CBG MEB

Public Assessment Report

Scientific discussion

Etoricoxib Glenmark 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets

(etoricoxib)

NL/H/3576/001-004/DC

Date: 5 July 2017

This module reflects the scientific discussion for the approval of Etoricoxib Glenmark 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets. The procedure was finalised on 18 August 2016. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Etoricoxib Glenmark 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets from Glenmark Pharmaceuticals Europe Limited.

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.

Etoricoxib Mylan is indicated in adults and adolescents (16 years of age and older) for the short-term treatment of moderate pain associated with dental surgery.

The decision to prescribe a selective cyclooxygenase-2 (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 product Arcoxia 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (NL License RVG 34279 and 27705-27707) which has been registered 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 this procedure were Germany, Greece, Spain, Italy 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

Etoricoxib is a film-coated tablet.

- 30 mg: blue-green round biconvex film coated tablets marked “11” on one side and ‘G’ on the other side.
- 60 mg: dark green round biconvex film coated tablets marked “76”on one side and “G” on the other side.
- 90 mg: white round biconvex film coated tablets marked “757”on one side and “G” on the other side.
- 120 mg: pale- green round biconvex film coated tablets marked “758”on one side and “G” on the other side.

Each film-coated tablet contains 30 mg, 60 mg, 90 mg or 120 mg of etoricoxib.

The film-coated tablets are packed in PVC/PVDC - Aluminium blisters.

The excipients are:
Tablet core: dicalcium phosphate anhydrous (calipharm A), microcrystalline cellulose (avicel PH 101), croscarmellose sodium (ac-di-sol), magnesium stearate and microcrystalline cellulose (avicel PH 200 LM).
Tablet coating:
For 30 mg, 60 mg and 120 mg – hypromellose, titanium dioxide (E171), macrogol, indigo carmine aluminium lake (E132), iron oxide yellow (E172), isopropyl alcohol and methylene chloride (dichloromethane).

For 90 mg – hypromellose, titanium dioxide (E171), macrogol, isopropyl alcohol and methylene chloride (dichloromethane).

The four tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is etoricoxib, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Etoricoxib is a white to pale yellow powder. The active substance is freely soluble in acetone, soluble in methanol, chloroform and dimethyl sulphoxide, sparingly soluble in ethanol and insoluble in water. Etoricoxib does not exhibit structural isomerism. The crystalline polymorphic form-1 has been confirmed and is routinely tested.

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 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
The active substance has been adequately characterised. Its manufacturing process consists of four steps to get the desired polymorphic form. Sufficient details of the manufacturing process have been presented.

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.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). In addition stability data have been provided of one scaled up batch stored at 25°C/60% RH (18 months). No changes were observed at long term or accelerated conditions. Based on the stability data the proposed retest period of 36 months without special storage conditions could be granted.

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. Also the manufacturing process development has been sufficiently described, including evaluation of the dry granulation method, lubrication time, compaction force and the effect of hardness.

A bioequivalence study was performed between the 120 mg strength of the test and the reference product. *In vitro* dissolution in 0.1N HCl is equally fast (>85% within 15 minutes) for both the test and reference product. Dissolution in pH 4.5 acetate buffer and pH 6.8 phosphate buffer is slower for both products. As proof of similarity f_2 values are provided.

A biowaiver of the lower strengths has been justified and is substantiated by the dissolution profiles at three different pH conditions (1.2, 4.5 and 6.8) of the 30 mg, 60 mg and 90 mg products versus the 120 mg product batch used in the bioequivalence study.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. The manufacturing process comprises of several phases: sifting, dry mixing, roll compaction and diminution, blending,

sifting, lubrication, compression, film coating and packaging. The manufacturing process is standard and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three exhibit batches in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. or in-house specifications. 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, colour, average weight, dissolution, uniformity of dosage units by mass variation, related substances, assay, water content, residual solvents and microbial quality. The limits for dissolution are acceptable. No batch release or stability results are present in the dossier of product tested at time point 15 minutes. The MAH committed that they will continue to perform the dissolution test at batch release and in the stability studies according to the approved dissolution release and shelf-life limits with testing at 15 minutes and that, should any results deviate from the limits, this will be reported to the authorities. 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 site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on a sufficient amount of batches stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH have been provided. The conditions used in the stability studies are according to the ICH stability guideline. Based on the available stability data the proposed shelf life limit of 12 months and storage conditions “store below 30°C” are justified. Photostability has been adequately demonstrated in accordance with ICH Q1B guideline.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Etoricoxib Glenmark 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 Etoricoxib Glenmark 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 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

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 Etoricoxib Glenmark 120 mg, film-coated tablets (Glenmark Pharmaceuticals Europe Limited, UK) is compared with the pharmacokinetic profile of the reference product Arcoxia 120 mg film-coated tablets (Merck Sharp & Dohme Ltd, UK).

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
Sufficient data have been provided to show that all criteria for biowaiving the results of the bioequivalence study performed with the 120 mg strength to the 30 mg, 60 mg and 90 mg strengths are met:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths.
- Appropriate *in vitro* dissolution data confirms the adequacy of waiving additional *in vivo* bioequivalence testing. The submitted dissolution data showed dissolution of more than 85% within 15 min (at pH 1.2) or the f_2 values were well above 50 (pH 4.5 and 6.8).

Design
A single dose, two-treatment, two-sequence cross-over bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 22-39 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. There were 2 dosing periods, separated by a washout period of 22 days.

Blood samples were collected pre dose and at 0.08, 0.16, 0.25, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12, 18, 24, 36, 48, 72, 96, 120 and 168 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.

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 for personal reasons. Therefore 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-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	50568.03	53896.19	2649.26	1.00 (0.50 – 3.50)	28.82
Reference	48270.89	51487.89	2433.85	1.75 (0.50 – 24.00)	30.26
***Ratio (90% CI)**	1.04 (0.99 – 1.09)	1.04 (1.00 – 1.09)	1.10 (1.03 – 1.18)	--	--
CV (%)	12.02	11.34	16.26	--	--

$AUC_{0-\infty}$ 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 Etoricoxib Glenmark 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).

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 Etoricoxib Glenmark.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Cardiovascular thrombotic events (myocardial infarction, stroke) • Serious gastrointestinal complications (perforation, ulcer, bleeding) • Cardio-renal risk – Fluid retention oedema and hypertension • Severe skin reactions • Hypersensitivity
Important potential risks	None
Missing information	• Use in patients with renal insufficiency • Use in patients with hepatic impairment • Use during pregnancy and lactation • Paediatric use (<16 years of age)

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

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 6 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Etoricoxib Glenmark 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Arcoxia 30 mg, 60 mg, 90 mg and 120 mg 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 Etoricoxib Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 August 2016.

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
Extension of shelf life (12 months to 18 months)	NL/H/3576/ 001-004/IB/001	IB	31-10-2016	30-11-2016	Approval	No
Addition of batch releaser	NL/H/3576/ 001-004/IA/002	IA	6-4-2017	6-5-2017	Approval	No
Extension of shelf life (18 months to 24 months)	NL/H/3576/ 001-004/IB/003	IB	20-4-2017	16-5-2017	Approval	No
Addition of a drug substance manufacturer	NL/H/3576/IA/004/G	IA	24-4-2017	5-5-2017	Approval	No