CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ibuprofen caps 200 mg PCH, capsule, soft
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 107152

23 January 2013

Pharmacotherapeutic group:	antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives
ATC code:	M01AE01
Route of administration:	oral
Therapeutic indication:	headache, fever and pain due to common cold or influenza, dental pain, pain during menstrual bleeding, muscular pain, backache, rheumatic pain, fever and pain following vaccination
Prescription status:	non prescription
Date of authorisation in NL:	9 September 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 caps 200 mg PCH, capsule, soft from Pharmachemie B.V. The date of authorisation was on 9 September 2011 in the Netherlands.

The product is indicated for:

- headache
- fever and pain due to common cold or influenza
- dental pain
- pain during menstrual bleeding
- muscular pain
- backache
- rheumatic pain
- fever and pain following vaccination

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

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.
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 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA 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 use.

This national procedure concerns a generic application claiming essential similarity with the innovator product Brufen® 200 mg capsules (NL License RVG 25572) which was first registered in the Netherlands by Knoll in 1969 (original product). This product is now registered as Advil Liquid-Caps 200, soft capsules, with Pfizer B.V. as marketing authorisation holder.

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 Nurofen 200 mg Liquicaps, registered in the UK. 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.*). Ibuprofen is practically insoluble in water, very soluble in alcohol, in acetone, in methanol and in chloroform and slightly soluble in ethyl acetate. Ibuprofen is a racemic mixture of two isomers.

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 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 drug substance specification is in line with the Ph.Eur. and the CEP. 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 one full-scale batch. Given the fact that a CEP is available, this is considered to be acceptable.

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.

** 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 caps 200 mg PCH are wine red coloured, oval shaped soft gelatin capsules, containing colourless to light pale yellow coloured, transparent, viscous liquid, printed “142” in white colour on the capsule shell.

The soft capsules are packed in PVC/PVdC-aluminium blisters.

The excipients are: polyethylene glycol 400, sorbitol, sorbitan monooleate, potassium hydroxide and purified water.
The capsule shell consists of gelatin, polyethylene glycol 400, sorbitol, purified water, medium chain triglycerides and Ponceau 4 R.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. An initial formulation was tested against the innovator. During the development the composition and process parameters were optimised several times until the final manufacturing formula and method were obtained.
The composition of the batch used in the bioequivalence studies is identical to the proposed composition and the optimised manufacturing process as described in the dossier was used. Comparative dissolution data versus the innovator have been provided. A bioequivalence study was performed against the UK reference product. This is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The various steps of the manufacturing process have been described in sufficient detail. The manufacturing process is seen as a standard process. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. The non-compendial excipients are the pharmaceutical ink for printing on the capsule shell and the colourant Ponceau 4R. The analytical methods used for the control of both the colouring substance and the printing ink have been provided.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units, loss on drying, dissolution rate, assay, related substances, residual solvent and microbiological purity. The release and end of shelf-life specifications are identical. The specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided for one batch of 200 mg ibuprofen, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three pilot-scale batches stored at 25°C/60%RH (24 months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months). Data of storage at 40°C/75%RH show that the dissolution test fails during analysis of 3 months samples. The 12 months stability data at 30°C/65%RH and 24 months stability data at 25°C/60%RH are satisfactory. Only a slight decrease in the dissolution values is observed. Photostability results are included but for capsules packed into the blisters. The drug product should be stored in the original container to protect from light. On the basis of the stability data a shelf-life of 2 years has been granted, when stored below 30°C in the original container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only excipient obtained from animal origin. A CEP of gelatine as well as a certificate with respect to the TSE/BSE safety is included. This is acceptable.

II.2 Non-clinical aspects

This product is a generic formulation of Advil Liquid-Caps which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

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.
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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen caps 200 mg PCH (Pharmachemie B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Nurofen capsules 200 mg (Cardinal Healthcare, UK).

The choice of the reference product
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-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (20 males/4 females), aged 22-37 years. Each subject received a single dose (200 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours period. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 12.00 and 24.00 hours after administration of the products.

The overall study design is considered acceptable taking into account the absorption rate and half-lives. Also the washout period is acceptable.

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
Two subjects were withdrawn before the second period due to positive urine drug abuse tests. A total of 22 subjects completed both periods and were included in the statistical analyses.

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

Treatment N=<X>	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	65.24 ± 17.61	68.07 ± 17.98	27.34 ± 6.42	0.50 0.33 – 0.83	1.75 ± 0.42
Reference	66.92 ± 14.43	69.74 ± 14.63	29.88 ± 5.19	0.50 0.33 – 0.83	1.74 ± 0.37
***Ratio (90% CI)**	0.97 (0.93 – 1.02)	0.97 (0.93 – 1.02)	0.92 (0.85 – 0.98)	--	--
CV (%)	8.5	8.1	13.6	--	--

$AUC_{0-\infty}$	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 caps 200 mg PCH and Nurofen capsules 200 mg 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 studies have 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 post authorisation 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 Advil Liquid-Caps.

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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability score was 75% in the first round. Based on the results, some revisions were made. In the second test round, readability was 94%. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibuprofen caps 200 mg PCH, capsule, soft has a proven chemical-pharmaceutical quality and is a generic form of Advil Liquid-Caps. Advil 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 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 caps 200 mg PCH, capsule, soft was authorised in the Netherlands on 9 September 2011.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the intermediate and long term studies.
- The MAH committed to include the first three commercial batches in the stability program.

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