COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen Spharma 200 mg and 400 mg soft capsules
(ibuprofen)

NL License RVG: 128503 - 128504

Date: 5 August 2024

This module reflects the scientific discussion for the approval of Ibuprofen Spharma 200 mg and 400 mg soft capsules. The procedure was finalised on 21 February 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ibuprofen Spharma, from Socium Pharma B.V.

This medical product is indicated for the short-term symptomatic treatment of mild to moderate pain such as headache, period pain, dental pain and fever and pain associated with the common cold. The 200 mg product is indicated for adults, adolescents and children from 20 kg body weight (around 6 years old), while the 400 mg product is indicated for: adults, adolescents and children from 40 kg body weight (12 years and older).

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between Ibuprofen Spharma 400 mg and the innovator product Nurofen Fastine Liquid Caps 400 mg, soft capsules, which has been in the Netherlands via national procedure (RVG 105812) since 6 February 2012. The essential similarity is proven between Ibuprofen Spharma 200 mg and the innovator product Nurofen Fastine Liquid Caps 200 mg, soft capsules, which has been in the Netherlands via national procedure (RVG 102120) since 19 April 2010.

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Spharma is a soft capsule.

Ibuprofen Spharma 200 mg is a red, oval, translucent capsule which contains a clear to light-red liquid. The capsule has an approximate length of 13.7 mm and width of 7.7 mm. The capsule contains as active substance 200 mg of ibuprofen.

Ibuprofen Spharma 400 mg is a colourless to light-yellow, oval, translucent capsule which contains a clear, colourless liquid. The capsule has an approximate length of 15.8 mm and width of 9.8 mm. The capsule contains as active substance 400 mg of ibuprofen.

The excipients are:
Filling – macrogol 600 (E1521), potassium hydroxide (E525) and purified water.
Capsule coating – gelatine 160 bloom (E441), liquid sorbitol (partially dehydrated) (E420), Ponceau 4R (E124) (200mg only) and purified water.

The fill of the two capsule strengths are dose proportional.

Ibuprofen Spharma 200 mg soft capsules are packed in PVC/PVdC-Al (polyvinyl chloride/ polyvinylidene chloride-aluminium) blisters. Ibuprofen Spharma 400 mg soft capsules are packed in PVC/PE/PVdC-Al (polyvinyl chloride/polyethelyne/ polyvinylidene chloride-aluminium) blisters. Both the 200 mg and 400 mg blisters are packed in carton boxes.

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a powder and practically insoluble in water. The active substance is racemic and there are no stereochemical issues. The polymorphic form of the drug substance is not relevant as the drug substance is dissolved in the capsule fill.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the CEPs, except for the test for residual solvents regarding one manufacturer. The specification is considered acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer (six total).

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 development was based on the characteristics of the reference product, knowledge from the manufacturing process and the excipients and drug substance characteristics. Compatibility of the excipients with the drug substance is adequately tested and the excipients are comparable to the reference product. The manufacturing process was optimised by a risk assessment approach and several

formulation development studies were performed. The optimal composition and manufacturing process parameters have been adequately investigated.

Manufacturing process

The manufacturing process consists of dispensing, shell preparation, medicament preparation, encapsulation, drying, wiping, inspection and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches of each strength and additionally on two full scaled batches for the 400 mg strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation and protocols have been provided.

Control of excipients

The excipients comply with Ph.Eur. or in-house requirements. 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 description, identification, average fill weight content, uniformity of dosage units, dissolution, related substances, assay, loss on drying and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three pilot scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies are performed at conditions according to the ICH stability guideline. Stability data has been provided on three pilot scaled batches of the 200 mg strength stored at 25°C/60% RH (30 months) and 40°C/75% (6 months). Stability data on three pilot scale batches of the 400 mg strength stored at 25°C/60% RH (36 months) and 40°C/75% (6 months) is provided. Related substances have been determined on two production scale batches stored at 25°C/60% RH at 20 months and 28 months respectively showing compliance with the proposed amended limits for related substances. Photostability studies in line with ICH Q1B have been provided and the drug products were shown to be photostable. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are 'Store below 30 °C. Store in the original package in order to protect from moisture'.

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

Scientific data and/or certificates of suitability issued by the EDQM gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting

Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Ibuprofen Spharma 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 Spharma 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 Nurofen Fastine Liquid Caps 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 MEB 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 MEB agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen Soft Gelatine Capsule 400 mg (Socium Pharma B.V) was compared with the

pharmacokinetic profile of the reference product Nurofen Express 400 mg Liquid Capsule (Reckitt Benckiser Healthcare [UK] Ltd.), United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The *in vitro* dissolution was determined at pH 1.2 (0.1 N HCl), pH 4.5 and pH 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Based on the outcome of the comparative dissolution study, a biowaiver for the lower strength of 200 mg was granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 32 healthy subjects (26 male, 6 female), aged 19 - 41 years. Each subject received a single dose (400 mg) of one of the two ibuprofen formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.42, 0.5, 0.59, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after administration of the products.

The design of the study is acceptable.

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

32 subjects enrolled in the study. Two subjects did not arrive for period 2 due to personal reasons and were lost to follow up. 30 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibuprofen, 400 mg under fasted conditions.

Treatment N=30	**AUC_{0-t} (µg.h/mL)**	**$AUC_{0-\infty}$ (µg.h/mL)**	**C_{max} (µg/mL)**	**t_{max} (h)**
Test	116.42 ± 27.65	118.99 ± 29.39	45.24 ± 10.23	0.67 (0.33- 2.00)
Reference	115.66 ± 27.10	117.64 ± 28.28	46.00 ± 9.56	0.67 (0.33- 2.50)
***Ratio (90% CI)**	1.01 (0.97 – 1.04)	1.01 (0.97 -1.05)	0.98 (0.92 – 1.05)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ibuprofen Spharma 400 mg is considered bioequivalent with Nurofen Express 400 mg.

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).

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 Spharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB 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 Nurofen. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Leidapharm Ibuprofen liquid Caps 200 mg, NL/H/3098/001. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ibuprofen Spharma 200 mg and 400 mg soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Nurofen Fastine Liquid Caps 200 mg and 400 mg soft capsules. Nurofen Fastine Caps 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 Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibuprofen Spharma with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 21 February 2023.

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
Type IA: B.III.1.a.2;	*Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:* *For an active substance* *For a starting material/reagent/intermediate used in the manufacturing process of the active substance* *For an excipient* • *European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.* ○ *Updated certificate from an already approved manufacturer*	No	27-03-2023	Approved	N/A
2x **Type IAin: B.II.b.2.c.1;**	*Change to importer, batch release arrangements and quality control testing of the finished product* • *Replacement or addition of a manufacturer responsible for importation and/or batch release* ○ *Not including batch control/testing*	Yes			
Type IAin: C.I.8.a **Type IB: A.2.b**	*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* *Change in the (invented) name of the medicinal product*	Yes	23-01-2024	Approved	N/A

	• *for Nationally Authorised Products*				
Type IB: C.I.3.a	*Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC* • *Implementation of wording agreed by the competent authority*	Yes	10-05-2024	Approved	N/A
Type IAin: B.II.b.2.c.1	*Change to importer, batch release arrangements and quality control testing of the finished product* • *Replacement or addition of a manufacturer responsible for importation and/or batch release* ○ *Not including batch control/testing*	Yes	27-05-2024	Approved	N/A