COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen Healthypharm liquid caps 400 mg, soft capsules (ibuprofen)

NL/H/5289/001/DC

12 January 2023

This module reflects the scientific discussion for the approval of Ibuprofen Healthypharm liquid caps. The procedure was finalised at 9 March 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
CQA	Critical quality attributes
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
QTPP	Quality target product profile
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 Healthypharm liquid caps 400 mg, soft capsules, from Healthypharm B.V.

Ibuprofen HTP liquid caps 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nurofen Fastine Liquid Caps 400 mg, capsule, soft (NL RVG 105812) which has been registered via the centralised procedure by Reckitt Benckiser Healthcare Ltd. since February 2012 (original product). The same reference product is used as a European Reference Product in concerned member state Slovenia.

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Ireland, Romania and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Healthypharm liquid caps are transparent, oval shape, soft gelatine capsules containing clear colourless liquid, imprinted with L 160 in black ink.

Ibuprofen Healthypharm liquid caps contains as active substance 400 mg of ibuprofen.

The capsules are packed in aluminium – white opaque PVC/PE/PVdC blisters and cartons.

The excipients are:

Capsule fill – macrogol 600 (E1521), potassium hydroxide (E525) and purified water.

Capsule shell – gelatine (E441), sorbitol – liquid partially dehydrated (E420) and purified water.

Printing ink – black iron oxide (E172), propylene glycol (E1520) and hypromellose (E464).

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is an almost white, crystalline powder and is practically insoluble in water. The active substance is racemic and there are no stereochemical issues. The polymorphic form of the drug substance is not applicable 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

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 in line with the CEPs with additional requirements for residual solvents. 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 in polyethylene bags and drums. 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. The development was based on the characteristics of the reference product, knowledge from previously approved products, the manufacturing process, the quality target product profile (QTPP) and critical quality attributes (CQAs), 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 to investigate the risk factors related to the drug product CQAs and optimise for each step of the manufacturing process. A standard manufacturing process was developed as no design space was claimed.

The quality control dissolution method is adequately established, and the discriminatory nature was demonstrated. Multimedia dissolution at three physiological pH's and the pH intended for drug product release were performed complementary to the BE study. The

optimal composition and manufacturing process parameters have been adequately investigated.

Manufacturing process

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 and two commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. The proposed prolonged holding time is adequately supported.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. The functionality related characteristics of the excipients, where relevant, are addressed. 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, related substances, dissolution, assay, loss on drying, disintegration time, pH of fill mass and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. All release and shelf-life acceptance criteria are identical. Risk evaluations on nitrosamines and elemental impurities are provided and considered adequately performed.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scaled batches and two full scaled batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Container closure system

The components of the primary commercial packaging and bulk pack are described. Specifications and certificates for the forming and lidding foils, as well as the bulk packaging, are provided.

Stability of drug product

Stability data on the product have been provided for three pilot scale batches stored at long-term (25°C/60% RH, 36 months) and at accelerated (40°C/75% RH, six months) conditions. Furthermore, two full scale batches stored at long-term (24 months) and accelerated (six months) were investigated as well. This was in accordance with applicable European guidelines demonstrating the stability of the product for three years. Photostability was demonstrated in line with ICH Q1D. The immediate packaging for marketing is suitable for its intended use. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are ‘This medicinal product does not require any special temperature storage conditions. Store in the original package 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 have been provided for gelatine 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 Ibuprofen Healthypharm liquid caps has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- When the analytical procedure for related substances will be revised after the marketing authorisation is granted, it has been committed by the applicant that all drug substance : excipient interactions of the capsule shell will be taken into account.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ibuprofen Healthypharm liquid caps 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 400 mg, capsule, soft 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 submitted 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 (Olive Healthcare, India) is compared with the pharmacokinetic profile of the reference product Nurofen Express liquid capsules 400 mg (Reckitt Benckiser Healthcare Ltd., United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Bioequivalence studies
Design
A randomised, single-dose, open label, two-period, cross-over, oral bioequivalence study was carried out under fasted conditions in 32 healthy male/female subjects, 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 a ten hour fasting period. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected at 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.

Ibuprofen's peak plasma level may be delayed with food-intake. 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.

Results
Out of a total of 32, 30 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn due to not reporting to the facility.

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} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	116.42 ± 27.65	118.99 ± 29.39	45.24 ± 10.23	0.67 (0.33-2.0)
Reference	115.66 ± 27.10	117.64 ± 28.28	46.00 ± 9.56	0.67 (0.33-2.5)
***Ratio (90% CI)**	100.55 (97.14-104.08)	100.96 (97.45-104.61)	98.10 (92.05-104.55)	--

$AUC_{0-\infty}$ 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
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 80% – 125%. Based on the submitted bioequivalence study Ibuprofen HTP liquid capsules 400 mg is considered bioequivalent with Nurofen Express liquid capsules 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 Healthypharm liquid caps.

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 Fastine Liquid Caps 400 mg, capsule, soft. 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 three 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 Healthypharm liquid caps 400 mg, soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Nurofen Fastine Liquid Caps 400 mg, capsule, soft. Nurofen Fastine 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibuprofen Healthypharm liquid caps with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 March 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/5289/001/IB/001	Changes to the product information to be in line with PRAC advice	Yes	21-12-2022	Approved	N/A