CBG MEB

Public Assessment Report

Scientific discussion

Ecoxyton 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets

(etoricoxib)

NL/H/3269/001-004/DC

Date: 24 November 2016

This module reflects the scientific discussion for the approval of Ecoxyton 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. The procedure was finalised on 19 November 2015. 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
BP	British 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 Ecoxyton 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets, from Synthon B.V.

The product is indicated in adults and adolescents (16 years of age and older) for:

- The symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.
- The short-term treatment of moderate pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see SmPC sections 4.3 and 4.4).

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 products Arcoxia 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (NL License RVG 34279, 27705-27707) which have been registered in the Netherlands by Merck Sharp & Dohme B.V. since 9 July 2002 (60, 90, 120 mg) and 22 January 2008 (30 mg) through procedure UK/H/0532/001-004.

The concerned member states (CMS) involved in the initial procedure were Finland, Germany and Spain, and Iceland was CMS in a subsequent repeat-use procedure (NL/H/3269/001-004/E/001).

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

II. QUALITY ASPECTS

II.1 Introduction

Ecoxyton is a white round biconvex film-coated tablet debossed with “E9OX” on one side and “30”, “60”, “90” or “120” on the other side. Each film-coated tablet contains 30 mg, 60 mg, 90 mg or 120 mg of etoricoxib.

The film-coated tablet is packed in aluminium/aluminium blisters.

The excipients are:
Tablet core - anhydrous calcium hydrogen phosphate, microcrystalline cellulose, sodium croscarmellose and magnesium stearate
Tablet coating - lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin

The tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is etoricoxib, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur., BP). The active substance is practically insoluble in water. Etoricoxib is manufactured as crystalline form I. The drug substance is not hygroscopic and has no chiral centres.

For both manufacturers, the Active Substance Master File (ASMF) procedure is used for 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 two manufacturers 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

Manufacturer-I

The manufacturing process consists of three chemical steps and a purification step. Starting materials have been defined. No class 1 solvents or heavy metal catalysts are used in the synthesis. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Manufacturer-II

Etoricoxib is produced from the two intermediates in one chemical step and one purification step. No class 1 solvents or heavy metal catalysts are used in the synthesis. All synthesis steps are adequately described, adequate specifications are applied for the starting materials, and adequate controls are applied.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches of each manufacturer.

Stability of drug substance

Manufacturer-I

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). One additional batch was stored at 25°C/60% RH for 12 months. No changes were observed at both conditions. Based on the stability data the proposed re-test period of 30 months without special storage conditions is accepted.

Manufacturer-II

Stability data on the active substance have been provided for six batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (3 months). In addition data for three batches are available at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). For all test parameters no significant changes were observed. Based on the available stability data, a retest period of two years has been accepted for etoricoxib. To ensure the quality of the drug substances even in warm climates the storage condition “Store below 25°C” is acceptable.

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. All the excipients used are well known and commonly used in immediate release formulations. The composition is qualitatively the same as the innovator product, Arcoxia.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Ecoxyton and reference product, Arcoxia. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Sufficient comparative dissolution data between the test and reference product have been provided.

For the lower strengths a biowaiver is requested. The 30 mg, 60 mg and 90 mg tablets are fully dose proportional. Comparative dissolution data in media with different pH (1.2, 4.5, and 6.8) between 120 mg tablets and the other strengths (30 mg, 60 mg and 90 mg) have been provided. The results show that all three tablet strengths have comparable dissolution characteristics throughout the physiological pH range.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process comprises the following steps: mixing, compaction, milling, mixing, blending, lubrication, compression, film-coating and packaging. It has been validated according to

relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients are all in compliance with the Ph.Eur. Specifications for Opadry coating material have been provided. 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 description, identification of the active substance, dissolution, uniformity of dosage units, HPLC related substances, HPLC assay, water content 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 from three batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two batches per strength per manufacturing site. The batches were stored at 25°C/60% RH (9 to 12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The results meet the set requirements. On basis of the data submitted, a shelf life was granted of 24 months without specific storage temperature. The product is photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is manufactured from milk which is sourced from healthy animals in the same conditions as milk collected for human consumption. Lactose is prepared without the use of other ruminant materials than milk and calf rennet. 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 Ecoxyton 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 Ecoxyton 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 Arcoxia which is available on the European market. Reference is made to the pre-clinical 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

Etoricoxib 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, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ecoxyton 120 mg film-coated tablets (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Arcoxia 120 mg film-coated tablets (MSD Sharp & Dohme B.V., the Netherlands).

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.

Biowaiver
The different tablets strengths are manufactured by the same manufacturing process, they contain the same excipients and they are dose-proportional to each other. Comparative dissolution testing was performed in three media (pH 1.2, 4.5, and 6.8) and demonstrated the similarity (with the mathematical calculation of f2) between the biobatch and all concerned tablet strengths. A biowaiver was granted for the additional strengths.

Design
A single dose, two-treatment, two-period, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 21-72 years. Each subject received a single dose (120 mg) of one of the 2 etoricoxib formulations. The tablet was orally administered with 240 ml water after an overnight fast of approximately 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and post-dose at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8,10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

The use of the highest strength to demonstrate bioequivalence is appropriate. In addition, fasting conditions are adequate as etoricoxib may be taken regardless of food. The wash-out period was 14 days which was more than 5 half-lives of etoricoxib (half-life is 22 hours). Furthermore, the sampling period was long enough and the sampling scheme was adequate to estimate the pharmacokinetic parameters.

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 from the study before dosing in period-II due to clinical events and was therefore not included in the statistical analysis. 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	AUC_{0-72} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	31837 ± 11015	2496 ± 823	1.25 ± 0.90 (0.50 - 4.0)
Reference	31699 ± 11260	2394 ± 745	1.49 ± 0.87 (0.75 – 4.0)
***Ratio (90% CI)**	1.00 (0.98 – 1.03)	1.03 (0.96 – 1.10)	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ecoxyton is considered bioequivalent with Arcoxia.

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).

Safety
Twenty-seven adverse events (AEs) were reported by 10 of the subjects who participated in this study. The AEs reported with the highest incidence were dysgeusia and headache. The incidence of AEs was similar for subjects dosed with the Test and Reference products. Overall, most of the AEs were deemed mild and moderate in severity. No severe adverse events were observed during the study. No subject was withdrawn for safety reasons.

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 Ecoxyton.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Thrombotic cardiovascular complications • Gastrointestinal complications • Cardio-renal risk – fluid retention, oedema and hypertension • Severe skins reactions and hypersensitivity • Severe hepatic reactions
Important potential risks	• Pregnancy • Off-label use
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 Arcoxia. 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

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 Arcoxia film-coated tablets. The bridging report submitted by the MAH has been found acceptable. In addition, the MAH has previously performed a successful user test of an Eplerenone 25 mg and 50 mg film-coated tablets PL. This user test supports the changes made to the PL compared to the parent PL (e.g. house style).

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ecoxyton 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Arcoxia film-coated tablets. Arcoxia 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 Ecoxyton with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 November 2015.

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
Addition of a site where batch control/testing takes place.	NL/H/3269/001 -004/IA/001	IA	15-3-2016	7-4-2016	Approval	N
Repeat-use procedure with Iceland as CMS.	NL/H/3269/001 -004/E/001	E	30-5-2016	30-5-2016	Approval	N