LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zoledronic acid Oresund Pharma
zoledronic acid (anhydrous), zoledronic acid monohydrate

SE/H/2273/01-02

This module reflects the scientific discussion for the approval of Zoledronic acid Oresund Pharma. The Public Assessment Report was written in June 2018 by the previous RMS (PT) after initial procedure PT/H/1405/001-002/DC and is attached at the end of this document. RMS transfer from PT to SE was completed 2022-05-17. For information on changes after this date please refer to the module 'Update'.

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Active substance	**zoledronic acid monohydrate**
Pharmaceutical form	**Solution for infusion**
Strength	**4 mg/100 ml, 5 mg/100 ml**
Applicant	**Øresund Pharma ApS**
EU-Procedure number (original)	**PT/H/1405/01-02**

infarmed
Autoridade Nacional do Medicamento
e Produtos de Saúde I.P.

Public Assessment Report

Scientific discussion

Ácido Zoledrónico Amneal

4 mg/100 ml and 5 mg/100 ml Solution for Infusion

(Zoledronic acid)

PT/H/1405/001-002/DC

Date: 07-06-2018

This module reflects the scientific discussion for the approval of Ácido Zoledrónico Amneal. The procedure was finalised at 29-06-2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed in granting a marketing authorisation for Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion, from Amneal Pharma Europe Limited.

The product is indicated for*:< include indications*>.

Ácido Zoledrónico Amneal 4 mg/100 ml Solution for Infusion 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).

Ácido Zoledrónico Amneal 5 mg/100 ml Solution for Infusion is indicated for:

Treatment of osteoporosis

- in post-menopausal women
- in adult 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 adult men

at increased risk of fracture.

Treatment of Paget's disease of the bone in adults.

A comprehensive description of the indications and posology is given in the SmPC.

Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion is submitted as an abridged application under article 10.1 (a) (iii) of Directive 2001/83/EC as essential similar to the product Zometa® 4 mg/ 5 ml concentrate for solution for infusion from Novartis Europharm Limited. Zometa® was authorized through Europe in May 2003 via a Centralised Procedure (EU/1/01/176/004-006).

The marketing authorization was granted on 07-06-2018 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Amneal Pharma Europe Limited.

II. QUALITY ASPECTS

II.1 Introduction

Solution for infusion

Clear and colourless solution

4 mg/100 ml

- The active substance of Zoledronic Acid Amneal is zoledronic acid. One bag contains 4 mg zoledronic acid, corresponding to 4.264 mg zoledronic acid monohydrate.
- The other ingredients are: mannitol (E-421), sodium citrate (E-331) and water for injections.

Ácido Zoledrónico Amneal 4 mg/100 ml Solution for Infusion is supplied as a solution in a clear, colourless polyolefin plastic bag. One bag contains 100 ml solution.

Ácido Zoledrónico Amneal 4 mg/100 ml Solution for Infusion is supplied as a unit pack containing one bag.

5 mg/100ml

- The active substance is zoledronic acid. Each bag with 100 ml of solution contains 5 mg zoledronic acid anhydrous (as monohydrate). One ml solution contains 0.05 mg zoledronic acid (as monohydrate).
- The other ingredients are mannitol (E-421), sodium citrate (E-331) and water for injections.

Ácido Zoledrónico Amneal 5 mg/100 ml Solution for Infusion comes in 100 ml polyolefin bags as a ready-to-use solution for infusion. It is supplied in packs containing one bag as unit pack.

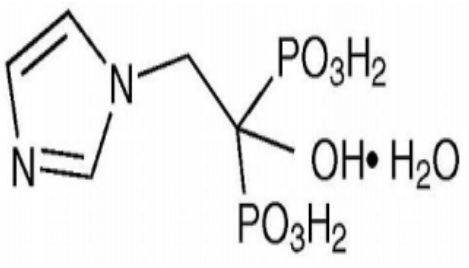
II.2 Drug Substance

General Information

Nomenclature

International non-proprietary name (INN):	Zoledronic acid
Chemical names (among others possible):	(1-Hydroxy-2-imidazol-l-yl-phosphonoethyl)-phosphonic acid monohydrate or [1-Hydroxy-2-(1*H*-imidazol-1-yl)ethylidene]-bisphosphonic acid monohydrate
CAS registry number:	[165800-06-06] - Zoledronic acid monohydrate [118072-93-08] - Zoledronic acid anhydrous
Molecular formula:	$C_5H_{10}N_2O_7P_2 \cdot H_2O$
Relative molecular mass:	290.11 g/mol

