CBG MEB

# Public Assessment Report

# Scientific discussion

# Kruidvat Ibuprofen Liquid Caps 200 mg, soft capsules

# (ibuprofen)

## NL License RVG: 115530

## Date: 4 April 2017

**This module reflects the scientific discussion for the approval of Kruidvat Ibuprofen Liquid Caps 200 mg. The marketing authorisation was granted on 14 August 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

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Kruidvat Ibuprofen Liquid Caps 200 mg, soft capsules from MAE Holding BV.

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. Kruidvat 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 national procedure concerns a generic application claiming essential similarity with the European reference product Nurofen 200 mg soft gelatine capsules which has been registered in the UK by Reckitt Benckiser since 26 August 1999. Nurofen was first registered as a 200 mg tablet formulation by Reckitt Benckiser in the UK in 1976.
The reference product currently registered in the Netherlands is Nurofen Fastine Liquid Caps 200 mg soft capsules (NL License RVG 102120), authorised since 19 April 2010 through Decentralised Procedure DE/H/0329/001.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Kruidvat Ibuprofen Liquid Caps 200 mg 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 WB White 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*

- Medium chain triglycerides
- Isopropyl alcohol
- 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 Kruidvat 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 for assay are identical, except for assay and dissolution. The limits are however justified in view of batch analytical data, behaviour of the biobatch and stability data. 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 months), 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), and a downward trend in the assay of ibuprofen were observed, under all conditions. 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 for 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 MEB considers that Kruidvat Ibuprofen Liquid Caps 200 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 Kruidvat 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 MEB 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 MEB 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 Kruidvat Ibuprofen Liquid Caps 200 mg (MAE Holding BV, 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. The washout 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. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of ibuprofen under fasted conditions.

| **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 – 1.10) | 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 Kruidvat 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 Kruidvat Ibuprofen Liquid Caps.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | Cardiovascular and cerebrovascular events (heart failure, MI and CVA)<br><br>Gastro-intestinal bleeding, ulceration, and perforations<br><br>Severe skin reactions (Stevens-Johnson syndrome, epidermal necrolysis)<br><br>Interaction with medication that can increase the risk of bleeding<br><br>Use during pregnancy and lactation<br><br>Medication Overuse Headache (MOH) |
| Important potential risks | - |
| Missing information | Use by children <20 kg body weight |

The MEB 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 not been evaluated via a user consultation study. The MAH submitted a bridging report. Reference is made to the user testing on the leaflet of Kruidvat Ibuprofen bruis 400 mg, effervescent granules. The contents of the text of the two leaflets are identical to a large extent.

The products differ in their administration form and their strength. The textual difference between the patient instruction leaflets exists only in small parts of the text parts related to the warnings, instructions for use and dose of Ibuprofen Kruidvat Liquid Caps 200 mg. Four questions were asked about the deviating text parts of the leaflet of Kruidvat Ibuprofen Liquid Caps 200 mg.
The bridging report has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kruidvat 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Kruidvat Ibuprofen Liquid Caps 200 mg was authorised in the Netherlands on 14 August 2015.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|
| Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Articles 30 or 31 of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC (referral procedure) | IA | 9-5-2016 | 1-6-2016 | Approval | N |
| Submission of an updated Ph. Eur. certificate of suitability: For an active substance, European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. – Updated certificate from an already approved manufacturer | IA | 10-5-2016 | 18-5-2016 | Approval | N |