CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6ml, concentrate for solution for infusion Ibandroninezuur Teva 3 mg/3 ml, solution for injection Teva Nederland B.V., the Netherlands

ibandronic 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/2124/001-003/DC
Registration number in the Netherlands: RVG 108319-108321

26 September 2012

Pharmacotherapeutic group:	bisphosphonates
ATC code:	M05BA06
Route of administration:	intravenous
Therapeutic indication:	2 & 6 mg: 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. 3 mg: treatment of osteoporosis in postmenopausal women at increased risk of fracture; a reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.
Prescription status:	prescription only
Date of authorisation in NL:	3 September 2012
Concerned Member States:	Decentralised procedure with: 2 & 6 mg - DE, IT, HU, LU, PL, RO, UK 3 mg - AT, BE, CZ, DE, IT, HU, LU, PL, RO, SK, 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 Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion, and Ibandroninezuur Teva 3 mg/3 ml solution for injection from Teva Nederland B.V. The date of authorisation was on 3 September 2012 in the Netherlands.

The 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion is 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 3 mg/3 ml solution for injection is indicated for:

- treatment of osteoporosis in postmenopausal women at increased risk of fracture.

A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

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

Ibandronate is a nitrogen-containing bisphosphonate in the same class as alendronate and risedronate. Ibandronate inhibits osteoclast-mediated bone resorption. All of the bisphosphonates prevent the breakdown of bone by bone cells called osteoclasts. In persons who are at high risk for osteoporosis, bisphosphonates not only result in increased amounts of bone and bone strength, they also reduce the risk of fractures.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Bondronat 2 and 6 mg concentrate for solution for infusion (MAH Roche Registration Limited, centralised procedure EU/1/96/012/004) and Bonviva 3 mg solution for injection (MAH Roche Registration Limited, centralised procedure EU/1/03/265/005). The reference product is Bondronat 1 mg/ml concentrate for solution for infusion (MAH Roche Registration Limited; EU/1/96/012/001; authorized 25 June 1996).

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 Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection are products for parenteral use, they 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 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 ibandronate sodium monohydrate, an established active substance however not described in the European or US Pharmacopoeia (Ph.Eur., USP*). It is a white to off-white powder, which is soluble in water, and practically insoluble in ethanol, acetone, tetrahydrofuran and acetonitrile. The active substance is used in polymorphic form B. The active substance shows no stereochemistry.

The Active Substance Master File (ASMF) procedure is used for the active substance by both suppliers. 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 processes of both suppliers are comparable. Sufficient information has been provided on the synthesis. No class 1 organic solvents are used. The starting material is 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 by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. The drug substance specification adequately covers the drug substance of both suppliers. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three pilot-scale batches of both suppliers.

Stability of drug substance
For one supplier, stability data on the active substance have been provided for four 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
For the second active substance manufacturer, stability data have been provided for three pilot-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Based on the data provided, a retest period of 30 months is justified. The proposed storage condition 'Store in the original container' is acceptable.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml are clear, colourless solutions. pH of the undiluted product is 4.9-5.5.

One vial with 2 ml concentrate for solution for infusion contains 2 mg ibandronic acid (as 2.25 mg ibandronic acid, monosodium salt, monohydrate).
One vial with 6 ml concentrate for solution for infusion contains 6 mg ibandronic acid, (as 6.75 mg ibandronic acid monosodium salt, monohydrate)
One ml concentrate for solution for infusion contains 1 mg ibandronic acid (as 1.13 mg ibandronic acid, monosodium salt, monohydrate).

The concentrate for solution for infusion is packed in a clear, colourless vials. The vials are closed with a rubber stopper. Two ml vials have an orange flip-off cap while 6 ml vials have a turquoise (greenish blue) flip-off cap.

Ibandroninezuur Teva 3 mg/3 ml is a clear, colourless solution. The pH of the solution is 4.9-5.5.
One pre-filled syringe of 3 ml solution for injection contains 3 mg ibandronic acid (as 3.375 mg ibandronic acid, monosodium salt, monohydrate). The syringe is made of colourless type I glass. The concentration of ibandronic acid in the solution for injection is 1 mg per ml.

The excipients for all strengths are: sodium chloride, sodium hydroxide (E524) (for pH adjustment), glacial acetic acid (E260), sodium acetate trihydrate, water for injections.

The different strengths are fully dose proportional (1 mg/ml solution). The strengths are distinguishable by presentation (i.e. vials and syringe) and colour of the flip-top.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies and container closure system studies. The aim of the development work was to develop a generic product with a formulation as close to the innovators (Bondronat and Bonviva) as possible, however the pH was targeted closer to the physiological pH of blood than the innovators. The pH of the innovator products is 4 and the targeted pH of this product is 5. The drug products are terminally sterilised at Ph.Eur. conditions for steam sterilisation. The drug product contains no antimicrobial preservative. Requirements are laid down for sterility and bacterial endotoxins for the drug product at release. The MAH has adequately justified the difference in pH between the drug product (pH 5) and the innovator product (pH 4). The osmolality of the drug product is about 296 mosmol/kg. The density of the solution is 1.004 g/ml. No formula overage is included in the product. An overfill of 0.2 ml is used for the vials and an overfill of 0.1 ml is used for the syringe to compensate for the amount of solution which remains attached to the glass wall of the container. The extractable volume was tested during process validation. The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing process is divided into the following steps: preparation of the bulk solution, filtration, filling and terminal sterilisation by autoclavation. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data of the product has been presented for three production-scale batches of each strength. Process validation for larger batches sizes will be performed post authorisation. The product is manufactured using conventional manufacturing techniques. The proposed maximum total holding time has been adequately justified.

Excipients
The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, pH, extractable volume, particulate matter, identification, assay, related substances, sterility and bacterial endotoxins. The release and shelf-life limits differ with regard to pH and total impurities. The drug product specification is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided of three production-scale batches of 2 mg vials, one production-scale batch of 6 mg vials and of five production-scale batches of 3 mg pre-filled syringes 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 glass (type I) vials with rubber (type I) stopper with fluoropolyme coating (2 mg and 6 mg) and in clear, colourless glass (type I) syringes with rubber stopper (type I) with and without fluoropolyme coating, rubber (type II) luer tip and silicone lubricant (3 mg).
In the vials (2 mg and 6 mg) an increase was observed for single unknown impurity and total impurities. In the pre-filled syringes lower values in the assay were observed after 6 months. This was due to an incorrectly assigned value of a reference standard. Photostability of the products has been demonstrated.
Based on the stability data provided, the proposed shelf life of 24 months without special storage conditions was granted.

In-use stability
Stability data have been provided demonstrating that the product remains stable for 24 hours following dilution with 0.9% NaCl or 5% glucose, when stored 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 Bondronat and Bonviva, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 ibandronic 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

Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection 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 Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection 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
Ibandronic acid was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ibandronic acid can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are

sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The product information is fully in line with the product information of the innovator products Bondronat and Bonviva and the current QRD-template.

Readability test
In the absence of user test results of the PL of Ibandronic acid, concentrate for solution for infusion and Ibandronic acid, solution for injection, the MAH submitted bridging reports in order to refer to the user test results from the PL of Ibandronic acid 50 & 150 mg film-coated tablets. The bridging reports present the differences between the PLs and discuss their impact on the readability. Regarding content, it should be noted that the intravenous forms are administered in a hospital setting by healthcare professionals. Furthermore, the content of the leaflets is harmonised with that of the innovators Bondronat and Bonviva. The lay out and style of the PL of the film-coated tablets is the same as the lay out and style of the PL of the intravenous pharmaceutical forms. Therefore, bridging of the user test results from the oral pharmaceutical form to the intravenous pharmaceutical form is considered justified.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Bondronat and Bonviva. Bondronat and Bonviva 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 Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 December 2011. Ibandroninezuur Teva 2 mg/2 ml and 6 mg/6 ml concentrate for solution for infusion and Ibandroninezuur Teva 3 mg/3 ml solution for injection were authorised in the Netherlands on 3 September 2012.

The date for the first renewal will be 25 May 2016.

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

<u>Quality - active substance</u>

- The MAH committed to continue the long term testing for up to 3 years to cover the desired retest period of 3 years.
- The MAH committed to incorporate at least one production-scale batch of Ibandronate sodium monohydrate drug substance per year (unless none is produced) in the stability monitoring program under the long term storage conditions, using the specifications current at the time.

<u>Quality - medicinal product</u>

- The MAH committed to validate the bulk solution, if produced, using a comparable protocol to those already used for the previous validations.
- The MAH committed to provide analytical data of full-scale batches once these are produced.
- The MAH committed to test large scale production batches in a yearly stability program under real time conditions.
- The MAH committed to continue on-going stability studies up to 36 months.

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