Public Assessment Report

Scientific discussion

Celecoxib Apotex 100 mg and 200 mg, capsules, hard
(celecoxib)

NL/H/2760/001-002/DC

Date: 29 April 2014

This module reflects the scientific discussion for the approval of Celecoxib Apotex 100 mg and 200 mg, capsules, hard. The procedure was finalised on 7 October 2013. 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 Celecoxib Apotex 100 mg and 200 mg, capsules, hard from Apotex Europe B.V.

The product is indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. 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 innovator product Celebrex Capsules 100 mg and 200 mg by Pfizer Limited UK, registered in the EU via Mutual Recognition Procedure SE/H/0198/001-002. The product was first approved in Sweden on 3 December 1999. In the Netherlands, Celebrex 100 mg and 200 mg (NL License RVG 25053-25054) has been registered since 4 May 2000.

The concerned member states (CMS) involved in this procedure were Belgium, Luxembourg and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Celecoxib Apotex 100 mg is a hard capsule with white opaque body and white opaque cap, imprinted “APO/C100” in blue ink.

Celecoxib Apotex 200 mg is a hard capsule with white opaque body and white opaque cap, imprinted “APO/C200” in yellow ink.

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

The excipients are:
- Capsule content - povidone (E1201), sodium lauryl sulphate (E487), crospovidone (E1202), magnesium stearate (E572)
- Capsule shell - gelatin, titanium dioxide (E171)
- Printing ink - 100 mg capsules: FD&C blue #2 Aluminum lake (E132), 200 mg capsules: Yellow iron oxide (E172)

The formulation of the two strengths is directly proportional.

II.2 Drug Substance

The active substance is celecoxib, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white or pale yellow powder, which is soluble in methanol, acetone, ethanol, ethyl acetate and ethylene chloride.

Four crystalline forms of celecoxib are known (Form I, II, III and IV) as well as amorphous celecoxib. The crystalline form of celecoxib used corresponds to Form II.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Details on characteristics, manufacturing process, impurity profile, specifications, analytical procedures and validations of drug substances are presented in Active Substance Master Files. The manufacturing has been sufficiently described and justified.

**Quality control of drug substance**
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents, particle size, polymorphic form and bulk density. 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 are provided for three batches of each supplier.

**Stability of drug substance**
Stability data on the active substance are provided for each supplier during storage at 25°C/60% RH and 40°C/75% RH. No significant changes in any parameters were observed. The proposed retest periods of 5 years and 4 years for the two suppliers are justified.

**II.3 Medicinal Product**

**Pharmaceutical development**
The development of the product is described, the choice of excipients is justified and their functions explained. Celecoxib is a BCS Class II drug (low solubility and high permeability). For such drugs, particle size is considered critical for dissolution, solubility and bioavailability. The MAH demonstrated that particle size is adequately controlled.
The biowaiver for the 100 mg capsule strength can be accepted on quality grounds based on the proportional formulation of the 100 mg and 200 mg capsules and the comparative pH dissolution study of the two strengths. The pharmaceutical development of the product is adequately performed.

**Manufacturing process**
The manufacturing process of the capsules is considered a standard process, it consists of wet granulation, drying, milling, blending and encapsulation.
The manufacturing process is adequately validated according to relevant European guidelines.
Process validation data on the product is presented for 8 pilot-scale batches of the common blend and 4 pilot-scale batches of each capsule strength.

**Control of excipients**
The excipients comply with compendial standards. These specifications are acceptable.

**Quality control of drug product**
The product specification includes tests for appearance, identity, average weight, water content, dissolution, uniformity of dosage units, assay, related substances and microbiological purity. The analytical methods are adequately described and validated.
Batch analytical data from the proposed production site are provided on 4 pilot-scale batches of each capsule strength, demonstrating compliance with the release specification.

**Stability of drug product**
Stability data on the product are provided for 4 pilot-scale batches of each capsule strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. No clear changes or trends were observed. All parameters remain within the specified limits at accelerated and long-term storage conditions. Photostability studies showed that the capsules are not sensitive to light.
Based on the data provided, the proposed shelf-life of 2 years is acceptable. No special storage requirements are necessary.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
The hard gelatin capsule shells are derived from animal origin and meet the EU BSE/TSE requirements for bovine derived materials.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
Based on the submitted dossier, the member states consider that Celecoxib Apotex 100 mg and 200 mg hard capsules have 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 Celecoxib 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 Celebrex capsules, 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

Celecoxib 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 Celecoxib Apotex 200 mg (Apotex Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Celebrex capsules 200 mg (Pfizer Limited, UK). The capsule was also compared to a non-EU reference product Celebrex, which is not considered relevant for the European market. The details and results from this second reference product are therefore not discussed below.

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

Biowaiver

A biowaiver is for the 100 mg strength is being applied for, with the following justification:

- Celecoxib Apotex 200 mg capsules is clinically bioequivalent to the reference product
- Up to 200 mg, AUC and C_max increase proportionally with dose.
- The formulation of the two strengths is directly proportional.
- Both strengths are manufactured in the same site with the same manufacturing process.

Comparative in vitro dissolution testing between the 100 mg strength and the 200 mg bioequivalence batch was performed at pH 1.2, 4.5, 6.8 and 12 (with surfactant) and at pH 1.2 and 6.8 (without surfactant) was done. The results without surfactant showed no essential dissolution with both test products (100 mg and 200 mg) and reference product (200mg). The overall conclusion on the comparative in vitro dissolution testing is that the biowaiver for the 100 mg strength is acceptable.
Bioequivalence studies

Design
A single-dose, randomised, three-way crossover bioequivalence study was carried out under fasted conditions in 90 healthy male subjects, aged 18-45 years. Each subject received a single dose (200 mg) of one of the 3 celecoxib formulations. The capsule was orally administered with 240 ml water after an overnight fast. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 13, 16, 24, 32, 40, 48 and 60 hours after administration of the products.

The design of the study is acceptable. The active substance can be taken with or without food. 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.

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
Seventy-six (76) subjects completed the study in its entirety (completed all the 3 periods) and 3 subjects completed 2 periods with at least one test and one UK reference treatment. Consequently, celecoxib plasma levels from seventy-nine (79) subjects were included in the pharmacokinetic/statistical analysis. Fourteen subjects were withdrawn at some stage of the study due to adverse events (4), positive drug test (3) or did not show for follow-up (7).

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=79</th>
<th>AUC\textsubscript{0-t} (ng h/ml)</th>
<th>AUC\textsubscript{0-∞} (ng h/ml)</th>
<th>C\textsubscript{max} (ng/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>8577 ± 4743</td>
<td>9160 ± 7101</td>
<td>814 ± 322</td>
<td>2.7 (0.8 – 4.5)</td>
<td>--</td>
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</tr>
<tr>
<td>Reference</td>
<td>9221 ± 5263</td>
<td>9897 ± 7944</td>
<td>853 ± 363</td>
<td>2.3 (0.8 – 8)</td>
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</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.92 (0.89–0.95)</td>
<td>0.92 (0.89–0.95)</td>
<td>0.97 (0.90–1.04)</td>
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<tr>
<td>CV (%)</td>
<td>--</td>
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\*ln-transformed values

The 90% confidence intervals calculated for AUC\textsubscript{0-t}, AUC\textsubscript{0-∞}, and C\textsubscript{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Celecoxib Apotex 200 mg is considered bioequivalent with Celebrex 200 mg capsules.

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).

The results of the study with the 200 mg formulation can be extrapolated to the 100 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan
The MAH has submitted a risk management plan (RMP), 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 Celecoxib Apotex.

Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Cardiovascular thrombotic events</th>
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<tbody>
<tr>
<td></td>
<td>Gastrointestinal ulceration-related events</td>
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<tr>
<td></td>
<td>Renal toxicity, fluid retention, and edema</td>
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<td></td>
<td>Hypertension</td>
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<td></td>
<td>Hypersensitivity reactions</td>
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<tr>
<td></td>
<td>Severe skin reactions</td>
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<tr>
<td></td>
<td>Severe hepatic reactions</td>
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</tbody>
</table>

| Important potential risks                                      | None                                                                   |
| Important missing information                                  | Safety in juvenile idiopathic arthritis (JIA)                          |
|                                                                | Use during pregnancy                                                  |

Routine risk minimisation activities are considered sufficient for this product, as there are currently no additional risk minimisation measures required for the innovator product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Celebrex. 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 the reference product Celebrex. 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 with 2 participants, followed by two rounds with 10 participants each. After the pre-round, as well as after the first round with 10 participants, no amendments of the PIL were considered necessary. 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

Celecoxib Apotex 100 mg and 200 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Celebrex capsules. Celebrex 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.

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 Celecoxib Apotex 100 mg and 200 mg capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 October 2013.

There were no post-approval commitments made during the procedure.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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