

# **Public Assessment Report**

## **Scientific discussion**

**Bixocel 100 mg and 200 mg, capsules, hard  
(celecoxib)**

**NL/H/2796/001-002/DC**

**Date: 28 July 2014**

**This report includes a summary, on pages 9-11.**

**This module reflects the scientific discussion for the approval of Bixocel 100 mg and 200 mg, capsules, hard. The procedure was finalised on 19 December 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 Bixocel 100 mg and 200 mg, capsules, hard from Synthon 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 Celebra 100 mg and 200 mg, capsules, hard, registered in Sweden by Pfizer AB since 3 December 1999. In the Netherlands, Celebex 100 mg and 200 mg (NL License RVG 25053-25054) was registered on 4 May 2000 through Mutual Recognition Procedure SE/H/0198/001-002.

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

The concerned member states (CMS) involved in this procedure were Czech Republic, France, Germany, Portugal, Romania, Spain and the United Kingdom.

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

## II. QUALITY ASPECTS

### II.1 Introduction

Bixocel 100 mg is an opaque, white, hard gelatin capsule. The body contains a blue band and white text "C9OX-100".

Bixocel 200 mg is an opaque, white, hard gelatin capsule. The body contains a yellow band and white text "C9OX-200".

The capsules are packed in PVC/Al blisters.

The excipients are:

*Granulate* - lactose monohydrate, povidone (E1201), croscarmellose sodium (E468), sodium lauryl sulphate (E487), magnesium stearate (E572)

Capsule shell - gelatin (E441), titanium dioxide (E171), iron oxide yellow (E172)

*Printing ink (100 mg)* - shellac (E904), propylene glycol (E1520), FD & C Blue #2 Aluminum Lake (E132)

*Printing ink (200 mg)* - shellac (E904), propylene glycol (E1520), iron oxide yellow (E172)

The capsule content of the two strengths is dose 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 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 III.

The Active Substance Master File (ASMF) procedure is used by both manufacturers 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 have been presented in an Active Substance Master File. 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 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 have been provided for three batches of each supplier.

#### Stability of drug substance

Stability data on the active substance have been provided for each supplier during storage at 40°C/75%RH and 25°C/60%RH. No significant changes in any parameters were observed. The proposed retest periods of 2 years and 5 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). 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, blending and encapsulation.

The manufacturing process is adequately validated according to relevant European guidelines. Process validation data on the product is presented for 3 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, 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 sites are provided on 3 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 3 pilot-scale batches of each capsule strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Additional batches from a second production site have been provided for 3 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 30 months 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 and lactose monohydrate are derived from animal origin and meet the EU BSE/TSE requirements for bovine derived materials. For lactose a TSE statement is provided

### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Bixocel 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 Bixocel 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 Celebra 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 Bixocel 200 mg (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Celebrex capsules 200 mg (Pfizer, Germany).

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 for the 100 mg strength has been granted, as the following conditions have been fulfilled:

- Bixocel 200 mg capsules is clinically bioequivalent to the reference product
- Up to 200 mg, pharmacokinetics of celecoxib is linear.
- The qualitative composition of celecoxib 100 and 200 mg capsules is the same.
- The ratio between the amount of active substance and the excipients of Celecoxib 100 and 200 mg capsules is the same
- Both strengths are manufactured in the same site with the same manufacturing process.
- The *in vitro* dissolution profiles of the 100 mg capsules and 200 mg capsules are similar.

#### Bioequivalence study

##### *Design*

A single-dose, randomised, four-period, two-treatment, two-sequence, replicate crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, 19 males and 17

females. Each subject received a single dose (200 mg) of one of the 2 celecoxib formulations. The tablet was orally administered with 200 ml water after an overnight fast of 10 hours. There were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 32.0, and 48.0 hours after administration of the products.

The design of the study is acceptable. Celebrex may be taken with or without food. The procedures followed for a fasting condition and a wash-out period of 7 days (*i.e.* at least 5 terminal half-lives to exclude carry-over effects) are 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*

Thirty-five (35) subjects, aged 18-44 years, completed all four study periods. One subject fully completed three study periods and dropped-out during the wash-out Period 3 due to personal reasons. She was included in the pharmacokinetic and statistical analysis, according to study protocol. The analysis was based on data from a total of 36 subjects.

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

Treatment	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test (n=72)</b>	4993.3 $\pm$ 34	5733.7 $\pm$ 38	552.1 $\pm$ 48	2.67 (1.00 – 5.00)	--
<b>Reference (n=71)</b>	4939.4 $\pm$ 32	5832.8 $\pm$ 41	540.3 $\pm$ 46	2.33 (1.00-8.00)	--
<b>*Ratio (90% CI)</b>	1.00 (0.97 – 1.03)	0.98 (0.94 – 1.02)	1.01 (0.94 – 1.09)	--	--
<b>CV (%)</b>	--	--	--	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80 – 1.25. The intra-subject CV% of C<sub>max</sub> for the reference product was in this study 28.84. Therefore, widening of the 90% CI was not necessary.

