. The container closure system complies with EC and Ph.Eur. requirements.

The following paremeters were routinely tested during stability studies: description, pH, related substances, assay, clarity and colour of solution. Particulate contamination, sterility and bacterial endotoxins are tested periodically.

Photostability testing was conducted on one commercial batch. Conditions were chosen according to the current "Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products (CPMP/ICH/279/95)": The finished product is not susceptible to light.

In-use stability studies show that product is stable for 36 hours at 2 °C to 8 °C after reconstitution in 0.9 % sodium chloride solution and 5 % glucose solution.

The stability results support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the 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 Accord manufactured by Accord Healthcare Limited 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 of zoledronic acid. Zoledronic Acid Accord contains the same active substance as Zometa 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

No new clinical data have been presented.

Exemption

The product concerned by the application contains the same active ingredient in the same concentration as the reference product. It has an identical qualitative and quantitative composition in terms of the active substance as its reference medicinal product.

The product is aqueous concentrate for solution for infusion and contains zoledronic acid as an active substance. Excipients are mannitol, sodium citrate and water for injection. Due to the parenteral administration mode, bioequivalence can be concluded without further studies and as the composition is the same, no differences in non-clinical or clinical effects are possible.

2.4.2. Pharmacodynamics

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

2.4.3. Post marketing experience

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

2.4.4. 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 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 3.0, the PRAC considers by consensus decision that the risk management system for zoledronic acid (Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion) could be acceptable provided an updated risk management plan and satisfactory responses to the List of Questions are submitted before final opinion.

Safety concerns

Having considered the data in the safety specification, and in line with the reference product, the PRAC considers that the potential risk “Potential interaction with anti-angiogenic drugs that can lead to ONJ” should be upgraded to an identified risk.

Pharmacovigilance plans

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.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

The PRAC, having considered the data submitted, considers that the proposed routine risk minimisation measures are sufficient for the safe and effective use of the product.

The CHMP endorsed this advice without changes.

Based on the review of the Risk Management Plan version 4.0, which responded the questions raised in PRAC advice adopted on the 14th November 2013, the CHMP considers that the risk management system for zoledronic acid (Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion) is acceptable.

Safety concerns

Category	**Safety concern**
Important identified risks	Renal function impairment Osteonecrosis of the jaw Acute phase reaction Hypocalcaemia Ocular adverse events Atrial fibrillation Anaphylaxis Interstitial lung disease Potential interaction with anti-angiogenic drugs that can lead to ONJ
Important potential risks	Atypical femoral fractures Cardiac arrhythmias Cerebrovascular AEs Focal Segmental Glomerulosclerosis Fracture healing impairment Medication errors Risk of off-label in osteogenesis imperfecta Potential interaction with products that can significantly affect renal function
Missing information	Races other than Caucasian Paediatric patients Fertility, pregnancy and lactation Patients with severe renal impairment Patients with hepatic insufficiency Paediatric patients with renal impairment

Pharmacovigilance plans

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

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

The CHMP, having considered the data submitted, considers that the proposed routine risk minimisation measures are sufficient for the safe and effective use of the product.

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/EC and published on the European medicines web-portal.

User consultation

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

3. Benefit-risk balance

This application concerns a generic version of zoledronic acid concentrate for solution for infusion. The reference product 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, and treatment of adult patients with tumour-induced hypercalcaemia (TIH). Non-clinical studies have not 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.

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

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

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

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zoledronic Acid Accord 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 treatment of adult patients with tumour-induced hypercalcaemia is favourable and therefore recommends the granting of the marketing authorisation.