COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nurofen Fastine Zavance 400 mg, soft capsules (ibuprofen)

NL/H/5368/002/DC

Date: 25 October 2024

This module reflects the scientific discussion for the approval of Nurofen Fastine Zavance 400 mg, soft capsules. The procedure was finalised on 23 November 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
BOS	Breakout session
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
ERP	European Reference Product
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
USNF	United States Pharmacopeia (USP)- National Formulary (NF)

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nurofen Fastine Zavance 400 mg, soft capsules, from Reckitt Benckiser Healthcare B.V.

The product is indicated in adults and adolescents weighing from 40 kg (12 years of age and above) 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.

A comprehensive description of the up-to-date 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 decentralised procedure, essential similarity is proven between the new product and the European Reference Product (ERP) Nurofen Express 400 mg soft capsules (NL/H/4313/001), which was initially registered in Bulgaria by Reckitt Benckiser Healthcare BG since 14 December 2011. The current Reference Member State (RMS) of the ERP is the Netherlands, justification to use this reference is based on RMS's own files. The ERP information was circulated during the validation period.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Spain.

General comments on the application

The initial application includes a second product strength (Ibuprofen Patheon Express mini 200 mg, soft capsules, NL/H/5368/001/DC) with Nurofen Express 400 mg soft capsules as reference product for both strengths. A bioequivalence study has been performed with the 400 mg strength and the reference. For the 200 mg strength, a biowaiver has been requested. The biowaiver results do not meet the criteria stated in the applicable guideline and similarity between the dissolution profiles of the 400 mg and 200 mg strengths was not demonstrated. Hence, the results of the bioequivalence study with the 400 mg strength cannot be extrapolated to the 200 mg strength according to the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6. Overall, the biowaiver was not approved and the bioequivalence of the 200 mg strength with the reference has not been proven. Therefore, the Board concluded that the marketing authorisation for the 200 mg product cannot be granted. See for more information the Public Assessment Report for NL/H/5368/001/DC.

II. QUALITY ASPECTS

II.1 Introduction

Nurofen Fastine Zavance 400 mg is a red, oval-shaped soft capsule with 'NURO400' printed in white ink. Each capsule contains as active substance 400 mg of ibuprofen.

The excipients are:
Fill - macrogol (E1521), potassium hydroxide (minimum 85% purity) (E525) and purified water.
Soft Capsule Shell - gelatin (E441), sorbitol liquid (E420), partially dehydrated and ponceau 4R (E124).
Printing Ink - opacode WB white NSP-78-180002 (consisting of titanium dioxide (E171), propylene glycol (E1520), SDA 35A alcohol (ethanol & ethyl acetate), isopropyl alcohol, polyvinyl acetate phthalate, purified water, macrogol/PEG MW400 (E1521) and ammonium hydroxide 28% (E527).
Processing Aids - soya lecithin (E322).

The soft capsules are packed in Opaque polyvinyl chloride/polyvinylidene dichloride/aluminium (PVC/PVdC-Al) blisters.

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 crystalline powder and is practically insoluble in water. The active substance is racemic mixture and there are no stereochemical issues. The polymorphic forms of the drug substance are not applicable as the drug substance is dissolved in macrogol 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.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the specifications stated in the CEP. Absence of a test for microbial control has been adequately justified. Batch analytical data

demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
The active substance is stable for 5 years 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. A fill formulation study was performed to ensure that a clear solution was obtained that was stable in a freeze thaw study. A shell formulation study was performed, followed by a capsule dimension study and a study of the encapsulation process in combination with the in-line print. The optimal composition and manufacturing process parameters have been investigated. The choices of packaging and manufacturing process are justified based on the dosage form. One bioequivalence study (BE) has been performed. Complementary to the BE, comparative *in vitro* dissolution data between test and reference have been performed (see IV.2 Pharmacokinetics). The discriminatory power of the dissolution method was demonstrated. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by an encapsulation process which consists of medicine fill preparation and gel mass fill preparation, encapsulation, drying, inspection (visual inspection, sizing and polishing), bulk- and blister packaging. Compliance with the Nederlandse Federatie Gezondheidszorg (NfG) on the start of shelf-life has been stated. The product is manufactured using conventional manufacturing techniques. Process validation for commercial scaled batches will be performed post authorisation on three consecutive commercial scale batches and at a batch size within the proposed batch size range.

