COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen-natrium Strides 200 mg and 400 mg film-coated tablets

(ibuprofen sodium dihydrate)

NL/H/4769/001-002/DC

Date: 5 October 2020

This module reflects the scientific discussion for the approval of Ibuprofen-natrium Strides. The procedure was finalised on 4 August 2020. 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-natrium Strides 200 mg and 400 mg film-coated tablets from Strides Pharma (Cyprus) Limited.

The product is indicated for Short-term symptomatic treatment of:

- mild to moderate pain, such as headache, menstrual pain, dental pain,
- acute migraine headaches with or without aura (400 mg only),
- fever.

Ibuprofen-natrium Strides is indicated in adults and adolescents from 40 kg body weight (12 years and above).

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 products Nurofen Express 200 mg film-coated tablets, registered in Poland by Reckitt Benckiser since 29 February 2008, and Nurofen Flextin 400 mg coated tablets (NL Licence RVG 100657) registered by Reckitt Benckiser Healthcare B.V. since 29 July 2010 in the Netherlands.

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Germany, Romania, Slovakia and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen-natrium Strides 200 mg is a white to off-white, round shaped, biconvex, film coated tablet plain on both sides. Each film-coated tablet contains ibuprofen sodium dihydrate equivalent to 200 mg ibuprofen.

Ibuprofen-natrium Strides 400 mg is a white to off-white, modified caplet shaped film coated tablet plain on both sides. Each film-coated tablet contains ibuprofen sodium dihydrate equivalent to 400 mg ibuprofen.

The film-coated tablets are packed in Alu/PVC/PVDC blisters.

The excipients are:
Tablet core - lactose monohydrate, sodium lauryl sulphate (E487), crospovidone (E1201), povidone, colloidal hydrated silica, talc (E553b), magnesium stearate (E470b)
Film-coating - hypromellose, lactose monohydrate, macrogol, titanium dioxide (E171), talc, sodium citrate-dihydrate

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is ibuprofen sodium dihydrate, an established active substance however not yet described in the European, British or United States Pharmacopoeia (Ph.Eur., BP, USP). It is a white powder which is soluble in water. It exists as a racemic mixture. Polymorphic study has been performed, demonstrating that there is no change in the polymorphic form.

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 final drug substance ibuprofen sodium dihydrate is manufactured at one manufacturing site, from a starting material which is covered by a CEP. Ibuprofen is classified as the intermediate. A sufficiently detailed description of the manufacturing process and process controls has been provided.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analysis results have been provided on three batches of the ASMF holder and 2 batches from the finished product manufacturer showing compliance.

Stability of drug substance
Two sets of stability data have been provided, one for the former production process (3 batches) and the other for the revised process (3 batches), containing both accelerated (40°C/75% RH) and long term conditions (30°C/65% RH). A retest period of 5 years has been granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described. The applicant has applied the principles of Quality by Design (QbD) in some aspects of the pharmaceutical/manufacturing development. The function of the various excipients has been adequately discussed.
The development of the dissolution method to be used for routine testing of the test product has been adequately discussed and the dissolution conditions are fully justified. The dissolution limit and the biowaiver of strength are acceptable.

Manufacturing process

The manufacturing process has been described into sufficient detail. The manufacturing process is considered as being a standard process and has been validated in accordance with the relevant European guidelines.

Control of excipients

The specifications of the excipients have been derived from BP/Ph.Eur. monographs. This is acceptable. For Opadry Fx special effects FC64F580006 White, test parameters are adopted as per the supplier's specification. 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, water content, uniformity of dosage units by weight variation, dissolution, assay, related substances, residual solvents and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Skip testing on microbiological quality is justified. The analytical methods have been described and validation of the analytical methods has been presented. Batch analysis results are provided showing that the finished product meets the pre-determined specification. The nitrosamine risk evaluation has been provided, no risk for nitrosamines has been identified.

Stability of drug product

Stability data for all strengths of the finished product in the proposed market packs has been provided. To support the claimed shelf life, stability studies (6 months at accelerated 40 ± 2˚C/75 ± 5% RH, and 12 months at long term conditions 25 ± 2˚C/60 ± 5% RH) have been conducted on three batches of each strength of the finished product. The conditions used in the stability studies are according to the ICH stability guideline. Based on these data, a shelf-life of 2 years can be granted. The proposed storage conditions (none) are acceptable in line with the results obtained in the photostability study.

