CBG MEB

Public Assessment Report

Scientific discussion

Kruidvat Ibuprofen bruis 400 mg, effervescent granules

(ibuprofen)

NL License RVG: 113861

Date: 29 November 2017

This module reflects the scientific discussion for the approval of Kruidvat Ibuprofen bruis 400 mg, effervescent granules. The marketing authorisation was granted on 18 November 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

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 bruis 400 mg, effervescent granules from MAE Holding B.V.

The product is indicated for treatment of mild to moderate pain, primary dysmenorrhoea and fever.

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 innovator product Neobrufen effervescent granules which has been registered in Spain by Abbott Laboratories, S.A. since 1 March 1998. The Dutch reference product is Brufen 400 mg effervescent granules (NL License RVG 110571), registered by BGP Products B.V.

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

II. QUALITY ASPECTS

II.1 Introduction

Kruidvat Ibuprofen bruis is formulated as white, orange-flavoured granules containing 400 mg ibuprofen packed in a single-dose paper/polyethylene/aluminium/Surlyn sachet.

The excipients are: citric acid (E330), sodium laurylsulfate povidone (E1201), saccharin sodium (E954), sodium carbonate (E500), sodium hydrogen carbonate (E500), colloidal anhydrous silica (E551), lactose and orange flavouring (containing a.o. dextrose, maltodextrine and Arabic gum (E414)).

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 or colourless crystals and is practically insoluble in water, freely soluble in acetone, methanol and methylene chloride. Ibuprofen dissolves in diluted solutions of alkaline carbonates and hydroxides. It has one chiral center and is used as racemate.

The CEP procedure is used for both suppliers 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 European Pharmacopoeia.

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

Quality control of drug substance
The specifications applicable are those established in the CEP and the monograph of the European Pharmacopoeia. Batch analytical data demonstrating compliance with the drug substance specification have been provided on two batches of one manufacturer, and three batches from the other manufacturer. The results are in compliance with the requirements of the Ph.Eur. monograph and the additional requirements of the CEP.

Stability of drug substance
The active substance from both manufacturers 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 development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to obtain a formulation similar to the reference product Neobrufen effervescent granules marketed by Abbott Laboratories S.A. in Spain. The formulation of the product was changed twice. The second optimisation formulation will be used for commercial supply. Bioequivalence studies are conducted using the initial and second optimization formulation. The bioequivalence studies are conducted using the 600 mg strength, however this strength is not been applied for in this application. Ibuprofen 400 mg and 600 mg effervescent granules are manufactured by exactly the same manufacturing process, the only difference between both strengths is the quantity of effervescent granules filled per sachet. A biowaiver for the 400 mg strength is applied for. The batch size and quality of the second optimisation batch used for the bioequivalence study is acceptable. Comparative dissolution profiles and f2-calculation for the 600 mg test and reference product are provided, demonstrating similarity.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. A solution is prepared to granulate the ibuprofen and citric acid. The granules are dried and sieved to produce intermediate granules. Anhydrous sodium carbonate, sodium hydrogen carbonate and the other excipients are sieved and mixed together with the intermediate granules to produce effervescent granules. This is followed by sieving and mixing in order to create effervescent granules. The effervescent granules are measured out into sachets to obtain sachets with 400 mg of ibuprofen. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data have been presented for three full scale batches of bulk granules. In addition, the filling process of the 600 mg product is validated. Validation of filling of the 400 mg will be provided when available.

Control of excipients
The excipients comply with the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, ibuprofen content, related substances, uniformity of dosage units, disintegration, pH, loss of drying, and microbial quality. The release and shelf-life limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analyses data of two full scale 400 mg batches and supporting data of four full scale 600 mg batches are provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on two 400 mg batches produced according to the new formulation have been provided. The batches were stored at 25°C/60%RH (up to 9 months). For the 600 mg effervescent granules results up to 18 months at long term stability conditions (25ºC/60%RH), up to 12 months at intermediate stability conditions (30ºC/65%RH) and up to 6 months at accelerated stability conditions (40ºC/75%RH) are available. These batches show a clear downward trend and significant change for ibuprofen content during 18 months storage. Also at accelerated and intermediate conditions significant changes were observed. No information on photostability testing is included. As the packaging material used is not permeable for light, this was accepted.
Based on the stability data presented a shelf life of 9 months was granted for the 400 mg product. The granted storage conditions are ”do not store above 25ºC; store in the original package in order to protect from moisture”.
Post approval new stability data have been provided, and the shelf life has been extended to 24 months.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only excipient of animal origin (milk). A TSE certificate has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Kruidvat Ibuprofen bruis 400 mg 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:
- The MAH committed to provide the validation data of the filling process for three full scale batches of the 400 mg product.
- The MAH committed to provide a third certificate of analysis for the 400 mg product.
- The MAH committed to perform the stability studies for the 400 mg strength at intermediate conditions (30ºC/65% RH). Results of additional stability studies have been provided, and the shelf life has been extended (see page 9).

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Kruidvat Ibuprofen bruis 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 Neobrufen effervescent granules, 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 agrees that no further clinical studies are required.

The bioequivalence study initially submitted in support of this application was conducted with a previously developed 600 mg formulation. However, the composition of the formulation for both the 400 mg and 600 mg was changed. The percentage lactose content of the granules was reduced. Hence, a new bioequivalence study was submitted with the 600 mg new formulation for the test product. This second study and the justification for a biowaiver for the 400 mg formulation is described below.

