CBG MEB

Public Assessment Report

Scientific discussion

Ibuprofen Apotex 400 mg capsules, soft (ibuprofen)

NL/H/2790/001/MR

Date: 9 December 2014

This module reflects the scientific discussion for the approval of Ibuprofen Apotex 400 mg capsules, soft. The procedure was finalised on 21 July 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ibuprofen Apotex 400 mg capsules, soft from Apotex Europe B.V.

The product is indicated in adults and adolescents from ≥40 kg (12 years of age and above) for the symptomatic relief of:

- mild to moderate pain
- fever

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Nurofen® 400 mg Liquicaps. Nurofen was first registered as a 200 mg tablet formulation by Reckitt Benckiser in the UK in 1983. In the Netherlands, Nurofen Zavance Lea 400 mg Liquid Capsules (NL License RVG 31555), registered since 2008, is used as reference product.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Apotex 400 mg is a clear oval transparent soft gelatin capsule.

The capsules are packed in PVC/PE/PVdC/Al blisters.

The excipients are:
Capsules content - macrogol 600, potassium hydroxide, purified water
Capsule shell - gelatin, sorbitol liquid partially dehydrated (420)
Capsule printing - opacode WB black NS-78-17821, consisting of purified water, black iron oxide, propylene glycol, isopropyl alcohol and HPMC 2910/Hypromellose 6cP

II.2 Drug Substance

The established active substance ibuprofen sodium is described in the European Pharmacopoeia (Ph.Eur.). Ibuprofen is a white crystalline powder or colourless crystals, practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

The CEP procedure is used for both manufacturers 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 chemical-pharmaceutical specifications in relation to ibuprofen are in accordance with the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up. Satisfactory batch analyses results on three batches have been provided by the MAH.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions for one manufacturer, and for 3 years for the second manufacturer. Assessment thereof was part of granting the CEPs 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. Comparative dissolution profiles have been provided for Ibuprofen Apotex and the UK innovator product Nurofen 400 Liquicaps used in the bioequivalence study. Similarity was adequately demonstrated.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients are controlled in accordance with Ph.Eur. monographs except for the Opacode WB black. Opacode WB black is composed of well-known excipients that are controlled according to Ph.Eur. monographs.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form, and include limits for appearance, disintegration, identity, uniformity of dosage units, assay, dissolution, degradation products and microbiological tests. Validations of the analytical methods have been presented and accepted. Batch analyses are provided for the five batches. The results are all within the proposed specifications.

Stability of drug product
Stability data have been provided for three batches stored at 25°C/60% RH (24 months), 40°C/75% RH (6 months) and 30°C/65%RH (24 months). The capsules were packed in PVC/PE/PVdC/Al blisters. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Photostability testing has not been performed on Ibuprofen 400 mg soft gelatin capsules. Based on the results of photostability testing with the 200 mg strength produced by the same manufacturer it can be concluded that the product is not sensitive to light. The proposed shelf-life of 24 months with no storage for the drug product is considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All excipients apart from gelatin are of non-animal origin. Suppliers have confirmed their products are BSE/TSE free and submitted TSE Certificates of Suitability.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ibuprofen Apotex 400 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 Ibuprofen Apotex 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, 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen Apotex 400 mg (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Nurofen® 400 mg Liquicaps (Reckitt Benckiser, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states. The study was performed with three reference products: besides Nuforen 400 mg Liquicaps (UK), two other references were used, i.e. Nurofen Ultra Forte 400 mg liquid capsule from Poland and Nurofen® 200 mg tablet.
The capsule formulation from the UK (Nurofen® 400 mg Liquicaps) is the reference product for this application, which is considered appropriate as this is a soft gel capsule formulation just like the test product.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, randomised, four-way crossover bioequivalence study was carried out under fasted conditions in 25 healthy male and female subjects, aged 18-50 years. Each subject received a single dose (400 mg) of one of the 2 ibuprofen formulations. The capsule was orally administered with 240 ml water after an overnight fast. The dosing periods were separated by a washout period of 48 hours.

Blood samples were collected pre-dose and at 10.0, 15, 20, 25, 30, 35, 40, 50 minutes and 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3.0, 4, 6, 8 and 12 hours after administration of the products.

The study design is acceptable for an immediate-release oral formulation. A study under fasting condition is appropriate as the medicinal product can be taken with or without food.
T_{max} is reported between 40 to 100 minutes and plasma half life is around 2 hours. Therefore, blood sampling and washout period of at least 48 hours (i.e. at least 5 terminal half-lives to exclude carry-over effects) are also agreed.

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
One subject withdrew consent (after 4-h blood sample during Period 1) and hence 24 subjects completed the study and were assessed.

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}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	125.8 ± 26.2	129.2 ± 26.3	49.9 ± 15.1	0.8 (0.3 – 1.5)	--
Reference	125.8 ± 34.1	129.2± 34.8	46.7 ± 14	0.6 (0.3 – 2.5)	--
***Ratio (90% CI)**	1.01 (0.96 –1.07)	1.01 (0.96 –1.07)	1.07 (0.98 – 1.17)	--	--

$AUC_{0-\infty}$ 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 Apotex 400 mg is considered bioequivalent with Nurofen® 400 mg Liquicaps.

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 Ibuprofen Apotex 400 mg capsules.

Summary of safety concerns

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, betablockers, 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 • Use in children < 12 years/<40kg body weight • Aseptic meningitis in patients with systemic lupus erythematosus and mixed connective tissue disease
Important missing information	Not applicable.

No additional risk minimization measures are proposed for the ibuprofen capsules, which is considered acceptable.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nurofen. 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

User testing-evaluation of the package leaflet (PL) was submitted. Although the results are satisfactory the content of the proposed PL and the PL used in the test are not identical as the PL has changed compared to version that was user tested. The MAH has therefore also submitted a satisfactory bridging report to allow bridging the results of the user test to the proposed leaflet. The user test and bridging report were assessed and approved in procedure UK/H/4613/001/DC. No further user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ibuprofen Apotex 400 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Nurofen 400 mg soft 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 marketing authorisation was granted in the Netherlands on 12 June 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibuprofen Apotex 400 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 21 July 2014.

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