IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Zoledronic Acid 4 mg / 5 mL Concentrate for solution for infusion
Zoledronic acid
PA1122/016/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4096/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 10th October 2018 under procedure number IE/H/0711/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/016/001
Marketing Authorisation Holder: Noridem Enterprises Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

ABOUT THE PRODUCT

Name of the product in the Reference Member State	Zoledronic Acid 4mg/5ml Concentrate for Solution for Infusion
Name(s) of the active substance(s) (INN)	Zoledronic acid
Pharmacotherapeutic classification (ATC code)	Drugs for treatment of bone diseases, bisphosphonate (ATC code: M05 BA 08)
Pharmaceutical form and strength(s)	Concentrate for solution for Infusion; 4mg/5ml
Reference number for the Decentralised Procedure	UK/H/4096/001/DC
ReferenceMemberState (RMS)	United Kingdom
Concerned Member States (CMS)	Austria, Germany, Greece, Spain, Ireland and Poland
Marketing Authorisation Number(s)	PL 24598/0029
Name and address of the authorisation holder	Noridem Enterprises Ltd Evagorou & Makariou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Zoledronic Acid 4mg/5ml Concentrate for Solution for Infusion (PL 24598/0029; UK/H/4096/001/DC) could be approved. The product is a prescription-only medicine (POM) for use 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).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Germany, Greece, Spain, Ireland and Poland as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Zometa 4mg powder and solvent for solution for infusion (Novartis Europharma Limited), which was authorised in the EEA via a Centralised procedure on 20 March 2001.

The active ingredient, zoledronic acid, is a heterocyclic imidazole bisphosphonate that acts primarily on bone and is an inhibitor of osteoclastic bone resorption.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

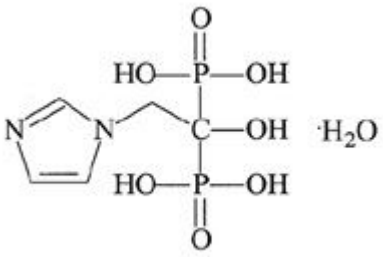
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 13 December 2012. After a subsequent national phase, a licence was granted in the UK on 25 January 2013.

II. QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Zoledronic acid
Chemical name: ([1-hydroxy-2-(1H-imidazol-1-)ethylidene]bisphosphonic acid;
2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid.
Structure:



Molecular formula: $C5H10N2O7P_2 \cdot H2O$
Molecular Mass: 290.11 (monohydrate)
Appearance: A white crystalline powder.
Solubility Sparingly soluble in 0.1N sodium hydroxide solution, slightly soluble in water and 0.1N hydrochloric acid and practically insoluble in organic solvents.

Zoledronic acid is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredient

Other ingredients consist of the pharmaceutical excipients, namely mannitol (E421), sodium citrate (E331) and water for injections. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specification.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients

Pharmaceutical Development
The objective of the development programme was to a produce product that could be considered as generic medicinal product of Zometa 4mg/5ml concentrate for solution for infusion (Novartis Europharma Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative physicochemical parameter data have been provided for this product and the reference product Zometa 4mg/5ml concentrate for solution for infusion (Novartis).

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is supplied in 5 ml plastic vials made of clear colourless cycloolefine copolymer with fluoropolymer-coated bromobutyl rubber stoppers and aluminium caps with plastic flip-off components.

The product is available in pack sizes of 1, 4 and 10 vials. Not all pack sizes may be marketed

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months has been proposed, with no special storage instructions for the product when stored in the vial.

Zoledronic Acid 4mg/5ml Concentrate for Solution for Infusion is stable for 24 hours at 2°C-– 8°C after further dilution in 100 ml physiological saline or 5% w/v glucose solution.

It is stated that, unless the method of opening or dilution precludes the risk of microbial contamination, the product should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application for a parenteral product.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL), Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of zoledronic acid are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the pharmacology and toxicology of zoledronic acid.

Suitable justification has been provided for non-submission of an environmental risk assessment. As the application is for a generic version s of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed product.

The grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

Clinical Pharmacololgy
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application for a parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 (NfG on the Investigation of Bioavailability and Bioequivalence).

Efficacy
No new efficacy data have been submitted and none are required for this type of application.

Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application. Zoledronic acid as an active ingredient has a well-established and an acceptable level of safety in the proposed indications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the innovator product The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with the current guidelines.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

Conclusion
The grant of a Marketing Authorisation is recommended.

V. OVERALL CONCLUSIONS

Quality
The important quality characteristics of Zoledronic Acid 4mg/5ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

EFFICACY
No new clinical data were submitted for this application. No bioequivalence studies were submitted or required for this application.

SAFETY
No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with zoledronic acid is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.

VI. REVISION DATE

June 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/4096/001/DC to IE/H/0711/001/DC	N/A	N/A	N/A	Approved 10/10/2018