IV.2 Pharmacokinetics

In the bioequivalence study the pharmacokinetic profile of the test product Ibuprofen bruis 600 mg is compared with the pharmacokinetic profile of the reference product Neobrufen 600 mg effervescent granules (Abbott Laboratories, Spain).

The choice of the test and reference product
The final test formulation is used the bioequivalence study. The choice of the Spanish reference product Neobrufen 600 mg is justified with regards to the qualitative and quantitative composition.

Biowaiver

The MAH applied for a waiver for the proposed product Kruidvat Ibuprofen 400 mg effervescent granules. The use of the 600 mg strength in the bioequivalence study is justified since:

- the pharmaceutical products are manufactured by the same manufacturing process
- the drug input has been shown to be linear over the therapeutic dose range
- the qualitative composition of the different strengths is the same
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for the 400 and 600 mg
- the dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study. The applicant has performed a comparative dissolution testing at pH 1.2, 4.5 and 6.8, in line with the guideline. At the three pH conditions, similarity in dissolution between the 600 mg biobatch and the 400 mg strength has been demonstrated as f2 was above 50.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects (22 females, 8 males; mean age 45 years). Each subject received a single dose (400 mg) of one of the 2 ibuprofen formulations.
The ibuprofen granules were dispersed in a glass of 250 ml water before the volunteer drank the suspension. Subsequently, the glass and spoon were rinsed with 30 ml of water at room temperature, which the volunteer drank immediately. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25,1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10 and 12 hours after administration of the products.

The study design is acceptable and in accordance to the Guideline on the Investigation of Bioequivalence. Ibuprofen may be taken without reference to food intake. Therefore the bioequivalence study under fasting conditions is appropriate. The start and the duration of the sampling is sufficient considering the t_{max} and half-life of ibuprofen (1-2 hours and about 2 hours, respectively). Based on the half-life of ibuprofen, the wash-out period is sufficient to exclude carry-over effects and in accordance to the recommended of at least ≤ 5x half-lives.

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.

Ibuprofen is a racemate. Bioequivalence was based on data from S-(+) ibuprofen. Data from R-(-) ibuprofen were reported and presented as supportive information. Based on the literature, S-(+) ibuprofen is believed to be the pharmacologically active enantiomer and R-(-) ibuprofen is inactive. According to the bioequivalence guideline, “if one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer”. Hence, bioequivalence based on the pharmacokinetics data of S-(+) ibuprofen with R-(-) ibuprofen data as supportive is agreed.

Results

All 30 subjects completed the study and 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 N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	90802 ± 21047	94335 ± 22965	22337 ± 4331	2 (1 – 6)	2.11 ± 0.32
Reference	86969 ± 20240	90186 ± 22222	24264 ± 3880	2 (1-4)	2.11 ± 0.31
***Ratio (90%**	1.04	1.05	0.91	--	--

CI)	(1.01 – 1.07)	(1.02 – 1.07)	(0.87 – 0.97)		
$AUC_{0-\infty}$ 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 N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	83847 ± 18326	85087 ± 18292	24599 ± 5888	2 (1 – 6)	1.34 ± 0.33
Reference	81341 ± 14477	82576 ± 14473	27047 ± 4661	2 (1-4)	1.28 ± 0.28
***Ratio (90% CI)**	1.02 (0.96 – 1.08)	1.02 (0.97 – 1.08)	0.89 (0.83 – 0.96)	--	--
$AUC_{0-\infty}$ 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 Ibuprofen bruis 600 mg is considered bioequivalent with Neobrufen 600 mg effervescent granules.

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 bruis 400 mg.

- Summary table of safety concerns as approved in RMP

Important identified risks	Heart failure Myocardial infarction (MI) Cerebrovascular accident (CVA) Gastro-intestinal bleeding, ulceration, and perforation Exacerbation of 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) Use by elderly Use by patients with (history of) bronchial asthma
Important potential risks	Impaired female fertility Medication Overuse Headache (MOH) Use during 1st and 2nd trimester of pregnancy Second myocardial infarction Off-label use of concomitant NSAIDs Use by children <12 years of age or < 40 kg Use for > 3-4 days Lactation
Missing information	--

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 Neobrufen effervescent granules. 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 a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. All 15 questions fulfil the requirements in both test rounds, i.e. at least 90% of respondents gave a correct answer in terms of traceability, of whom 90% of the respondents gave a correct answer in terms of comprehensibility/applicability.
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

Kruidvat Ibuprofen bruis 400 mg, effervescent granules has a proven chemical-pharmaceutical quality and is a generic form of Neobrufen effervescent granules. Neobrufen is a well-known medicinal poduct with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents based on a study with the 600 mg formulation. A biowaiver has been gratned for Kruidvat Ibuprofen bruis 400 mg.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity with the reference product has been demonstrated, and has therefore granted a marketing authorisation. Kruidvat Ibuprofen bruis 400 mg, effervescent granules was authorised in the Netherlands on 18 November 2014.

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
Extension of the shelf life from 9 to 12 months.	IB	13-2-2015	23-3-2015	Approval	N
Introduction of the Pharmacovigilance System Master File	IA/G	27-5-2015	26-6-2015	Approval	N
Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance - European Pharmacopoeia Certificate of Suitability to the relevant Ph. Eur. Monograph. – New certificate from a new manufacturer (replacement or addition)	IA	16-12-2015	15-1-2016	Approval	N
Extension of the shelf life from 12 to 24 months.	IB	22-12-2015	16-3-2016	Approval	N
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/G	9-5-2016	8-6-2016	Approval	N