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

The only excipient of animal origin in the formulation is lactose monohydrate. Lactose monohydrate is derived from milk that has been sourced from healthy cows. TSE/BSE free declarations of all excipients have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ibuprofen-natrium 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-natrium 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, 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 sodium 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 a 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-natrium Strides 400 mg (Strides Pharma (Cyprus) Limited, Cyprus) is compared with the pharmacokinetic profile of:

- 2 tablets of reference product B Nurofen Express 256 mg (ibuprofen sodium) film-coated tablets (Reckitt Benckiser (Poland) S.A., Poland)
- 2 tablets of reference product C Nurofen 200 mg (ibuprofen) film-coated tablets (Reckitt Benckiser (Poland) S.A., Poland)

The choice of the reference products in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Both strengths are manufactured by the same process and the composition of the different strengths is qualitatively and quantitatively the same. The linearity of pharmacokinetics in the dose range of 200 to 600 was sufficiently shown by the MAH.
f2 calculation could not be applied on the dissolution data due to too high RSDs; the MAH provided a bootstrap analysis of the data. In pH 4.5 acetate buffer similarity was demonstrated. Similarity in this medium can be concluded. In 0.1 N HCl, the bootstrap did not demonstrate similarity as the results of the 5% percentile was found below 50 (47.058). Information provided regarding the bootstrap is considered sufficient. The MAH has shown that the drug release is found comparable meeting the f2 criteria using a bootstrap when 2 tablets of 200 mg are compared with 1 tablet of 400 mg.
In addition, the MAH studied the effects of addition of a surfactant to the dissolution medium. Although this data cannot be used to demonstrate similarity, it does substantiate that the solubility of the ibuprofen in 0.1 N HCl is low and increases when a surfactant is added. Based on the data provided, a biowaiver has been granted for the 200 mg strength.

Bioequivalence studies

Design

A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male (30) and female (6) subjects, aged 20-43 years. Each subject received a single dose (400 mg) of one of the 3 ibuprofen formulations. One tablet of either test (A) or two tablets reference products (B or C) were orally administered with 240 ml water after an overnight fast of at least 10 hours. The washout period was 7 days between period I and period II and the washout period was 8 days between period II and period III.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The test product (A) was considered bioequivalent to reference product (B), if 90% confidence intervals for ratio (test/reference i.e. A/B) of geometric least square means based on log transformed primary pharmacokinetic parameters - C_{max} and AUC_{0-t} fall within acceptable bioequivalence limits of 0.80 – 1.25 for ibuprofen.
The test product (A) was considered bioequivalent to reference product (C), if 90% confidence intervals for ratio (test/reference i.e. A/C) of geometric least square means based on log transformed primary pharmacokinetic parameter – AUC_{0-t} fall within acceptable bioequivalence limits of 0.80 – 1.25 for ibuprofen.

The design is acceptable, the wash-out long enough, and sampling period long enough. The sampling scheme is adequate to estimate pharmacokinetic parameters considering the $t_{1/2}$ of approximately 2 hours and the t_{max} of 45 minutes. The 7-8 day wash-out period as well as the 24 hour sampling period is considered sufficient. Fasting is considered to be the most sensitive condition to detect a potential difference between formulations for immediate release tablet. Hence, this is agreed.

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
A total of 36 subjects were dosed and completed the study. Samples of 36 subjects were analysed. Data of 36 subjects was considered for pharmacokinetic and statistical analysis. One subject did not report to the clinical facility for check-in activity of period II (treatment B), due to personal reason, hence considered as dropped out for period II.

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

Treatment N=36	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test (A)	134 +/- 34	136 +/- 35	50 +/- 11	0.5 (0.3-2.0)	--
Reference (B)	141 +/- 37	143 +/- 38	48 +/- 14	0.5 (0.3-2.7)	--
Reference (C)	140 +/- 40	142 +/- 41	38 +/- 9	1.7 (0.5-4.0)	--
***Ratio A-B (90% CI)**	0.96 (0.92-1.00)	--	1.06 (0.97-1.16)	--	--
CV A-B	9	--	19	--	--
***Ratio A-C (90% CI)**	0.96 (92.29-1.00)	--	1.31 (1.21-1.43)	--	--

CV A-C	9	--	19	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals for ratio A/B (test/reference) of geometric least square means based on log transformed PK parameters – C_{max} and AUC_{0-t} – were found within the bioequivalence acceptance range of 0.80 – 1.25 and 90% confidence intervals for ratio A/C (test/reference) was found within the bioequivalence range of 0.80 – 1.25 for AUC_{0-t} of ibuprofen. Also the other pharmacokinetic variables and safety results were comparable between test A and reference B. Except for the t_{max} and C_{max}, the pharmacokinetic variables and safety results were comparable between test A and reference C.

Based on the submitted bioequivalence study Ibuprofen-natrium Strides is considered bioequivalent with Nurofen Express 256 mg (ibuprofen sodium) film-coated tablets.

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-natrium Strides.

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

Important identified risks	- Gastrointestinal bleeding, ulceration and perforation (and related complications) - Cardiovascular risk - Serious skin reactions - Renal disorders
Important potential risks	- Interaction with low-dose aspirin (Reduction of cardioprotective effect of low-dose aspirin)
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 Express/Flextin. 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 test consisted of a pilot test, followed by two rounds with 10 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-natrium Strides 200 mg and 400 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Nurofen Express 200 mg film-coated tablets and Nurofen Flextin 400 mg coated tablets. Nurofen Express/Flextin are well-known medicinal products 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-natrium Strides 200 mg and 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 August 2020.

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