COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibandroninezuur Sandoz 150 mg, film-coated tablets

(ibandronate sodium monohydrate)

NL/H/4472/001/DC

Date: 12 June 2018

This module reflects the scientific discussion for the approval of Ibandroninezuur Sandoz 150 mg, film-coated tablets. The procedure was finalised at 14 July 2010. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ibandroninezuur Sandoz 150 mg, film-coated tablets, from Sandoz B.V..

The product is indicated for:
Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see SmPC section 5.1).
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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Bonviva 150 mg film-coated tablets which has been registered in the EEA since 15 September 2005. The originator product for this application is Bondronat 5 mg/ml concentrate for infusion, which was granted a licence on 25 June 1996 by the Centralised Procedure to Roche Registrations Limited (EU/1/03/265).

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Germany, Spain, Italy, Portugal, Romania, Slovakia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibandroninezuur Sandoz is a white, round biconvex film-coated tablet.

Each film-coated tablet contains 150 mg ibandronic acid, as ibandronate sodium monohydrate.

The film-coated tablets are packed in (PA/Aluminium/PVC-Aluminium) foil blisters (alu-alu blisters).

The excipients are:
Tablet core – povidone, cellulose microcrystalline, maize starch pregelatinised, crospovidone, colloidal anhydrous silica and glycerol dibehenate.

Tablet coat – Opadry OY-LS-28908 (White II) consisting of: hypromellose, lactose monohydrate, titanium dioxide (E171) and macrogol 4000.

II.2 Drug Substance

The active substance is ibandronate sodium monohydrate, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Ibandronate sodium monohydrate is a white to almost white crystalline powder, sparingly soluble in water, with no chiral centres and exhibiting polymorphism.

Manufacturing process

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Quality control of drug substance

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Stability of drug substance

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The objective of the development programme was to formulate robust, stable tablets containing 150 mg ibandronic acid that could be considered as generic medicinal products of Bonviva 150 mg film-coated tablets (Roche Registrations Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator product.

Manufacturing process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of excipients
The specifications are acceptable.

Quality control of drug product
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of drug product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The date from these studies support a shelf-life of two years, with no special storage conditions.

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 Ibandroninezuur Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibandronic acid are well known, no new non-clinical studies are required and none have been provided.

The MAH's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibandronic 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.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a randomised, single-dose, two-period, two-sequence, crossover, single-centre bioequivalence study in which the pharmacokinetic profile of the test product Ibandroninezuur Sandoz 150 mg, film-coated tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Bonviva 150 mg film-coated tablets (Roche Registration Limited, Greece) in healthy adult volunteers under fasted conditions.

Bioequivalence studies

Design

All volunteers received the allocated drug after an overnight fast. Blood samples were waken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least four weeks.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD,) of ibandronic acid under fasted conditions.

Treatment	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)
Test	253.67	267.88	60.04
Reference	230.46	244.09	62.42
***Ratio (90% CI)**	1.07 (0.92 – 1.23)	1.06 (0.92 – 1.23)	0.98 (0.84 – 1.55)

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals for AUC and Cmax for the test versus reference product are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Thus, the data support the claim that the test product is bioequivalent to the reference product. As the Greek and Dutch versions of Bonviva 150 mg film-coated tablets can be considered to be identical, bioequivalence has been shown between the test product and the reference product (Bonviva 150 mg film-coated tablets).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for these applications.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. During the bioequivalence study gastrointestinal side effects were observed following administration of the test product and reference product in both treatment periods. The gastrointestinal side-effects experienced are recognised averse effects of the active substance ibandronate and are all reported as common in the reference product SmPC. There were no withdrawals due to adverse events and no serious events were recorded during the study.

IV.6 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PL), Labels

The SmPC, PL and labels are medically acceptable. The SmPC is consistent with that for the originator product. The PL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

IV.7 Clinical expert report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

IV.8 Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

IV.9 Discussion on the clinical aspects

There are no objections to the approval of these applications from a clinical viewpoint.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality
The important quality characteristics of Ibandroninezuur Sandoz 150 mg, film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding issues that would have a negative impact on the benefit-risk balance.

