CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zoledroninezuur Synthon 4 mg/5 ml, sterile concentrate Zoledroninezuur Synthon 5 mg, solution for infusion Synthon B.V., the Netherlands

zoledronic acid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2312/001-002/DC
Registration number in the Netherlands: RVG 109522, 109523

1 February 2013

Pharmacotherapeutic group:	bisphosphonates
ATC code:	M05BA08
Route of administration:	intravenous
Therapeutic indication:	prevention of skeletal related events in adult patients with advanced malignancies involving bone; treatment of adult patients with tumour-induced hypercalcaemia (TIH); osteoporosis; Paget's disease of the bone.
Prescription status:	prescription only
Date of authorisation in NL:	7 January 2013
Concerned Member States:	Decentralised procedure with AT, DE, EL, ES, FI, FR, PT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Zoledroninezuur Synthon 4 mg/5 ml, sterile concentrate and Zoledroninezuur Synthon 5 mg, solution for infusion from Synthon B.V. The date of authorisation was on 7 January 2013 in the Netherlands.

The 4 mg/5 ml product 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).

The 5 mg solution for infusion is indicated for:

- osteoporosis in post-menopausal women and in men at increased risk of fracture, including those with recent low-trauma hip fracture.
- osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in 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 SPC.

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. In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zometa 4 mg/5 ml concentrate for solution for infusion and Aclasta 5 mg solution for infusion, registered by Novartis Europharm Limited. Zometa 4 mg/5 ml has been authorised via centralized procedure EU/1/01/176 since 20 March 2001 and Aclasta has been authorised via centralised ¨procedure EU/1/05/308 since 30 March 2010.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Zoledroninezuur Synthon 4 mg/5 ml and 5 mg are products for parenteral use in an aqueous solution, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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, non-hygroscopic powder, which is freely soluble 1N sodium hydroxide, 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 monohydrate exhibits polymorphism; form I is used.

The Active Substance Master File (ASMF) procedure is used for 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
Zoledronic acid is manufactured in three reaction steps. No class I organic solvents or heavy metal catalysts have been 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 specifications of the DMF-holder. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). From the provided stability data no changes or trends are observed at both long-term and accelerated conditions. The claimed retest period of 3 years was granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Zoledroninezuur Synthon 4 mg/5 ml is a clear, colourless solution with pH 6.0-6.6.
The concentrate for solution for infusion is packed in type 1 colourless glass vials with fluoropolymer-coated bromobutyl rubber stopper and aluminium cap with flip-top component.

Zoledroninezuur Synthon 5 mg is a clear, colourless solution with pH 6.2-6.8 in 100 ml water for injection.
The solution for infusion is packed in a transparent plastic (polyolefin film) bag with one port and one connector with a grey rubber membrane.

For both products, the excipients are: mannitol (E421), sodium citrate dihydrate (E331), sodium hydroxide (E524) for pH-adjustment, hydrochloric acid (E507) for pH-adjustment, water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH has shown that the formulations are identical to the products of the innovator. The properties of the solution are also identical. All excipients used are well known and the same as in the reference product. The choices of the packaging and manufacturing process are justified. No overage is used.

Comparative data between the innovator products and proposed formulations were submitted regarding pH, osmolality, impurity profiles, assay and density. The results were considered comparable with the innovator products.

The pharmaceutical development has been described in sufficient detail.

Manufacturing process

Zoledronic acid 4 mg/5 ml sterile concentrate and 5 mg/100 ml solution for infusion are manufactured by compounding, sterile filtration, filling and terminal sterilization.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the products have been presented for three pilot-scale batches of each product. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorization.

Control of excipients

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

Quality control of drug product

The product specification includes tests for appearance, identification, pH, osmolality, particulate contamination, extractable volume, water loss, assay, related substances, sterility and bacterial endotoxins.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 pilot-scale batches, demonstrating compliance with the release specifications.

Stability of drug product

Concentrate

Stability data on the product have been provided for three pilot-scale batches stored at 25°C/60% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type I glass vials with type I bromobutyl rubber stopper, sealed with aluminium flip off seals.