Based on the submitted bioequivalence study Bixocel 200 mg is considered bioequivalent with Celebrex 200 mg capsules.

Both Bixocel 200 mg and Celebrex 200 mg capsules were well tolerated in healthy volunteers as a single oral dose administered under fasting conditions. No serious adverse event (SAE) appeared. Two (2) subjects experienced a total of three (3) mild adverse events (AEs) over the course of the study. None of the AEs were considered related to test or reference product

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 Bixocel.

Summary table of safety concerns as approved in RMP

<b>Important risks identified</b>	<b>Cardiovascular thrombotic events</b>
	<b>Gastrointestinal ulcer related events</b>
	<b>Hypertension</b>
	<b>Hypersensitivity reactions</b>
	<b>Renal toxicity, fluid retention and edema</b>
	<b>Safety in juvenile idiopathic arthritis (JIA)</b>
	<b>Severe hepatic reactions</b>
	<b>Severe skin reactions</b>
<b>Important information missing</b>	<b>Children</b>
	<b>Overdose</b>
	<b>Pregnancy and lactation</b>

Only routine risk minimization activities are planned for Bixocel, which comprises warnings/ comments in the SmPC and PL. This is acceptable.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Celebra. 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 Celebra. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the innovator product Celebrex.

The MAH has submitted:

- comparison of the proposed package leaflet and the PL of the innovator product, including evaluation of differences
- a bridging report regarding the design and layout of the package leaflet applied for.

Regarding the comparison of the proposed package leaflet with the innovator product, the MAH concludes that only minor content-related differences between the proposed PL and innovator PL exist. It is concluded that the proposed PL of Bixocel 100 mg and 200 mg hard capsules does not substantially differ from the Celebrex PL and is considered readable and acceptable to the patient. The member states agree that further user testing is not required.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bixocel 100 mg and 200 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Celebra capsules. Celebra 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 Bixocel 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 19 December 2013.

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

## 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

# **Summary Public Assessment Report**

## **Generics**

**Bixocel 100 mg and 200 mg, capsules, hard  
(celecoxib)**

**NL/H/2796/001-002/DC**

**Date: 28 July 2014**

# Summary Public Assessment Report

## Generics

Bixocel 100 mg and 200 mg, capsules, hard

Active substance: celecoxib

This is a summary of the public assessment report (PAR) for Bixocel 100 mg and 200 mg, capsules, hard. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Bixocel.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

### **What is Bixocel and what is it used for?**

Bixocel is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Celebrex Capsules 100 mg and 200 mg.

This medicine is used for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in adults.

### **How is this medicine used?**

The medicine can only be obtained with a prescription. The recommended daily dose is 200 mg and can be increased by the doctor to a maximum of 400 mg, if needed.

The capsules can be taken at any time of the day, with or without food. However, patient should try to take each dose at the same time each day.

This medicine should be swallowed with a sufficient amount of water (e.g. one glass).

### **How does this medicine work?**

The active substance in Bixocel, celecoxib, belongs to a group of medicinal products called nonsteroidal anti-inflammatory drugs (NSAID), and specifically a sub-group known as (COX-2) inhibitors. The human body makes prostaglandins that may cause pain and inflammation. In conditions such as rheumatoid arthritis and osteoarthritis the body makes more of these. This medicine acts by reducing the production of prostaglandins, thereby reducing the pain and inflammation.

### **How has this medicine been studied?**

Because Bixocel is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Celebrex capsules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

### **What are the benefits and risks of this medicine?**

Because Bixocel is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine.

### **Why is this medicine approved?**

It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be bioequivalent to Celebrex. Therefore, the view was that, as for Celebrex, the benefit outweighs the identified risk.

### **What measures are being taken to ensure the safe and effective use of Bixocel?**

A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Bixocel, including the appropriate precautions to be followed by healthcare professionals and patients.

### **Other information about this medicine**

The marketing authorisation for Bixocel was granted in the Netherlands on 26 May 2014.

The full PAR for this medicine can be found on the website <http://mri.medagencies.org/Human>. For more information about treatment with Bixocel 100 mg and 200 mg capsules, read the package leaflet:

([http://mri.medagencies.org/download/NL\\_H\\_2796\\_001\\_FinalPL.pdf](http://mri.medagencies.org/download/NL_H_2796_001_FinalPL.pdf)) or contact your doctor or pharmacist.

This summary was last updated in July 2014.