Non-clinical
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of ibandronic acid are well known.

Efficacy
Bioequivalence has been demonstrated between the Ibandroninezuur Sandoz 150 mg, film-coated tablets and the reference product Bonviva 150 mg film-coated tablets.

No other clinical data have been submitted with the application and none are required.

Safety

During the bioequivalence study, gastrointestinal side effects were observed following administration of the test product and reference product in both treatment periods. The gastrointestinal side-effects experienced are recognised adverse effects of the active substance ibandronate and are all reported as common in the reference product SmPC. There were no withdrawals due to adverse events and no serious adverse events were recorded during the study.

No new or unexpected safety concerns arise from these applications.

Product literature

The SmPC, PL and labelling are satisfactory and consistent with that for the reference products.

Benefit-risk assessment

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the MAH's product and the originator product are interchangeable. Extensive clinical experience with risedronate sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

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
UK/H3375/IB/001/G	Change in the name of the product for nationally authorised products Introduction of a new pharmacovigilance system which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH		9-11-2011	Approval	
UK/H/3375/IA/002/G	Addition of primary and secondary packagers		1-2-2011	Partially approved	
UK/H/3375/IA/003/G	Addition of batch release and batch control testing sites		18-7-2011	Approval	
UK/H/3375/1/IB/005	Registration of a replacement DDPS as a consequence of MA transfer		10-10-2011	Approval	
UK/H/3375/1/IB/004	Change outside the range of currently approved pack sizes	SmPC	4-10-2011	Approval	
UK/H/3375/1/IB/006	Update SmPC and PL in line with the article 31 referral	SmPC and PL	14-11-2014	Approval	
UK/H/3375/IB/007	To update the DMF with amending the active substance specification by loewering the limit of phosphite content from 0.50% to 0.30%, adding another test method for identification: other updates include extending the retest period from 24 to 48 months: changing the address of the administrative site and finally making		27-1-2012	Approval	

	some editorial changes.				
UK/H/3375 /IB/009/G	Implementation of change(s) for which no new additional data are submitted by the MAH	SmPC and PL	28-6-2012	Approval	
UK/H/3375 /1/IA/010	To register the introduction or change of the Pharmacovigilance System Master File (PSMF). Consequently description of the pharmacovigilance system has been updated		17-1-2013	Approval	
UK/H/3375 /IA/011/G	To register an increased batch size of the active substance Minor changes to an approved test procedure		17-5-2013	Approval	
UK/H/3375 /1/IB/012	Implementation of change(s) for which no new additional data are submitted by the MAH.		20-2-2014	Approval	
UK/H/3375 /IB/013/G	To add a manufacturing site of the bulk product, batch releaser including batch control/testing, primary and secondary packager for the finished product due to commercial reasons. The manufacturing process, the batch size and the quality of the finished product remain the same.	PL	10-6-2013	Approval	
UK/H/3375 /001/II/01 4	Introduction of a new manufacturer of the active substance that is supported by an ASMF		7-8-2013	Approval	
UK/H/3375 /001/IB/01	Implementation of change(s) for which		7-11-2014	Approval	

5	no new additional data are submitted by the MAH.				
UK/H/3375/IB/017/G	Change in the name and/or address of a manufacturer Addition of a new specification parameters to the specification with its corresponding test method		17-9-2014	Approval	
UK/H/3375/001/IA/018	Deletion of primary and secondary packaging site		2-10-2015	Approval	
UK/H/3375/001/IB/019	Other variation	SmPC and PL	1-12-2015	Approval	
UK/H/3375/001/IB/020	Implementation of change(s) for which no new additional data are submitted by the MAH.	SmPC and PL	18-3-2016	Approval	
UK/H/3375/001/IA/021	Implementation of wording agreed by the competent authority	SmPC and PL	3-8-2016	Approval	
UK/H/3375/001/R/001	Renewal		12-1-2018	Approval	
UK/H/3375/001/IA/022	Implementation of wording agreed by the competent authority	SmPC and PL	10-10-2016	Approval	
UK/H/3375/IA/449/G	Change of the address in Spain of the MAH		14-4-2017	Approval	