CBG MEB

Public Assessment Report

Scientific discussion

Leidapharm Ibuprofen Liquid Caps 200 mg capsules, soft

(Ibuprofen)

NL/H/3098/001/DC

Date: 20 June 2016

This module reflects the scientific discussion for the approval of Leidapharm Ibuprofen Liquid Caps 200 mg capsules, soft. The procedure was finalised at 18 March 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Leidapharm Ibuprofen Liquid Caps 200 mg soft capsules from Leidapharm B.V.

The product is indicated for the short-term symptomatic treatment of mild to moderate pain, such as headache, menstruation pain, dental pain, and fever and pain in the common cold. Leidapharm Ibuprofen is indicated for the use in adults, adolescents and children from 20 kg body weight (around 6 years old).
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 200 mg soft gelatine capsules which has been registered in the UK by Reckitt Benckiser since 26 August 1999. In the Netherlands, Nurofen 200 mg soft capsules (NL License RVG 27102) was registered on 20 February 2002 through Mutual Recognition Procedure DE/H/0329/001. This product was withdrawn in 2008.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Leidapharm Ibuprofen Liquid Caps 200 mg soft capsules is a pale yellow, oval-shaped (size 8.5) transparent soft gelatin capsule with a print “I200” in white ink.

Each capsule contains 200 mg of Ibuprofen as active substance.

The soft capsules are packed in a blister pack consisting of opaque, white polyvinyl chloride (PVC) / polyethylene (PE) / polyvinylidene chloride (PVdC) laminate, heat sealed to aluminium foil.

The excipients are:

Fill
- Macrogol 600
- Potassium hydroxide (E525)
- Purified water

Capsule shell
- Gelatin (E441)
- Liquid Sorbitol, partially dehydrated (E420)
- Purified water

Printing ink
- Opacode NS-78-18011
- Names of the components of the printing ink
    - Purified water
    - Titanium dioxide (E171)
    - Propylene glycol (E1520)
    - Isopropyl alcohol
    - HPMC 2910/Hypromellose 3cP

Trace substances
- Isopropyl alcohol
- Medium chain triglycerides
- Soya lecithin

II.2 Drug Substance

The active substance is Ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ibuprofen is a white crystalline powder which is practically insoluble in water, but freely soluble in acetone, methanol and methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. Ibuprofen is a chiral compound but is marketed as the racemate. In dynamic liquid systems, Ibuprofen may form esters with polyols. As the drug substance is in solution, product limits for particle size and polymorphic form are not required as these parameters will have no impact on the performance of the finished product.

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 drug substance specification is in line with the Ph.Eur. monograph and the additional requirements of the CEPs. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches, from each supplier.

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 fill formulation was optimised for solubility of Ibuprofen in macrogol 600 and reduced formation of Ibuprofen macrogol esters. The concentration of potassium hydroxide was optimised to keep the water concentration in the fill formulation as low as possible. The gel formulation was optimised for plasticizer and concentration of the plasticizer in the gelatine mass.

A bioequivalence study was submitted to demonstrate bioequivalence between Leidapharm Ibuprofen Liquid Caps 200 mg soft capsules and the reference medicinal product, Nurofen 200 mg liquid capsules. The manufacture and composition of the bio-batches used in bioequivalence study are identical to the marketed product. The dissolution profiles for the batches used in the bioequivalence study show comparable results for the test and reference product. For both formulations more than 85% of the drug substance was released within 10 minutes.

Manufacturing process
The manufacturing process consists of the following steps: preparation of the fill material, preparation of the gel mass, encapsulation, inspection and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches.

Control of excipients
All the mentioned excipients, except for the printing ink, comply with the Ph.Eur.. All the individual components of the printing ink also comply with the Ph.Eur.. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, disintegration, identity, uniformity of dosage units, assay, dissolution, degradation, and microbiological quality. The release and shelf-life limits are not identical, as the shelf-life specification has higher limits for degradation products, and slower dissolution is proposed. As the wider limits at shelf-life have been supported by stability data, the proposed specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on five development scale batches and one full scale batch, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three pilot scale batches and one full scale batch stored at 25°C/60% RH (36 months), 30°C/65% RH (36 moths), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC/Al blister packs. Increases in the content of macrogol esters of Ibuprofen, sorbitol esters, total esters of ibuprofen and total degradation products of ibuprofen (excluding esters) were observed. However all tested parameters remained within the specifications for the full scale batch stored at 25°C/60% RH. Based on these data a shelf-life of 36 months with the temperature restriction “Do not store above 25°C” is granted. The drug product is photo-stable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is of bovine origin. Relevant Ph. Eur. TSE Certificates of Suitability of the gelatin suppliers are provided. None of the other excipients are of animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Leidapharm Ibuprofen Liquid Caps 200 mg soft capsules 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 Leidapharm Ibuprofen 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 200 mg liquid capsules 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Leidapharm Ibuprofen Liquid Caps 200 mg (Leidapharm B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Nurofen 200 mg soft gelatine capsules (Reckitt Benckiser, 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.

