CBG MEB

Public Assessment Report

Scientific discussion

Ibuprofen Sandoz 600 mg, granules for oral solution

(ibuprofen sodium dihydrate)

NL/H/3371/001/DC

Date: 26 January 2017

This module reflects the scientific discussion for the approval of Ibuprofen Sandoz 600 mg, granules for oral solution. The procedure was finalised on 17 December 2015. 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 Ibuprofen Sandoz 600 mg, granules for oral solution from Sandoz B.V.

The product is indicated for:

- Inflammatory joint disorders:
  - rheumatoid arthritis
  - ankylosing spondylitis
- Degenerative joint disorders:
  - osteoarthritis including spondyloarthritis
- Extra-articular disorders:
  - adhesive capsulitis
  - tendovaginitis
  - epicondylitis
  - bursitis
  - synovitis
  - tendinitis
- Postoperative pain, pain after dental or oral surgery
- Primary dysmenorrhoea
- Fever and pain due to influenza and the common cold or after vaccination, tooth ache, headache, muscle pain and rheumatic pain

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 Spidifen 600 mg, granules for oral solution. This European reference product has been registered in Italy by Zambon Italia s.r.l. since 1 June 1993.

The concerned member state (CMS) involved in this procedure was Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Sandoz 600 mg is formulated as white to off-white granules. Each granule contains 768.0 mg sodium dihydrate (equivalent to 600 mg ibuprofen). The content of the sachets is 4.0 g granulate.

The granules for oral solution are packed in paper-polyethylene-aluminium-polyethylene sachets.

The excipients are: sucrose, potassium hydrogen carbonate, sorbitol (E420), orange flavouring (carrier: flavouring preparations and substances, natural flavouring substances, maltodextrin, arabic gum (E414), ascorbic acid (E300) and butylated hydroxyanisole (E320)), mint-liquorice flavouring (carrier: flavouring preparations and substances, natural flavouring substances, maltodextrin, arabic gum (E414), triacetin (E1518)), acesulfame potassium, aspartame (E951), sucralose, colloidal silicon dioxide.

II.2 Drug Substance

The active substance, ibuprofen sodium dihydrate, is not described in the European Pharmacopoeia (Ph.Eur.) or United States Pharmacopoeia. The substance is a salt of the well-known Ph.Eur. described substance ibuprofen. It is a white powder with a soft and soap-like appearance. It contains one chirale centre and is racemic. Polymorphism is not known. The substance is freely soluble in

methanol and ethanol, very slightly soluble in acetone and practically insoluble in water at pH 1 but freely soluble at higher pH values.

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
For the supplier the synthesis is limited to the conversion of ibuprofen to ibuprofen sodium. The quality of the starting material ibuprofen is certified by a Certificate of Suitability of the EDQM. Acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the Ph.Eur. monograph on ibuprofen with additional requirements for sodium, water content and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines stored at 30°C/65%RH (60 months) and 40°C/75%RH (6 months). The stability results show that the active substance is stable at both tested conditions. Based on the data submitted, a retest period could be granted up to 5 years, without specific storage conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form. The development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.
As both the product and reference product are administered as a solution, this application was exempted of a bioequivalence study. A dissolution study has been performed by comparison of the assays of the filtered and unfiltered solution of test and reference product. The filtered and unfiltered test and reference product solutions show similar concentrations of ibuprofen. A non difference between the obtained data has been considered as a positive result. In addition, a comparative impurity profile study has been performed. The results obtained from this study between the test and reference product are considered comparable.

Manufacturing process
The manufacturing process has been validated according to relevant ICH guidelines and consists of pre-granulation, granulation, blending and packaging. The process is adequately described and is considered a standard manufacturing process. Process validation data on the product have been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients
Specifications are provided for all excipients. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH of solution, residual humidity, average mass, uniformity of dosage units, dissolution, identification, content, related substances and microbial quality. Limits in the specification have been justified. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Microbiological attributes
Microbiological studies are performed in compliance with the Ph. Eur. Microbiological characteristics are checked on the first three production batches and subsequently on one batch in a five. The microbiological attributes are checked on the product submitted to stability studies, according to the stability protocol.

Stability of drug product
In accordance with applicable European guidelines, stability data on the product have been provided from two pilot scaled batches stored at 25°C/60%RH (36 months), 30°C/60%RH (12 months) and 40°C/75%RH (6 months). Three recent production scaled batches, stored at 25°C/60%RH (18 months), 30°C/60%RH (12 months) and 40°C/75%RH (6 months), were included. Out of specification results for appearance of the granules and appearance of solution were observed at accelerated and intermediate storage conditions. All other results remained within limits. Photostability studies were not performed, however, in view of the packaging it is deemed unnecessary. On basis of the data submitted, a shelf life was granted of 36 months. Due to the out of specification results the labelled storage condition 'Do not store above 25°C' is acceptable.