Stability results showed that no significant changes or trends occur in the parameters tested. A photo-stability study was conducted according to the ICH Q1B guideline. The results showed no changes or trends in any of the parameters tested.

The proposed shelf-life of 24 months without specific storage condition was granted.

Solution for infusion

Stability data on the product have been provided for three pilot-scale batches stored at 25°C/60% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in infusion bags.

Stability results showed that no significant changes or trends occur in the parameters tested. A photo-stability study was conducted according to the ICH Q1B guideline. The results showed no changes or trends in any of the parameters tested.

The proposed shelf-life of 24 months and the storage condition “store below 25 °C” are justified.

Compatibility/In-use stability

Concentrate

To avoid potential incompatibilities, zoledronic acid 4 mg/ 5 ml, sterile concentrate is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. No incompatibility is observed when zoledronic acid 4 mg/ 5 ml, concentrate for solution for infusion is diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. In-use stability is 24 hours at 2°C – 8°C.

Solution for infusion
The drug product must not be allowed to come into contact with any calcium-containing solutions. Additional compatibility studies are not required, the finished product is used as it is.

The compatibility/in-use stability recommendations are in conformity with the recommendations in the SmPCs of the innovator.

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.2 Non-clinical aspects

These products are generic formulations of Zometa and Aclasta, which are available on the European market. 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 Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of zoledronic acid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 Board agreed that no further clinical studies are required.

Zoledroninezuur Synthon 4 mg/5 ml, sterile concentrate and Zoledroninezuur Synthon 5 mg, solution for infusion are parenteral formulations and therefore fulfil 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 Synthon 4 mg/5 ml and 5 mg 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 products can be used instead of their reference product.

Risk management plan
Zoledronic acid was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of zoledronic acid can be considered to be well established. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Additionally, the following pharmacovigilance activities are laid down in the Risk management plan:

- Targeted follow-up of all serious spontaneous and post marketing surveillance reports regarding the following important identified risks: atypical femoral fracture, renal function impairment, osteonecrosis of the jaw, ocular adverse events, atrial fibrillation
- Targeted follow-up of all serious spontaneous and post marketing surveillance reports regarding the following important potential risks: cardiac arrhythmias and cerebrovascular adverse events.

Product information

SPC
The content of the SPCs approved during the decentralised procedure is in accordance with those accepted for the reference products Zometa and Aclasta.

Readability test
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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The test was performed in English.
The developed questionnaire contained 15 questions addressing the key safety issues and presentation of information. In formulating the questions, firstly all the key safety messages in the PIL were identified and then questions were designed around those issues that would ensure a patient's comprehension and ability to act upon.
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.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zoledroninezuur Synthon 4 mg/5 ml, sterile concentrate and Zoledroninezuur Synthon 5 mg, solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Zometa 4 mg/5 ml concentrate for solution for infusion and Aclasta 5 mg solution for infusion. Zometa and Aclasta are well-known medicinal products with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Synthon 4 mg/5 ml and 5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 May 2012. Zoledroninezuur Synthon 4 mg/5 ml, sterile concentrate and Zoledroninezuur Synthon 5 mg, solution for infusion were authorised in the Netherlands on 7 January 2013.

The date for the first renewal will be: 31 July 2016.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the ongoing stability studies. The results at least up to the shelf life will be provided.

Pharmacovigilance

- The MAH committed to follow the PSUR cycle of the innovator product, which is in a 1-yearly PSUR cycle. The first PSUR will cover the period from approval until the DLP for Zometa of 31 August 2013. Furthermore, in line with the reference product, the MAH will:
    - closely monitor cases of osteonecrosis of the jaw (ONJ), using the official MedDra SMQ for Osteonecrosis (broad search)
    - closely monitor and comment, in a specific PSUR section, all the cases of ONJ when zoledronic acid is co- administered with anti-angiogenic drugs
    - report and assess, all the cases of ONJ involving sunitinib and bevacizumab, both as suspected and/or as concomitant drug, in order to avoid missing cases.
    - evaluate the quality and the clinical effect of ONJ educational activities directed towards patients and health care providers in forthcoming PSURs.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached