COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen Strides 400 mg soft capsules (ibuprofen)

NL/H/5144/002/DC

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Ibuprofen Strides 400 mg soft capsules. The procedure was finalised at 11 April 2022. 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 Strides 400 mg soft capsules, from Strides Pharma (Cyprus) Limited.

The product is indicated for adults, and adolescents with a body weight of 40 kg or more (12 years and above) for short-term symptomatic treatment of:

- mild to moderate pain,
- acute migraine headaches with or without aura,
- fever.

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 Nurofen 400 tablet, coated tablets 400 mg by Reckitt Benckiser Healthcare B.V., registered in the Netherlands since 18 February 1998 (RVG 22100) by national procedure.

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, France, Germany, Italy, Poland, Romania and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Strides is a reddish pink coloured transparent, oval shaped soft gelatine capsule containing clear to pink coloured viscous liquid. It contains as active substance 400 mg of ibuprofen.

The capsules are packed in white opaque PVdC/PVC-aluminium blister packs.

The excipients are:
Capsule filling – macrogol 600 (E1521), potassium hydroxide (E525) and purified water.
Capsule shell – purified water, partially dehydrated sorbitol liquid (E420), gelatine (E441), hydrolysed gelatine, erythrosine (E127), soy lecithin and medium chain triglycerides.

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ibuprofen is a powder and is practically insoluble in water. It is racemic and there are no stereochemical issues. The polymorphic forms of the drug substance are not applicable as it is dissolved in macrogol 600 in the capsule.

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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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 choice of excipients is justified and their functions explained. Two formulation development studies were performed. Moisture migration studies have been performed. Based on assay results, the MAH has implemented additional fill weight during encapsulation. Feasibility trials have been performed to evaluate the physical characteristics of the fill solution and encapsulation parameters. The optimal composition and manufacturing process parameters have been adequately investigated. The choices of packaging and manufacturing process are adequately justified based on the dosage form. Comparative dissolution at three pHs has been studied in support of bioequivalence. The quality control dissolution method has been sufficiently justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by a capsulation process which consists of preparation of the shell and the fill, encapsulation, drying, sorting, wiping, lubrication and inspection. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three minimum scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

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, moisture content, loss on drying of the shell, disintegration time, dissolution, related substances, uniformity on dosage units, assay and microbial limits. Except for related substances, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The evaluated risk concerning the presence of nitrosamine impurities in the drug product was acceptable.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three minimum-scale batches from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three minimum scaled batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. A significant decreasing trend in assay is observed in the accelerated and intermediate stability data. Under long term conditions the capsules remain within specification. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 21 months. The labelled storage conditions are “store below 25°C”.

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

TSE / BSE risk free certificates from the drug substance manufacturer and the excipient manufacturers have been provided, along with two certificates of suitability issued by the EDQM for both gelatines. 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 member states consider that Ibuprofen Strides 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 Strides 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 400 tablet 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, the MAH has performed 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 Strides 400 mg soft capsules (Strides Pharma (Cyprus) Limited, Cyprus) is

compared with the pharmacokinetic profile of the reference product Nurofen Extra Strength 400 mg liquid capsules (Reckitt Benckiser Healthcare (UK) Ltd).

The reference product was deemed as representative for the innovator product (Nurofen 400 tablet). The formula and preparation of the Ibuprofen Strides bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study was carried out under fasted conditions in 36 healthy subjects, aged 22 - 43 years. Each subject received a single dose (400 mg) of one of the two ibuprofen formulations. The capsule was orally administered with 240 ml water after an overnight fast of 10 hours. There were two dosing periods, separated by a washout period of 4 days. Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.33, 03.67, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Ibuprofen may be taken regardless of food intake. From the literature it is known that food does not interact with the absorption of ibuprofen. Therefore, a food interaction study is not deemed necessary. 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 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 samples were handled adequately. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The pharmacokinetic parameters comply with the “Ibuprofen oral use immediate release formulations 200 – 800 mg product-specific bioequivalence guidance” by the EMA.

Results

Two subjects dropped out before the second dosing period of the study as they did not report for the check-in at that time. This left 34 subjects eligible for pharmacokinetic analysis.

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

Treatment N = 34	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	124.3 ± 19.45	127.7 ± 19.84	35.84 ± 11.96	0.83 (0.33 - 4.00)	2.70 (1.76- 5.47)
Reference	122.0 ± 17.37	125.7 ± 17.71	36.60 ± 10.94	0.83 (0.33 - 4.50)	2.66 (1.81 - 4.55)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	--	0.97 (0.87 – 1.09)	--	--
CV (%)	9.8	--	27.8	--	--

$AUC_{0-\infty}$ 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 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation
***** 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 performed bioequivalence study Ibuprofen Strides 400 mg soft capsules is considered bioequivalent with Nurofen Extra Strength 400 mg liquid capsules.

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 Strides.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 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. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 Strides 400 mg soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Nurofen 400 tablet, coated tablets 400 mg. Nurofen 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.

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 Strides with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 April 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A