COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pathofen 100 mg, chewable capsules, soft

(ibuprofen)

NL/H/4843/001/MR

Date: 24 September 2019

This module reflects the scientific discussion for the approval of Pathofen 100 mg, chewable capsules, soft. The procedure was finalised on 16 August 2019. 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 Pathofen 100 mg, chewable capsules, soft from Patheon Softgels B.V.

The 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.

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

This mutual recognition procedure concerns a hybrid application claiming similarity with the innovator product Nurofen 200 mg tablet which has been registered in the UK by Reckitt Benckiser (UK) Ltd since August 1976. This is the reference medicinal product chosen for the purposes of establishing the expiry of the data protection period.
In the Netherlands the following reference medicinal product is referred to: *Nurofen voor kinderen suikervrije suspensie, suspensie voor oraal gebruik 100 mg/5 ml* (NL Licence RVG 19838). The medicinal product has registered since 15 July 1997 by Reckitt Benckiser Healthcare B.V.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC; it concerns a hybrid application, as there is a difference in pharmaceutical form and strength compared to the innovator product.

II. QUALITY ASPECTS

II.1 Introduction

Pathofen 100 mg is a light to dark yellow, square shaped chewable soft gelatin capsule with a hashtag (#) print in white ink. Each capsule contains as active substance 100 mg of ibuprofen.

The chewable capsules are packed in PVC/PE/PVdC/Al blisters.

The excipients are: gelatin, purified water, liquid glucose, sucrose, fumaric acid (E297), sucralose, citric acid (E330), acesulfame K (E950), disodium edetate, glycerine, Natural Orange Flavour (containing (R)-p-mentha-1,8-diene (d-limonene), ethyl acetate and alpha-pinene);

capsule printing: Opacode White NS-78-18011 (containing purified water, titanium dioxide (E171), propylene glycol, isopropyl alcohol, HPMC 2910/hypromellose 3cP (E464))

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white, crystalline powder which is practically insoluble in water, freely soluble in alcohol, acetone, ether, chloroform and in methylene chloride. It dissolves in dilute aqueous solutions of alkali hydroxides and carbonates and is slightly soluble in ethyl acetate.

The CEP procedure is used for both manufacturers of 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

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

Quality control of drug substance

The drug substance specification for ibuprofen applied by the MAH complies to the Ph. Eur. monograph for ibuprofen and the two CEPs from the respective two CEP sources with additionally a test and limit for drug substance particle size distribution. The control tests and specifications for the drug substance are adequately drawn up.

Stability of drug substance

The proposed retest period of five years for drug substance from the two sources is accepted. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The purpose of the proposed formulation was to develop chewable soft gelatin capsules comparable in clinical performance to the existing products Nurofen 100 mg/5 ml oral suspension and Nurofen 200 mg tablets. Overall, the choice of excipients, the formulation development and the manufacturing process development have been sufficiently described. It has been concluded that the selected formulation provides the required taste masking and consistency for a chewable formulation, which is physically and chemically stable and

exhibits a comparable pharmacokinetic performance to the current registered reference products.

Manufacturing process

The manufacturing process is sufficient. The critical process parameters have been identified and relevant in-process controls are in place. The process is a standard manufacturing process. The manufacturing process has been validated according to relevant European/ICH guidelines.

Control of excipients

The excipients comply with their respective Ph.Eur. paragraphs, except for Natural Orange Flavour and Opacode White NS-78-18011. An adequate in-house specification has been laid down. Natural Orange Flavour also complies with relevant European Directives. The specifications are acceptable.

Quality control of drug product

The drug product specification, and tests are acceptable. The specification includes tests for appearance, uniformity of dosage units, identity, assay, dissolution, water content, degradation products and microbial contamination. The product specifications cover appropriate parameters for this dosage form.

The specification limits for the degradation products are in accordance with ICH limits. The disintegration test has been replaced with dissolution test, which is acceptable as per the Ph. Eur. monograph for capsules. The analytical procedures have been adequately described and validated. Adequate validations of the analytical methods have been presented.