Design
A single-dose, randomised, two-treatment, two-crossover bioequivalence study was carried out under fasted conditions in 20 healthy male (n=7) and female (n=13) subjects, aged 19-47 years. Each subject received a single oral dose (200 mg) of one of the 2 Ibuprofen formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 48 hours.

Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 7, 9 and 12 hours after administration of the products.

The design of the study is acceptable. The start and the duration of the sampling is sufficient considering the t_{max} and half-life (circa 1 h and 2 h, respectively) of ibuprofen. A wash-out period of 48 hours (i.e. at least 5 terminal half-lives) is according to the guideline. The study under fasting conditions is justified. If taken shortly after eating, the onset of action of Ibuprofen 200 mg soft capsules may be delayed.

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
All 20 subjects completed the study and were eligible for pharmacokinetic analysis. Their samples were included in statistical data analysis and subsequent bioequivalence assessment.

Table 1. Ibuprofen pharmacokinetic parameters under fasting conditions (non-transformed values; arithmetic mean ± SD, T_{max} median, range)

Treatment N=20	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**T_{max}** h	**$t_{1/2}$** h
Test	68 ± 17	73 ± 18	25.6 ± 4.5	0.8 (0.3 – 1.3)	2.5 ± 1.9
Reference	67 ± 21	70 ± 22	25.9 ± 7.5	0.8 (0.3 – 3.0)	2.0 ± 1.2
***Ratio (90% CI)**	1.03 (0.96 – 110)	1.05 (0.97 – 1.12)	1.01 (0.91 – 1.12)	--	

CV (%)	28	28	24	

$AUC_{0-\infty}$	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 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 Leidapharm Ibuprofen Liquid Caps 200 mg are considered bioequivalent with Nurofen 200 mg soft gelatine 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 Leidapharm Ibuprofen Liquid Caps 200 mg.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Heart failure • Myocardial infarction • Cerebrovascular accident (CVA) • Gastrointestinal bleeding, ulceration, and perforation • Ulcerative colitis and Crohn's disease • Severe skin reactions (including Exfoliative dermatitis, Stevens Johnson syndrome, Toxic Epidermal necrolysis) • Renal toxicity/ renal failure • Use during third trimester of pregnancy • Interaction with medication that can increase the risk of bleeding and ulceration, such as corticosteroids, anticoagulants such as warfarin, selective serotonin uptake inhibitors (SSRIs) or anti-platelet agents such as aspirin • Interaction with antihypertensive agents (e.g. diuretics, beta blockers, ACE inhibitors, AT-II antagonists, etc.) • Hepatic disorders • Use by elderly • Use by patients with (history of) bronchial asthma • Medication Overdose Headache (MOH) • Lactation
Important potential risks	• Impaired female fertility • Use during the 1st and 2nd trimester of pregnancy • Second myocardial infarction after treatment with Ibuprofen • Off-label use in children <6 years / <20 kg body weight • Aseptic meningitis in patients with systemic lupus erythematosus and mixed connective tissue disease
Missing information	• Not applicable

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 200 mg soft gelatine 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 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 two rounds with 10 participants each. Sufficient questions were asked (19). The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
All participants were able to trace the information for the questions 100% of the time. Each of these participants showed they understood the information by answering all questions correctly. The results show that the package leaflet 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

Leidapharm Ibuprofen Liquid Caps 200 mg have a proven chemical-pharmaceutical quality and are a generic form of Nurofen 200 mg soft gelatine capsules. 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.

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 Leidapharm Ibuprofen Liquid Caps 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 March 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the number of units (tablets) in a pack.	NL/H/3098/001/IB/001	IB	11 Aug 2015	15 Sep 2015	Approval	No
Updated certificate (CEP) from an already approved manufacturer.	NL/H/3098/001/IA/002	IA	12 Dec 2015	7 Jan 2016	Approval	No
Update to SmPC and PIL as per the CMDh advice included in their report published on 22-May-2015, Ibuprofen referral and update as per latest QRD template.	NL/H/3098/001/IB/003	IB	16 Feb 2016	17 May 2016	Approval	No
Updated Certificate of Suitability from an already approved API supplier	NL/H/3098/001/IA/004	IA	03 Mar 2016	25 Mar 2016	Approved	No