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 Ibuprofen Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ibuprofen Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Spidifen which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen 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, no bioequivalence studies are submitted. The MAH has submitted an argumentation why *in vivo* bioequivalent studies are considered not necessary and requested a biowaiver which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

As Ibuprofen Sandoz 600 mg, granules for oral solution and the reference product Spidifen 600 mg granules for oral solution are both administered as a solution, a bioequivalence study is in general not necessary. Therefore, a biowaiver was requested. To meet the requirements as mentioned in the Appendix II of the "Guideline on Investigation of bioequivalence", for oral solutions the test product should be an aqueous oral solution at time of administration and contain an active substance in the same concentration as an approved oral solution. However if the excipients may affect gastrointestinal transit, absorption or *in vivo* stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers (Appendix III, Section IV.2 Excipients).

Ibuprofen Sandoz and Spidifen have the same pharmaceutical form. Furthermore, they have the same composition in terms of drug substance. Although Ibuprofen Sandoz contains sodium ibuprofen whereas the reference product contains ibuprofen arginine salt, the two products can be considered as containing the same active substance. At the time of administration the pH of the solutions obtained by disintegration of both products are the same (pH 8.0) and the drug substance in the solutions is mostly consisting of ibuprofenate ions.

Dissolution

A dissolution test for the determination of the dissolution rate is not applicable to granules for oral solution. Therefore a dissolution study has been performed by comparison of the assays of the filtered and unfiltered solution of test and reference product. The filtered and unfiltered test and reference product solutions show similar concentrations of ibuprofen. The mean dissolution time for the test product was 30 seconds and for the reference product 98 seconds. The test solution was colourless and opalescent and the reference solution was colourless and clear.

Bioavailability

As Ibuprofen Sandoz contains sorbitol in contrast to the reference product, the bioavailability may be different due to slower absorption in the presence of sorbitol. Therefore, further argumentation to support the biowaiver was submitted: the results of two bioavailability studies performed with other ibuprofen products which contain sorbitol and mannitol (an isomer of sorbitol) versus a reference product that does not contain sorbitol. The test formulations were ibuprofen 200 mg orodispersible tablets and ibuprofen 400 mg orodispersible granules.

The results of these two two-way cross-over studies in healthy volunteers showed that in low amounts sorbitol does not affect the bioavailability of s-ibuprofen. Ibuprofen Sandoz contains a smaller amount of total polyols than the two test products. Therefore, it is considered sufficiently shown that the amount of sorbitol in the Ibuprofen Sandoz granules will not affect the bioavailability in a significant way and the biowaiver can be granted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ibuprofen Sandoz granules for oral suspension.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Cardiovascular and cerebrovascular events (heart failure, myocardial infarction and cerebrovascular accident) - Gastro-intestinal bleeding, ulceration and perforations - Severe skin reactions (Steven-Johnson syndrome, epidermal necrolysis)

	- Interaction with medication that can increase the risk of bleeding - Use during pregnancy and lactation - Medication Overuse Headache (MOH)
Important potential risks	None
Missing information	- Use by Children <12 years of age - Use for > 14 days

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Spidifen. No new clinical studies were conducted. Essential similarity has been shown based on chemical-pharmaceutical data. The pharmacokinetic profile of Ibuprofen Sandoz is not affected by the difference in composition compared to the innovator formulation. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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. A total of 20 questions were asked about all parts of the leaflet and key safety issues were addressed. Three tests rounds were held: one pilot test with 4 participants and two test rounds with 10 participants each. After the pilot round, no amendments were made. After the first test round the layout was amended following comments from participants, although the readability results were good. The report was found to be clear and of good quality. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ibuprofen Sandoz 600 mg, granules for oral solution has a proven chemical-pharmaceutical quality and is a generic form of Spidifen 600 mg granules for oral solution. Spidifen is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for administration as a solution, no bioequivalence study is deemed necessary.

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 Ibuprofen Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 December 2015.

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
Change in the (invented) name of the medicinal product for Nationally Authorised products	NL/H/3371/ 001/IB/001	IB	03-05-2016	02-06-2016	Approved	N
Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/3371/ 001/IA/003	IA	28-04-2016	26-05-2016	Approved	N