CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ibuprofen bruis 600 mg PCH, effervescent granules
Pharmachemie B.V., the Netherlands

ibuprofen

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 101715

24 August 2011

Pharmacotherapeutic group:	antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives
ATC code:	M01AE01
Route of administration:	oral
Therapeutic indication:	inflammatory joint conditions; degenerative joint conditions; extraarticular conditions; post-operative pain, post-operative dental pain; primary dysmenorrhoea; fever and pain (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	11 May 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Ibuprofen bruis 600 mg PCH, effervescent granules from Pharmachemie B.V. The date of authorisation was on 11 May 2011 in the Netherlands.

The product is indicated for:

- Inflammatory joint conditions
  - rheumatoid arthritis
  - ankylosing spondylitis
- Degenerative joint conditions
  - Arthrosis including spondylarthrosis
- Extraarticular conditions
  - Periarthritis humeroscapularis
  - Tendovaginitis
  - Epicondylitis
  - Bursitis
  - Synovitis
  - Tendinitis.
- Post-operative (dental) pain
- Primary dysmenorrhoea
- Fever and pain due to influenza, common cold or following vaccination, toothache, headache, muscular pain and rheumatic pain.

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

Ibuprofen is a NSAID with analgesic and antipyretic properties. It belongs to the group of propionacid derivates The mechanism of action of ibuprofen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

This national procedure concerns a generic application claiming essential similarity with the innovator product Brufen Bruis 600 mg effervescent granules (NL License RVG 13331) which has been registered in the Netherlands by Abbott B.V. since 5 September 1989.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Neobrufen 600 effervescent granules, registered in Spain. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application. No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white, crystalline powder or 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 new 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
A CEP has 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 recent batches of each 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.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ibuprofen bruis 600 mg PCH consists granules with orange flavour packed in a single-dose paper/polyethylene/aluminium/Surlyn sachet.

The excipients are: citric acid (E330), sodium laurilsulfate (E494), povidone (E1201), saccharin sodium (E954), sodium carbonate (E500), sodium hydrogen carbonate, colloidal anhydrous silica (E551), lactose and orange flavouring.

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 600 mg effervescent granules marketed by Abbott Laboratories S.A. in Spain. The dissolution profiles of biobatch and the reference product were compared at two different pH values. The results indicate similarity between both products. The formula has been adjusted after bioequivalence testing. The excipient sucrose has been removed from the formulation and the amount of sodium saccharin was increased. This change results in a reduction of the weight per sachet from 6500 mg to 3758 mg.. Comparative dissolution profiles demonstrated that the change did not affect the dissolution profile. As the change in excipients is not expected to affect the absorption, the biobatch is considered to be representative for the final product.

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 600 mg of ibuprofen. The manufacturing process has been adequately validated according to relevant European guidelines.
Process validation data have been presented for three pilot-scale and three full-scale batches. In addition, validation data of two pivotal batches produced according to the new formulation have been included.

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 analytical methods have been adequately described and validated. Batch analyses data of four pilot-scale batches and three production batches have been provided, demonstrating compliance with the release specification. Batch analysis results on the first two production batches according to the new formulation are also available.

Stability of drug product
Stability data on two pilot-scale batches and three full-scale batches produced according to the new formulation have been provided. The batches were stored at 25°C/60%RH (24-36months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months). At long-term and intermediate conditions, all results comply with the requirements of the specification. A decrease in assay content is observed. At accelerated conditions out-of-specification data for assay content are 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 a shelf life of 24 months is granted, when stored below 30°C in the original package in order to protect from moisture.

Specific measures concerning 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.2 Non clinical aspects

This product is a generic formulation of Brufen Bruis, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ibuprofen released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ibuprofen is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen bruis 600 mg PCH (Pharmachemie B.V.), 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 choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results.
The formula and preparation of the bioequivalence batch is not entirely the same as the formula proposed for marketing. The excipient sucrose has been removed from the formulation and the amount of sodium saccharin was increased. Results have been provided, demonstrating that the proposed formulation does not affect the *in vitro* dissolution. The biobatch is considered to be sufficiently representative for the new proposed formulation.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male and female subjects. Mean age was 23. Each subject received a single dose (600 mg) of one of the 2 ibuprofen formulations. The granules were orally administered under fasted conditions after dissolving them in a glass containing 150 mL of water; immediately after administration (swallowing) the participants drank additional 150 mL of water in order to ensure the entire contents of the entire effervescent sachets were taken. Liquid intake in the morning of the trial was restricted to the 300 mL of water used for the administration of the drug. 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, 2.5, 3, 4, 6, 8, 10 and 12 hours after administration of the products.

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
The clinical phase included 24 volunteers. All completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** mcg.h/ml	**$AUC_{0-\infty}$** mcg.h/ml	**C_{max}** mcg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	163.30 ± 43.62	168.40 ± 47.57	41.23 ± 9.58	2.25 (1.0-6.0)	1.90 ± 0.40
Reference	147.65 ± 40.92	151.81 ± 44.64	38.96 ± 8.64	2.25 (0.5-6.0)	1.93 ± 0.40
***Ratio (90%**	1.10	1.11	1.05	--	--

CI)	(1.05-1.17)	(1.05-1.17)	(0.96-1.15)		
CV (%)	10.4	10.8	18.6	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of ibuprofen under fasted conditions, it can be concluded that Ibuprofen bruis 600 mg PCH and Neobrufen 600 mg effervescent granules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Ibuprofen may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ibuprofen. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

Risk management plan
Ibuprofen was first approved in 1969 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ibuprofen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Brufen Bruis.

Readability test
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. Based on the results of the first test round, four points for clarification were identified. The suggested amendments were adopted. The approved PIL was tested in the second test round, with readability results of 88%. No further points for improvement were identified.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibuprofen bruis 600 mg PCH effervescent granules has a proven chemical-pharmaceutical quality and is a generic form of Brufen Bruis 600 mg. Brufen Bruis 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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. Ibuprofen bruis 600 mg PCH effervescent granules was authorised in the Netherlands on 11 May 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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