Structural Formula:



Zoledronic acid (monohydrate)

General Properties

Description:	White to off white powder.
Solubility:	- Freely soluble in 1 N Sodium hydroxide - Sparingly soluble in water and 0.1 N HCl - Insoluble in Methanol and acetonitrile
pH *(0.7 % w/v aq. suspension)*	1.5 – 2.5
Potential Isomerism:	The substance is not optically active as no chiral centres are present. No other type of isomers are present.
Polymorphism:	The drug substance is the monohydrate form.
Melting point:	231 – 235 °C

The drug substance manufacturer states that the drug substance in non-hygroscopic based on experimental hygroscopic studies conducted as per Ph.Eur.

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Ácido Zoledrónico Amneal are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

The data already available from the accelerated and long-term stability studies confirm that the quality profile of the drug substance is kept unchanged up to 6 months for accelerated conditions and up to 48 months for long term storage conditions. Therefore, the re-test period for Zoledronic acid proposed by the applicant can be accepted: 4 years.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 36 months and no special storage conditions are required for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of zolendronic acid is well known. Zolendronic acid a widely used, well-known active substance combination, in addition to published literature, the applicant has only provided a new comparative local tolerance study. Further studies are not required.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

the application is for a generic medicinal product of the reference product Zometa® / Aclasta® solution for infusion (Novartis Europharm Ltd.). The reference product has been authorized in

the EU since 20th March 2001, and therefore Zometa® solution for infusion is considered as the innovator drug product that has been licensed for not less than 6/10 years).

IV.2 Pharmacokinetics

Biowaiver

The product was developed as solution for infusion, and therefore intended to be administered as an aqueous intravenous solution containing the same active substance of the innovator. For this type of drug product, the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr (appendix II) do not require bioequivalence studies if the Test product contains the same excipients in similar amounts of the currently approved product.

4 mg/100 mL strength
According to module 3.2.P.1, the proposed formulation uses zoledronic acid (4 mg) on the form of monohydrate and as excipients, 5100 mg of mannitol as isotonic agent (corresponding to a concentration of 5.1% (w/v)), sodium citrate (as pH adjusting agent, q.s. (20-30 mL) to pH 6.5) and water for injections q.s. (95-100 mL) as solvent.

The innovator product "Zometa 4 mg/100 mL solution for infusion", contains zoledronic acid (4 mg) also on the form of monohydrate, 5100 mg of mannitol as isotonic agent (corresponding to a concentration of 5.1% (w/v)), 24 mg of sodium citrate (as pH adjusting agent) and water for injections q.s. to 100 mL (solvent). The product developed by Laboratorios Normon has the same composition of the reference product Zometa.

5 mg/100 mL strength
According to module 3.2.P.1, the proposed formulation uses zoledronic acid (5 mg) on the form of monohydrate and as excipients, 5100 mg of mannitol as isotonic agent (corresponding to a concentration of 5.1% (w/v)), sodium citrate (as pH adjusting agent, q.s. (25-35 mL) to pH 6.5) and water for injections q.s. (95-100 mL) as solvent.

The innovator product "Aclast 5 mg/100 mL solution for infusion", contains zoledronic acid (5 mg) also on the form of monohydrate, 4950 mg of mannitol as isotonic agent (corresponding to a concentration of 4.95% (w/v)), 30 mg of sodium citrate (as pH adjusting agent) and water for injections q.s. to 100 mL (solvent).

The difference in the quantities of mannitol between the two formulations is considered to have no impact on zoledronic acid disposition. Moreover, this excipient is considered as an inactive excipient at the concentration used on the developed pharmaceutical form. According to FDA's Inactive Ingredient Database, the maximum potency approved for mannitol is 47% (w/v) for the dosage form «solution for intravenous infusion». Therefore, concentrations below are considered as safe for use in a similar manner and for a similar type of product.

For the above reasons it is accepted to biowaive a bioequivalence study for Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion.

IV.3 Pharmacodynamics

Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion.

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Renal function impairment Hypocalcaemia Atrial fibrillation Hypersensitivity Acute phase reaction Musculo-skeletal pain
Important potential risks	Hepatic impairment
Important missing information	Pregnancy Lactation Fertility

IV.5 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that

the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Ácido Zoledrónico Amneal 4 mg/100 ml and 5 mg/100 ml Solution for Infusion contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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