COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen Catalent 200 mg and 400 mg soft capsules (ibuprofen)

NL/H/5256/001-002/DC

Date: 12 December 2022

This module reflects the scientific discussion for the approval of Ibuprofen Catalent 200 mg and 400 mg Soft Capsules. The procedure was finalised on 27 April 2022. 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
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Member States have granted a marketing authorisation for Ibuprofen Catalent 200 mg and 400 mg Soft Capsules, from Catalent Germany Eberbach GmbH.

The product is indicated for the short-term symptomatic treatment of mild to moderate pain such as headache, dental pain, period pain, minor aches and sprains, fever and pain associated with the common cold. It is indicated in adults and adolescents from 40 kg body weight and aged 12 years and above.

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

This decentralised procedure concerns a generic application claiming essential similarity with the European reference products (ERP) products Moment 200 mg capsule molli (soft capsules) and Momentact 400 mg capsule molli (soft capsules), which have been registered in Italy by Aziende Chimiche Riunite Angelini Francesco - A.C.R.A.F. (Italy) since 2010.

The concerned member states (CMS) involved in this procedure were Estonia, Lithuania, Latvia, Poland and Romania.

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

Paediatric population

The applicant has provided an adequate discussion on the suitability of the drug product in relation to the relevant paediatric population (12 to 18 years) as per Guideline on the Pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2).

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Catalent are soft, oval capsules with a clear red gelatin shell printed with a logo in white ink and containing a clear liquid fill. The capsules contain as active substance 200 mg or 400 mg ibuprofen.

The soft capsules are packed in PVC/PVDC-aluminium or PVC/PE/PVDC-aluminium blister strips containing different number of capsules. The PVC layer may be clear or opaque. The blister strips are packed in a cardboard carton.

The excipients are:
Fill - macrogol 600, potassium hydroxide (E525), purified water.
Capsule shell - gelatin, sorbitol (liquid, partially dehydrated (E420)), ponceau 4R (E124) and purified water.
White printing ink (the following remain after printing) - propylene glycol (E1520), titanium dioxide (E171), polyvinyl acetate phthalate, macrogol 400 and ammonium hydroxide (E527).
Processing aids - triglycerides (medium chain), lecithin (E322).

The composition of the fill material of the two strengths is fully dose-proportional, where the 400 mg capsule fill contains exactly twice of each component as the 200 mg capsule fill.

II.2 Drug Substance

The active substance is ibuprofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder or colourless crystals and is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. Ibuprofen exists as a racemic mixture of the two optically active forms. Physical characteristics of particle size and polymorphism have no impact on this formulation as the drug substance is in solution.

The Certificate of Suitability to the monographs of the European (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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additionally tests for total phosphorus and hexane are included as described in the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Based on the data submitted, a retest period could be granted of 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 choice of excipients is justified and their functions explained. During the development of the manufacturing process, optimal formulation and mixing steps for the soft capsules were investigated and adjusted. A bioequivalence study was performed with the 400 mg product strength versus the respective reference product strength. For the additional 200 mg strength a biowaiver was claimed. For this, comparative dissolution testing at three pH's has been successfully submitted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches of each strength, in accordance with the relevant European guidelines. The manufacturing process consist of the preparation of the fill solution and the gelatin shell, followed by encapsulation of the fill and is finalised with a drying step.

Control of excipients

The excipients comply with Ph. Eur. and/or USP requirements, except for the colourant Ponceau-4R and the white printing ink Opacode NSP-78-18022. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for capsule appearance and dimensions, uniformity of dosage units, assay, identity (two methods), disintegration time, related substances, Ponceau 4R identity, dissolution and microbiological testing. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data of three batches per strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies have been performed with pivotal batches and full-scaled batches according with the ICH guidelines.

Stability data have been submitted for three pivotal batches of each strength packaged in (PVC/PVdC) and (PVC/PE/PVdC) clear duplex and triplex blisters. The batches were stored at 25°C/60% RH and 30°C/65% RH (both 36 months) and 40°C/75% RH (6 months). Furthermore, stability data have been submitted for full scaled batches of each strength, packaged in (PVC/PVdC) and (PVC/PE/PVdC) opaque (three batches) and clear (five batches) duplex blisters. The batches were stored at 25°C/60% RH and 30°C/65% RH (both 36