Control of excipients
The excipients comply with Ph.Eur. or United States Pharmacopeia (USP)- National Formulary (NF) (USNF) 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 appearance, disintegration, identification, uniformity of dosage units (by mass variation), assay, dissolution, degradation products and microbial tests. The limits for the tests are identical for the release and shelf-life specification, except for disintegration, assay, and degradation products. 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. A detailed risk evaluation concerning the presence of nitrosamine impurities in the product has been provided, all

potential sources of nitrosamine impurities have been addressed. An assessment on elemental impurities in line with ICH Q3D has also been provided.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from eight batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two commercial scale batches stored at 25°C/ 60% RH (12 months), 30°C/ 65% RH (12 months) and 40°C/ 75% RH (stopped after 2 months). Supportive stability data on the product (not commercial packaging; similar protection compared to duplex blister was justified) has been provided on four pilot scaled batches of each strength stored at 25°C/ 60% RH (24 months), 30°C/ 65 % RH (12 months) and 40°C/ 75 % RH (discontinued after 1 month). The stability was tested in accordance with applicable European guidelines. When stored at 30°C/ 65% RH for 12 months, a trend of decrease in hardness is observed over time. Therefore, a test for hardness, with adequately justified limits for release and shelf-life, is included in the drug product and appropriate storage conditions were specified. 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 2 years. The labelled storage conditions are *'Do not store above 25°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 for the excipient gelatin 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 member states consider that Nurofen Fastine Zavance 400 mg 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 Nurofen Fastine Zavance 400 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nurofen Express 400 mg which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nurofen Fastine Zavance 400 mg, soft capsules, (Reckitt Benckiser Healthcare B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Nurofen Express 400 mg soft capsules (Reckitt Benckiser Healthcare BG, Bulgaria).

The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The comparative dissolution data do not show comparability between the test and reference product at all pH's tested (pH 1.2, 4.5 and 6.8). An explanation for these results has been given. Despite the *in vitro* results, *in vivo* bioequivalence has been demonstrated; the latter prevails.

Bioequivalence studies

Design

A single-dose, randomised, open label, two-period, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male and female subjects, aged 22-53 years. Each subject received a single dose (400 mg) of one of the two ibuprofen formulations. The tablet was orally administered with 200 mL water after a fasting period of at least 10 hours prior to dosing. There were two dosing periods, separated by a washout period of at least 48 hours.

Blood samples were collected pre-dose (-1) and at 0.17, 0.25, 0.33, 0.41, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours after administration of the products.

According to the ibuprofen oral use immediate release formulations 200-800 mg product-specific bioequivalence guidance (EMEA/CHMP/356876/2017), a study under fasting conditions is appropriate. Furthermore, the wash-out of 2 days and the sampling period up to 12 hours are long enough since the elimination half-life of ibuprofen is 1.8-3.5 hours.

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 24 subjects were enrolled in the study. There were not serious adverse events. One subject experienced one mild adverse event (mild headache) after administration of the reference, this was not possibly related to the investigational medicinal product. No subjects withdrawn from the study; all 24 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=24	**AUC_{0-t} (µg.h/mL)**	**$AUC_{0-\infty}$ (µg.h/mL)**	**C_{max} (µg /mL)**	**t_{max} (h)**
Test	123.9 ± 28.9	127.2 ± 31.6	45.1 ± 9.3	0.7 (0.3 – 2.5)
Reference	124.3 ± 29.2	127.7 ± 31.9	47.2 ± 8.5	0.7 (0.4 – 1.3)
***Ratio (90% CI)**	1.00 (0.97– 1.03)	--	0.95 (0.88 – 1.03)	--

$AUC_{0-\infty}$	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 / to t = 12 hours
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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nurofen Fastine Zavance 400 mg, is considered bioequivalent with Nurofen Express 400 mg soft 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 Nurofen Fastine Zavance 400 mg.

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 Express 400 mg soft capsules. 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 4 participants, 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

Nurofen Fastine Zavance 400 mg, soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Nurofen Express 400 mg soft capsules. Nurofen Express 400 mg 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 application was discussed in the board meeting of 20 October 2022. Furthermore, a breakout session (BOS) was held in November 2022.

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 Nurofen Fastine Zavance 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 November 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
NL/H/5368/ IA/002/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: - Secondary packaging site. - Primary packaging site. Change to importer, batch release arrangements and quality control testing of the finished product: - Replacement or addition of a site where batch control/testing takes place. - Replacement or addition of a manufacturer responsible for importation and/or batch release. Not including batch control/testing.	No No Yes	19-1-2024	Approved	N.A.
NL/H/5368/ 002/P/001	Art.61(3): Update the outer labelling.	Yes	19-1-2024	Approved	N.A.
NL/H/5368/ 002/IB/003	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products: - Other variation.	Yes	28-2-2024	Approved	N.A.
NL/H/5368/ 002/IA/005	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: - Secondary packaging site.	No	13-2-2024	Approved	N.A.