CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ibandroninezuur Mylan 150 mg film-coated tablets
Mylan 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/1446/001/DC
Registration number in the Netherlands: RVG 102935

18 August 2010

Pharmacotherapeutic group:	drugs affecting bone structure and mineralization; bisphosphonates
ATC code:	M05BA06
Route of administration:	oral
Therapeutic indication:	osteoporosis in postmenopausal women at increased risk of fracture
Prescription status:	prescription only
Date of authorisation in NL:	14 June 2010
Concerned Member States:	Decentralised procedure with BE, BG, CY, CZ, DK, EL, ES, FI, FR, HU, IE, IT, MT, PL, PT, RO, SI, 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 Mylan 150 mg film-coated tablets, from Mylan B.V. The date of authorisation was on 14 June 2010 in the Netherlands.

The product 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.

Ibandronic acid is a potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Bonviva 150 mg film-coated tablets. As required by Art. 10(1), the product is a generic of a reference medicinal product which has been authorised under Art. 6 for no less than 10 years in the Community. Bonviva 150 mg film-coated tablets belongs to the same global marketing authorisation as Bondronat concentrate for infusion as per Directive 2001/83/EC Article 6, paragraph 1. Art. 6 requires that *when a medicinal product has been granted an initial marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be (...) included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same marketing authorisation, in particular for the purposes of Article 10(1)*.

Bondronat concentrate for infusion has been registered in Europe through centralised procedure EU/1/03/265/003/004 by Roche Registration Ltd. since 25 June 1996.
Art. 6(1) provides for the notion of global marketing authorisation and is designed to reflect the fact that new versions of an original medicinal product form part of the same marketing authorisation for the purpose of assessing data exclusivity. Therefore, Bonviva is a new version of Bondronat (which has been approved for more than 10 years) and does not benefit from a new period of exclusivity, and the application for Ibandroninezuur Mylan 150 mg film-coated tablets meets the requirements of Article 6 and 10(1).

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. 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. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Bonviva 150 mg film-coated tablets, registered in the European Union. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic 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 not described in the European, British or US Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder, freely soluble in water and 0.1N sodium hydroxide. The drug substance has three known polymorphic forms. During the manufacturing process, only one polymorphic form is formed.

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 process consists of 4 stages, in which different intermediates are formed finally resulting in the drug substance. No class 1 solvents are used in the manufacture; the by-products are adequately controlled. No heavy metal catalysts are used during the manufacturing process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

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. Batch analytical data demonstrating compliance with the drug substance specification have been provided on four full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided on 6 full-scale batches stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes are seen under both conditions; the proposed retest period of 12 months without any special storage requirements could therefore be granted.

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

Medicinal Product

Composition
Ibandroninezuur Mylan 150 mg is a white, film-coated, capsule-shaped, biconvex tablet marked "I-150" on one side and "G" on the other side.

The film-coated tablets are packed in OPA-Al-PVC/Al blisters.

The excipients are:
Core – lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate.
Coating – hydroxypropylcellulose, macrogol 3350, macrogol 400, titanium dioxide.

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 in respect to optimizing the tablet compression method and the coating process. The choices of the packaging and manufacturing process are justified.
During the development process, dissolution profiles were used for *in vitro* comparisons and for optimizing the manufacturing process. Dissolution testing in different media showed no significant differences in release profiles. The physical characteristics of two UK brand leader samples and one NL brand leader sample have been determined and compared in order to verify that the originator product is identical across Europe. Physical characteristics were shown to be comparable. Comparative dissolution profiles have been provided, demonstrating a similar dissolution profile to the UK and NL batches.
Products containing bisphosphonates are known for their potential of causing oesophageal irritation. Therefore it is considered to be important that the tablet dimensions and coating are similar to the originator product. These parameters are considered to be sufficiently comparable to the originator Bonviva.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process mainly consists of blending the tablet components, compressing the blend into tablets, film-coating the tablets and finally packaging the tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 1 laboratory-scale and 2 pilot-scale batches. The product is manufactured using conventional manufacturing techniques. Process validation on three consecutive production-scale batches will be performed post authorisation.

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

Quality control of drug product
The product specification includes tests for appearance, dimensions, identity, uniformity of dosage units, assay, residual solvents, disintegration, dissolution, water content, related substances and microbial limits. The shelf-life limits are similar to the release limits with the exception of water content, for which the limit is wider at the end of shelf-life. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches, demonstrating compliance with the release specification. The MAH committed to submit batch analysis data on the first three consecutive production batches when available.

Stability of drug product
Stability data on the product has been provided on two pilot scale batches stored at 25°C/60% RH (12 months and 24 months respectively) and at 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 OPA-Al-PVC/Al-blisters. No changes are seen at both conditions. The proposed shelf-life of 24 months without additional storage requirements was granted.
The MAH committed to performing process validation studies on the first three production-scale batches of ibandronic acid 150 mg film-coated tablets in line with the NfG on Process Validation. In addition, the MAH committed to perform a blend hold time study on ibandronic acid 150 mg to confirm the proposed hold time of 6 months for the bulk blend.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

With the exception of lactose monohydrate no excipients of human or animal origin are used. Lactose monohydrate is derived from bovine milk sourced from healthy animals in the same conditions as milk collected for human consumption and is manufactured in compliance with the NfG on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. Magnesium stearate is derived from material of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Bonviva 150 mg, which is 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

Ibandronic acid is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ibandroninezuur Mylan 150 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Bonviva 150 mg film-coated tablets (Roche Registration Ltd, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study is justified, since the product has been registered through the centralised procedure and is considered identical throughout Europe.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 104 healthy male and non-childbearing female subjects, aged 20-60 years. Each subject received a single dose (150 mg) of one of the 2 ibandronic acid formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours. Except for water given with the study medication, no fluids were allowed from 1 hour before dosing until 1 hour post dose. Meal plans were identical for both periods. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.125, 0.5, 0.75, 1, 1.333, 1.667, 2, 3, 4, 5, 9, 12, 24, 48, 72 and 96 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Three subjects did not show up for study participation in period 2. One subject withdrew from the study following the 72 hour blood draw in period 2 due to personal commitments. 100 volunteers completed the two study periods and were used for statistical analyses as per protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibandronic acid under fasted conditions.

Treatment N=100	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	538 ± 350	565 ± 370	126 ± 100	1.179 (0.5-4.0)	34.9 ± 8.3
Reference	541 ± 424	571 ± 445	121 ± 106	1.0 (0.4-4.1)	34.9 ± 7.9
***Ratio (90% CI)**	1.04 (0.94-1.14)	1.04 (0.95-1.15)	1.08 (0.96-1.21)	-	-
CV (%)	42.7	42.5	51.1	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of ibandronic acid under fasted conditions, it can be concluded that Ibandroninezuur Mylan 150 mg and Bonviva 150 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The bioequivalence study was conducted under fasted conditions. This is considered acceptable since both the test and reference formulations are immediate release tablets and ibandronic acid should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water). The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 post authorisation 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

Readability test

The MAH did not perform a user consultation study on the proposed package leaflet. A bridging report was provided using the user tested parent leaflet for Alendronic Acid 70 mg tablets (Pliva Pharma Ltd.). The proposed PIL is considered to be a daughter leaflet of Alendronic Acid 70 mg tablets that is considered to be the parent leaflet for this class of substances.
The user test report for Alendronic Acid 70 mg tablets has been assessed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and has been approved. The MAH performed a bridging study to show that target patient population, key safety messages, design and layout issues and content issues are similar in both the parent and daughter PIL. This comparison is made according to a MHRA guidance document. Readability of the PIL at issue has been sufficiently demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibandroninezuur Mylan 150 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Bonviva 150 mg. Bonviva is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ibandronic acid containing products.

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 Mylan 150 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 July 2009. Ibandroninezuur Mylan 150 mg film-coated tablets was authorised in the Netherlands on 14 June 2010.

The first PSUR will cover the period from July 2009 to the date of the first renewal, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 24 February 2012.

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

Quality - medicinal product

- The MAH committed to submit batch analysis data on the first three consecutive production batches when available.
- The MAH committed to place the first three production batches on long term stability studies throughout the proposed shelf life and on accelerated studies for 6 months.
- The MAH committed to performing process validation studies on the first three production-scale batches of ibandronic acid 150 mg film-coated tablets in line with the NfG on Process Validation.
- The MAH committed to perform a blend hold time study on ibandronic acid 150 mg to confirm the proposed hold time of 6 months for the bulk blend.

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
MHRA	Medicines and Healthcare products Regulatory Agency
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