Batch analysis has been performed on four batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product

Stability studies have been performed on five batches of chewable capsules stored in PVC/PE/PVdC/Al blister packs in line with ICH guidelines. Results of 24 months long-term (25°C/60% RH) and 12 months intermediate (30°C/65% RH) data have been provided. After 3 months under accelerated stability conditions significant trends were observed. Therefore, no further studies were conducted under accelerated stability conditions. Based on the stability studies and results, ashelf-life of 24 months has been granted. The applicable storage condition is “Do not store above 30°C”.

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

The only ingredient used in the production of the chewable capsules which is of animal origin is gelatin. The gelatin is from bovine origin and is supplied by several suppliers. CEPs are provided for all sources of gelatin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pathofen 100 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 Pathofen 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 hybrid 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 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 hybrid 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 Pathofen 100 mg chewable capsules, soft (Patheon Softgels B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Nurofen 100mg/5ml oral suspension and Nurofen 200 mg tablets (Reckitt Benckiser Ltd, UK).

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

Bioequivalence study

Design

A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (14 females and 22 males). Each subject received a single dose (200 mg) of one of the ibuprofen formulations, administered as 2 x 100 mg chewable soft gelatine capsules, 1 x 10 ml of 100 mg/5ml oral suspension or 1 x 200 mg capsule after an overnight fast of at least 10 hours. There were 3 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and up to 10 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

One subject withdrew consent during the study. The remaining subjects were eligible for pharmacokinetic analysis.

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

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/m)	t_{max} (h)	$T_{1/2}$ (h)
Test (Ibuprofen)	38086.2±7449.1	39476.5±8301.8	11280.0±2250.8	1.33 (0.333 -3.00)	2.29±0.31 (13.36)
Reference1 (Nurofen Suspension)	36302.4±7572.7	37514.4±8250.7	9931.7±1914.5	1.00 (0.400 – 4.00)	2.24±0.32 (14.36)
***Ratio (90% CI)**	105.1 (102.9-107.4)	105.4 (103.1-107.7)	112.9 (105.8-120.5)		
Reference2 (Nurofen Tablets)	37722.1±7372.9	39290.5±8307.8	9766.5±1470.0	1.50 (0.667 – 4.00)	2.27±0.31 (13.83)
***Ratio (90% CI)**	101.0 (98.5-103.5)	100.6 (97.9-103.3)	114.8 (107.74-122.3)		

$AUC_{0-\infty}$	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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of (R)-ibuprofen under fasted conditions.

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/m)	t_{max} (h)	$T_{1/2}$ (h)
Test (Ibuprofen)	31623.7±6362.9	32042.1±6342.8	11315.5±2349.5	1.33 (0.333 -3.00)	1.63±0.26 (16.16)
Reference1 (Nurofen Suspension)	29475.7±8905.5	29914.3±8997.6	9835.0±2296.7	0.833 (0.333 – 4.00)	1.60±0.27 (16.55)
***Ratio (90% CI)**	110.1 (104.7-115.8)	109.9 (104.5-115.67)	115.4 (107.6-123.7)		
Reference2 (Nurofen Tablets)	31918.5±6223.5	32344.4±6591.0	10116.1±1956.5	1.33 (0.667 – 3.00)	1.61±0.0.25 (15.81)
***Ratio (90% CI)**	99.1 (96.1-102.2)	99.1 (96.1-102.2)	111.9 (104.6-119.7)		

$AUC_{0-\infty}$	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

**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 Pathofen 100 mg chewable capsules, soft is considered bioequivalent with Nurofen 100 mg/5 ml oral suspension and Nurofen 200 mg 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 Pathofen.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Gastrointestinal toxicity including perforation, ulceration and bleeding (PUB) • Cardiovascular and cerebrovascular disorders events (heart failure, MI and CVA) • Use during pregnancy (first and second trimester)
Important potential risks	--
Missing information	• Use during breastfeeding

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 hybrid 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 with four 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

Pathofen 100 mg, chewable capsules, soft has a proven chemical-pharmaceutical quality and is a hybrid form of Nurofen. 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. Pathofen 100 mg was registered in the Netherlands on 25 January 2019.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pathofen with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 16 August 2019.

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