CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zoledroninezuur SUN 5 mg, solution for infusion
Sun Pharmaceutical Industries Europe 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/2646/001/DC
Registration number in the Netherlands: RVG 111818

30 July 2013

Pharmacotherapeutic group:	bisphosphonates
ATC code:	M05BA08
Route of administration:	intravenous
Therapeutic indication:	osteoporosis in post-menopausal women and in men at increased risk of fracture; osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture; Paget's disease of the bone in adults.
Prescription status:	prescription only
Date of authorisation in NL:	23 July 2013
Concerned Member States:	Decentralised procedure with DE, DK, ES, FI, FR, IT, NO, SE, 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 SUN 5 mg, solution for infusion from Sun Pharmaceutical Industries Europe B.V. The date of authorisation was on 23 July 2013 in the Netherlands.

The product 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 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 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 Sun 5 mg is a product for parenteral use in an aqueous solution, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product 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 this product 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.*). It is a white to almost white, crystalline powder, which is slightly soluble in water. The active substance is used in polymorphic Form I and does not show stereochemistry.

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
The manufacturing of zoledronic acid monohydrate consists of three steps. No class 1 organic solvents are used. The proposed starting materials are acceptable. For all raw materials adequate specifications have been laid down to guarantee an adequate quality of the drug substance.

Quality control of drug substance
The drug substance specification has been established in-house. The specification is considered acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). Based on the data provided, a retest period of 5 years is justified. No special storage condition is required.

** 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 SUN 5 mg is a clear and colourless solution with a pH between 6.00 to 7.00 and an osmolarity between 260 to 340 mOsm/kg.
The solution for infusion is packed in a 100 ml colourless type-I glass vial with grey chlorobutyl rubber stopper, sealed with flip off aluminium seal.

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

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim was to develop a generic product that would be pharmaceutically equivalent to the innovator. The main development studies performed were compatibility studies and container closure system studies. The choices of the packaging and manufacturing process are justified.

Comparative data between the innovator products and proposed formulations were submitted regarding appearance, pH, absorbance, transmittance, osmolality, related substances, assay of zoledronic acid and buffer capacity. The results were considered comparable with the innovator products.
The product is sterilized by terminal sterilization. This method is justified, as it is in line with the Ph.Eur.
No drug substance overage is included. An overfill is used in the drug product to compensate for the amount of solution which remains in the container closure system. The overfill is acceptable, since the drug product complies with the requirements for extractable volume of the Ph.Eur. at release.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: preparation of the bulk solution, filtration, filling and terminal sterilisation by steam sterilisation.
Satisfactory process validation data on the product has been provided for three full-scale batches.
The product is manufactured using conventional manufacturing techniques. The proposed holding times between the subsequent individual production steps have been adequately justified.

Control of excipients
The excipients comply with Ph.Eur. These specifications are acceptable.

Microbiological attributes
The drug product contains no antimicrobial preservative. Container closure integrity was tested by testing sterility according to the Ph.Eur. in the final primary packaging and by microbial challenge testing. Based on the results it was concluded that the container closure system adequately protects the drug product.

Quality control of drug product
The product specification includes tests for appearance, identification of zoledronic acid and mannitol, pH, extractable volume, volume variation, absorbance, transmittance, osmolality, particulate matter, bacterial endotoxins, sterility, related substances and assay of zoledronic acid and mannitol.
The release and shelf-life limits are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided of three full-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 clear, colourless siliconised glass (type I) vials with rubber (type I) stopper in upright and inverted orientation.
The assay values showed some variability at accelerated conditions, but were relatively stable at long-term conditions. All other parameters tested remained relatively stable. All results remained within specification limits. The drug product was shown to be photostable.
Based on the results of the stability data provided, a shelf life of 24 months without special storage conditions was granted. Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°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.2 Non-clinical aspects

This product is a generic formulation of Aclasta, which is 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 member states 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 SUN 5 mg, solution for infusion is a parenteral 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 SUN 5 mg is 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.

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 MAH provided the (abbreviated core) Risk Management Plan for bisphosphonates as agreed by the Pharmacovigilance Working Party. The MAH should submit a proposal for the (national) educational pack targeting all physicians who are expected to prescribe/use zoledronic acid, including the Presciber Guide, and the educational material for patients, in each member state post approval. Prior to distribution of the prescriber guide, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product 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 was conducted with 20 participants. The overall test is considered insufficient. However, as the content of the package leaflet is harmonised with that of the innovator Aclasta, the most important goal of this user test was testing the lay-out of the leaflet. Considering participants generally did not have difficulty to find the information requested and considering the positive comments on the lay-out given by the participants at the end of the questionnaire, the lay-out meets the criteria.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zoledroninezuur SUN 5 mg, solution for infusion has a proven chemical-pharmaceutical quality and is a generic forms of Aclasta 5 mg solution for infusion. Aclasta is a well-known medicinal product 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 SUN 5 mg, solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 7 May 2013. Zoledroninezuur SUN 5 mg, solution for infusion is authorised in the Netherlands on 23 July 2013.

The date for the first renewal will be: 7 May 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the on-going long term studies up to 36 months.

Risk management plan

- The MAH committed to market the product after approval of educational materials by the National Competent Authority. For the educational material, the identical wording will be used in the Prescribers Guide as agreed by the national authorities for the Prescribers Guide of the reference product.

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