COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen Liquid caps 400 mg Teva, capsule, soft (ibuprofen)

NL/H/5387/001/DC

Date: 11 July 2024

This module reflects the scientific discussion for the approval of Ibuprofen Liquid caps 400 mg Teva, capsule, soft. The procedure was finalised on 30 May 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Liquid caps 400 mg Teva, capsule, soft from Teva B.V.

The product is indicated for: 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 innovator product Nurofen Fastine Liquid caps 400 mg, capsule, soft, which has been registered in the Netherlands via national procedure (RVG 105812) since 6 February 2012.

The concerned member states (CMS) involved in this procedure were Austria, Finland and Portugal.

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Liquid caps 400 mg Teva, is a light red and oval soft capsule. It contains as active substance 400 mg of ibuprofen.

The excipients are:
Capsule fill: macrogol 600 (E1521), potassium hydroxide (E525), purified water and Allura Red (E129).
Capsule shell: gelatine, sorbitol liquid (E420) and purified water.

The soft capsule is packed in polyvinyl chloride/polyvinylidene chloride-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 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 relevant 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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The active substance specification is also in line with the CEP, with additional requirements for residual solvents. Absence of a test for microbiological purity has been justified. Batch analytical data demonstrating compliance with this specification have been provided for five commercial scale batches.

Stability of drug substance

The active substance is stable for five 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 development of the product has been described, the choice of excipients is justified, and their functions explained. The MAH has developed a drug product similar to the reference product in terms of characteristics and impurity profiles. The development of the QC dissolution method is adequately discussed and its discriminatory power demonstrated. Comparative dissolution profiles in support of the BE study at three different media (pH 1.2, 4.5, 6.8) are provided as required according to the EMA Guideline on the Investigation of Bioequivalence. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The development of the manufacturing process of Ibuprofen 400 mg soft capsules is based on a standard pharmaceutical process which includes the following steps: manufacture of gelatine mass, manufacture of inner solution, encapsulation/ dosing, drying, and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients but Allura Red comply with Ph. Eur. requirements. These specifications are acceptable. The proposed specifications for Allura Red comply with Regulation 231/2012, and are accepted.

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, identity, disintegration, dissolution, assay, related substances, microbial limits, and uniformity of dosage units. 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. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three commercial scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (3 months) in accordance with applicable European guidelines. The accelerated study (40°C/75%RH) showed significant changes of the finished product after 3 months, i.e., description, impurity J, assay, dissolution, and disintegration not meeting acceptance criteria. The long-term and intermediate stability data comply with the drug product specification. A photostability study according to ICH Q1B recommendations is provided and the additional storage condition "Store in the original package in order to protect from light" based on this study is accepted. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition is "Do not store above 30 °C".

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for gelatine 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 Ibuprofen Liquid caps 400 mg Teva 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 Liquid caps 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 Fastine Liquid caps 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 one bioequivalence study, which is discussed below.

Comparative dissolution profiles were submitted in support of the BE study at three different media (pH 1.2, 4.5, 6.8) as required according to the EMA Guideline on the Investigation of Bioequivalence. The profiles are visually not similar, and f2-calculation would not be valid due the high standard deviation (>10%) at the first three time-points. However, similar trends are observed between the test and reference batches. Due to the low solubility of ibuprofen at low pH, the comparative dissolution profiles determined at pH 1.2 and 4.5 are acceptable despite the high standard deviation. Therefore, the comparative dissolution profiles were accepted. The comparative dissolution profile at pH 6.8 was accepted.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen Liquid caps 400 mg Teva, capsule, soft (Teva B.V., Netherlands) was compared with the pharmacokinetic profile of the reference product Nurofen Fastine Liquid caps 400 mg, capsule, zacht (Reckitt Benckiser Healthcare B.V., Netherlands).

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

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-sequence, two-way crossover, open-label bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 23-54 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 at least 10 hours pre-dose. There were two dosing periods, separated by a washout period of 3 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 14 hours after administration of the products.

The design of the study is acceptable. No specific drug intake conditions are defined in the SmPC of ibuprofen, so a fasting study is sufficient. This is also recommended in the product specific guidance for ibuprofen.

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

24 subjects were enrolled and 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} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	99957 ± 19686	101451 ± 20483	40492 ± 6295	0.50 (0.33-1.25)
Reference	103867 ± 19553	105717 ± 20440	37958 ± 9596	0.58 (0.33-1.50)
***Ratio (90% CI)**	0.96 (0.93 – 1.00)	-	1.09 (1.02 – 1.16)	-

$AUC_{0-\infty}$	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 = 14 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ibuprofen Liquid caps is considered bioequivalent with Nurofen.

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 Liquid caps 400 mg Teva

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 test consisted of: a pilot test with two 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

Ibuprofen Liquid caps 400 mg Teva, capsule, soft has a proven chemical-pharmaceutical quality and is a generic form of Nurofen Fastine Liquid caps 400 mg, capsule, soft. Nurofen Fastine Liquid caps 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 Liquid caps 400 mg Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 May 2023.

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/5387 /IB/002/G	**Type IB: C.I.3.z;** *Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC* • *Other variation* **Type IB: C.I.2.a** *Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product* • *Implementation of change(s) for which no new additional data are submitted by the MAH*	Yes Yes	07-03-2024	Approved	N/A
NL/H/5387 /001/IB/001	**Type IB: C.I.z** *Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products* • *Other variation*	Yes	20-03-2024	Approved	N/A