months). Stability results for pivotal and full scale batches were within specifications and no trends were observed. Photostability studies were performed on both pivotal and full scaled batches and showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life was granted of three years. The labelled storage conditions are 'Do not store above 30°C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For the excipient gelatin (sourced from bovine origin), scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ibuprofen Catalent 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 Catalent 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 Moment 200 mg capsule molli (soft capsules) and Momentact 400 mg capsule molli (soft capsules), which are 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 one bioequivalence study with the highest strength 400 mg, which is discussed below. For the 200 mg strength, a biowaiver was granted. Additionally, the MAH has submitted results of a previous bioequivalence study of ibuprofen 400 mg soft capsules (which is not the test product) versus 2 x 200 mg of Nurofen tablets. The latter study was executed in 2004.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ibuprofen Catalent 400 mg Soft Capsules (Catalent Germany Eberbach GmbH – Eberbach, Germany) is compared with the pharmacokinetic profile of the reference product Momentact 400 mg capsule molli (soft capsules), (Aziende Chimiche Riunite Angelini Francesco - A.C.R.A.F. (Italy).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

Based on acceptable bioequivalence study with the 400 mg product strength, a bio-waiver was requested for the 200 mg strength. A biowaiver can be granted if the following criteria are met:

- the strengths are manufactured by the same manufacturing process,
- the qualitative composition of the strengths is the same and is quantitatively proportional with regards to the fill material (capsule shell and colourants are exempt),
- similarity *in vitro* dissolution profiles of the strengths (dissolution, >85% in 15 min. at all three pH levels of 1.0-1.2, 4.5 and 6.8 using paddle apparatus at 100 rpm,
- a bioequivalence study is conducted on the highest strength

The comparative dissolution testing was assessed. The reference and tests batches used in the bioequivalence study were also use for the dissolution testing. The submitted data demonstrated that: the batch used in the bioequivalence study and dissolution testing was manufactured according to the finalised composition and manufacturing process at a

representative scale, the results of the bioequivalence study show a correlation dose-plasma concentrations ($AUC_{0-\infty}$), the qualitative composition of the two strengths is the same, and the dissolution profiles of the 200 mg strength tested at three pH's, was similar to the 400 mg strength. Based on the submitted information and *in vitro* data, it has been demonstrated that the criteria described above was met. Therefore, a biowaiver has been granted.

Bioequivalence study

Design

A single-dose, randomised, single centre, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male (n=13) and female (n=17) subjects, aged 20-56 years. Each subject received a single dose of 400 mg Ibuprofen. The soft capsule was orally administered in the morning with approx. 240 mL water after overnight fasting for at least ten hours. Fasting continued for at least four hours following drug administration, after which a standardised lunch was served. A supper was served thereafter, but not before nine hours after dosing. Water was allowed ad libitum until one hour pre-dose and beginning one hour after drug administration. There were two dosing periods, separated by a washout period of at least seven days.

Blood samples were collected at 0.00 (pre-dose), 0.17, 0.25, 0.33, 0.42, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, and 12.00 hours after administration of the products.

Ibuprofen is well absorbed from the gastrointestinal tract and extensively bound to plasma proteins. Following administration of ibuprofen liquid capsules on an empty stomach, median peak plasma concentration is achieved in approximately 30 minutes. When taken with food, peak plasma concentration of ibuprofen may be delayed. Consequently, the study bioequivalence study was performed under fasted conditions, the consumption of food was controlled and standardised for each confinement period and for all subjects.

The design of the study 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

Three subjects were withdrawn, one subject due to COVID-19 related precautions and two subjects due to difficulties with blood draws after doses of period 1. A total of 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibuprofen 400 mg soft capsules under fasted conditions.

Treatment N=27	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)
Test	133.7 ± 32.60	137.9 ± 36.01	45.38 ± 8.44	0.67 (0.33 – 1.50)	2.18
Reference	130.1 ± 29.12	134.7 ± 32.89	44.77 ± 10.58	0.67 (0.33 – 2.00)	2.32
***Ratio (90% CI)**	1.02% (0.99 – 1.06)	--	1.02% (0.94 – 1.11)	--	--
CV (%)	6.6	--	18.5	--	--

$AUC_{0-\infty}$ 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 Ibuprofen Catalent 400 mg is considered bioequivalent with Momentact 400 mg. The results of the bioequivalence study with the 400 mg formulation can be extrapolated to the 200 mg strengths according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr, section 4.1.6.

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 Catalent.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states 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 Momentact 400 mg. 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 (PL) 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 with three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Ibuprofen Catalent 200 mg and 400 mg Soft Capsules have a proven chemical-pharmaceutical quality and are generic forms of the respectively reference products Moment 200 mg capsule molli (soft capsules) and Momentact 400 mg capsule molli (soft capsules). Both reference products are well-known medicinal products 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibuprofen Catalent with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 April 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse