Public Assessment Report

Scientific discussion

Zoledroninezuur CF 5 mg/100 ml, solution for infusion

(zoledronic acid)

NL/H/3727/001/DC

Date: 5 December 2017

This module reflects the scientific discussion for the approval of Zoledroninezuur CF 5 mg/100 ml, solution for infusion. The procedure was finalised on 19 January 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zoledroninezuur CF 5 mg/100 ml, solution for infusion from Centrafarm B.V.

The product 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aclasta 5 mg solution for infusion, registered by Novartis Europharm Limited. Aclasta has been authorised via centralised procedure EU/1/05/308 since 15 April 2005. The first zoledronic acid authorisation was granted for Zometa 4 mg/5 ml concentrate for solution for infusion via centralised procedure EU/1/01/176 on 20 March 2001.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, France, Luxembourg and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Zoledroninezuur CF is a clear and colourless solution for infusion, free from visible particles, with pH 5.50-7.00 and osmolality (Osmol/kg) 0.23-0.33.

The solution for infusion is packed in clear type I silicon dioxide inner coated glass vials, capped with type I bromobutyl rubber stoppers and sealed with aluminum polypropylene flip off seals. Each vial with 100 ml of solution contains 5 mg zoledronic acid (as monohydrate).

The excipients are: mannitol (E421), sodium citrate (E331) and water for injections.

II.2 Drug Substance

The active substance is zoledronic acid, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off white crystalline powder, which is non-hygroscopic in nature. Zoledronic acid does not exhibit stereochemistry and isomerism. The substance is freely soluble in 1N sodium hydroxide and slightly soluble in water. The active substance exhibits polymorphism and is used in a specific and stable polymorphic form.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access

to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
In the manufacturing process of both suppliers, zoledronic acid is formed in three reaction steps. No class I solvents or heavy metal catalysts are used. The manufacturing process has been described in sufficient detail.

Quality control of drug substance
The drug substance specification of the MAH has been established in-house and is in line with the specification of the ASMF-holders. Batch analytical data demonstrating compliance with the drug substance specification have been provided by both drug product manufacturer.

Stability of drug substance
One active substance manufacturer provided stability data on the active substance for full scaled batches stored at 25°C/60% RH (48 months, 4 batches,) and 40°C/75% RH (6 months, 3 batches). From the provided stability data no changes or trends are observed at both long-term and accelerated conditions. The claimed retest period of 48 months is justified.
The second active substance manufacturer provided stability data on the active substance for full scale batches stored at 25°C/60% RH (up to 60 months for 3 batches) and 40°C/75% RH (6 months for 3 batches). From the provided stability data no changes or trends are observed at both long-term and at accelerated conditions. The claimed retest period of 60 months and storage conditions (no special storage conditions) are justified.
The MAH confirmed that the same re-test periods are used as stated in the corresponding ASMFs.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known and the same as in the reference product. The choices of the packaging and manufacturing process are justified. The aim of the formulation development was to develop a finished product which is equivalent to the innovator product Aclasta.
The MAH's formulation is similar to the innovator product in terms of route of administration, qualitative and quantitative composition of active substance. No bioequivalence study was required for this aqueous solution for infusion.

Manufacturing process
Zoledronic acid 5 mg/100 ml solution for infusion is manufactured by compounding, sterile filtration, filling and terminal sterilisation under nitrogen purging. Process parameters of the manufacturing have been provided. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 commercial scale batches. The product is manufactured using conventional manufacturing techniques. Process validation on 3 production batches of the highest batch size will be performed post authorisation.

Control of excipients
All excipients used comply with the requirements of the Ph.Eur. These specifications are acceptable.

Microbiological attributes
The sterility and the bacterial endotoxins of the finished product are tested on a routine basis at release and until the end of shelf life to ensure the integrity of the product, according to the European Pharmacopoeia method 2.6.1 and 2.6.14, respectively.

Quality control of drug product
The product specification includes tests for description, identification, pH, assay, extractable volume, related substances, particulate contamination, bacterial endotoxins and sterility. The release and shelf-life limits are generally the same except for related substances where particularly the maximum unknown impurity and total impurities are different. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 commercial scale batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for 8 commercial scale batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored upright and inverted in the proposed packaging. No significant trends or changes were seen. A photostability study was conducted on 1 pilot scale batch. No change was seen in the test product solution when stored in the marketed packaging (with carton box). The product is considered photostable.
On the basis of the currently available data the claimed shelf-life of 36 months (without additional temperature restrictions) can be granted. From a microbiological point of view, the product 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 room temperature (25^{o}C) or at 2°C - 8°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Zoledroninezuur CF 5 mg/100 ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following commitments regarding the post-approval stability protocol are made by the MAH:

- The stability studies of the Zoledronic acid 5 mg solution for infusion will be continued as stated in the stability protocol in 3.2.P.8.1, in order to firmly establish the shelf-life.
- One batch per year will be placed on stability program, under long term storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Zoledroninezuur CF 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.1 Discussion on the non-clinical aspects

This product is a generic formulation of Aclasta, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Zoledronic acid is a well-known active substance with established efficacy and tolerability.
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. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
Zoledroninezuur CF 5 mg/100 ml, solution for infusion is a parenteral aqueous formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral

solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Zoledroninezuur CF is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 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 Zoledroninezuur CF.

Summary table of safety concerns as approved in RMP

Important identified risks	• Anaphylactic reaction • Hypocalcaemia • Ocular adverse events • Osteonecrosis of the jaw • Post-dose symptoms (acute phase reaction) • Renal dysfunction
Important potential risks	• Atrial fibrillation • Atypical femoral fractures • Cerebrovascular adverse events • Gastrointestinal adverse events • Interaction with paracetamol • Interaction with products that can effect renal function • Osteonecrosis outside the jaw (AVN, fracture nonunion and/or fracture delayed union)
Important Missing information	• Use in pregnancy and lactation • Use in patients with severe renal impairment

The safety specification as submitted by the MAH is acceptable. The routine pharmacovigilance activities for all important risks and missing information are accepted as this is in line with the RMP of the reference product. The routine risk minimisation measures are also in line with those for Aclasta.

The MAH shall ensure that the educational programme implemented for 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 is updated. The educational programme contains the following:

- Physician educational material
- Patient information pack

The physician educational material should contain the following key elements:

- The SmPC
- Reminder card with the key messages as specified in annex II of Aclasta.
- Patient information pack

The patient information pack should be provided and contain the key messages as specified in annex II of Aclasta, and additionally contain:

- The Package leaflet
- Patient reminder card on osteonecrosis of the jaw

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aclasta 5 mg solution for infusion. No new clinical studies were conducted. The MAH demonstrated that the product is similar to the reference product based on chemical-pharmaceutical characteristics. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59 (1) and 59(3) and 63(2) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The test contained 15 questions and was performed by face-to-face interviews. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. There were no changes made to the PL based on pilot testing. The data show all 15 questions met these passing criteria in the first and second round. Based on quantitative and qualitative results, there were no revisions to the PL after the first and second round of testing.
The results of the test were satisfactory. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zoledroninezuur CF 5 mg/100 ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Aclasta 5 mg solution for infusion. Aclasta is a well-known medicinal product with an established favourable efficacy and safety profile.

Zoledroninezuur CF is a product for intravenous use. Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Zoledroninezuur CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 January 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse