IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ibandronic Acid 6 mg Concentrate for Solution for Infusion
Ibandronate sodium monohydrate
PA1122/018/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4472/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 10th October 2018 under procedure number IE/H/0705/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/018/001
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.

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Ibandronic Acid 6 mg Concentrate for Solution for Infusion
(PL 24598/0036; UK/H/4472/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated in adults for:

- prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases
- treatment of tumour-induced hypercalcaemia with or without metastases.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Germany, Greece, Ireland, Spain and Poland as Concerned Member States (CMSs). The application was submitted under Article 10(1) of Directive 2001183/EC, as amended, claiming to be a generic medicinal product of Bondronat 6 mg/6 ml concentrate for infusion, which was registered via the Centralised Procedure (EU/1/96/012/011-013) on 25 June 1996 in the UK. The Marketing Authorisation Holder was originally Boehringer Mannheim GmbH and subsequently changed to Roche Registration Limited.

Ibandronic acid is a synthetic bisphosphonate analogue of pyrophosphate, and an inhibitor of osteoclast-mediated bone resorption. Ibandronic acid is used to prevent skeletal related events in patients with breast cancer and bone metastasis, and to treat tumour-induced hypercalcaemia and osteoporosis.

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 (aqueous solution).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 or 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 14 March 2013. After a subsequent national phase, a licence was granted in the UK on 16 April 2013.

ABOUT THE PRODUCT

Name of the product in the Reference Member State	Ibandronic Acid 6 mg Concentrate for Solution for Infusion
Name(s) of the active substance(s) (INN)	Ibandronic acid as ibandronate sodium monohydrate
Pharmacotherapeutic classification (ATC code)	Bisphosphonates (M05B A06)
Pharmaceutical form and strength(s)	Concentrate for solution for infusion 6 mg/6 ml
Reference numbers for the Decentralised Procedure	UK/H/4472/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Germany, Greece, Ireland, Spain and Poland
Marketing Authorisation Number(s)	PL 24598/0036
Name and address of the authorisation holder	Noridem Enterprises Ltd Evagorou & Makmiou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus

II. QUALITY ASPECTS

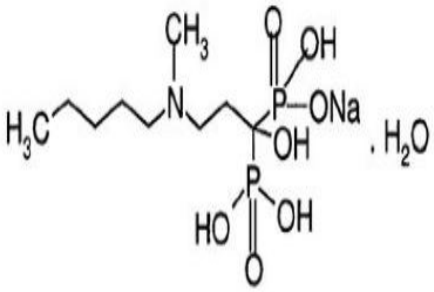
ACTIVE SUBSTANCE
Ibandronic acid

Nomenclature:

INN: Ibandronate sodium monohydrate

Chemical name: 3-(N-methyl-N-pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate

Structure:



Molecular formula: $C_9H_{22}O_7NP_2Na\text{-}H_2O$

Molecular weight: 359.24 g/mol

Physical form: A white to off-white powder

Solubility: Freely soluble in water and practically insoluble in organic solvents such as methanol, ethanol and dimethyl formamide.

The active substance, ibandronic acid, is not the subject of a European Pharmacopeia (Ph. Eur.) or British Pharmacopeia (B.P.) 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 to support a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredient
Other ingredients consist of the pharmaceutical excipients, sodium chloride, acetic acid (E260), sodium acetate (E262) and water for injections. Appropriate justification for the inclusion of each excipient has 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 specifications.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms (GMO).

Pharmaceutical development

The objective of the development programme was to a produce a product that could be considered a generic medicinal product of Bondronat 6 mg/6 ml concentrate for infusion (Roche Registration Limited).
Suitable pharmaceutical development data have been provided for this application. Comparative physicochemical data have been provided for this product and the reference product Bondronat 6 mg/6 ml concentrate for infusion (Roche Registration Limited).

Manufacture

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 is acceptable. Test methods have been described and have been validated adequately. 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 packs containing 1**,**5 and 10 vials (6 ml type 1 glass vials). The vials are closed with rubber stoppers complying with Ph.Eur.

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 guidance concerning materials in contact with parenteral products.

Stability of the Product

Finished product stability studies have been conducted in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been proposed, with no special storage instructions for the product when stored in the vial.

Chemical and physical in-use stability has been shown for 24 hours under refrigeration and 25 °C when the product is diluted with either 0.9 % sodium chloride or 5% glucose to a concentration of 0.012 mg/ml.

It is stated that, after dilution, from a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C.

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

Bioequivalence Study

A bioequivalence study was not necessary to support this application for an aqueous solution that is a parenteral product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and 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)

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Ibandronic Acid 6 mg Concentrate for Solution for Infusion from a pharmaceutical point of view.

III. NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibandronic 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 ibandronic acid.

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

The grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

Clinical Pharmacology
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 an aqueous parenteral product. According to CHMP guidance, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev.1/Con (Note for guidance on the Investigation of 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 concems arose from this application. As an active ingredient, Ibandronic acid has a well-established safety profile and an acceptable level of safety in the proposed indications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and 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 cunent guidance. The labelling is in line with current guidance.

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 Ibandronic Acid 6 mg 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 applications of this type.

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 arose from this application.

PRODUCT LITERATURE

The SrnPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

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 support the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with ibandronic acid is considered to have demonstrated the therapeutic value of the compound. 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/4472/001/DC to IE/H/0705/001/DC	N/A	N/A	N/A	Approved 10/10/2018