CBG MEB

Public Assessment Report

Scientific discussion

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

(etoricoxib)

NL/H/3151/001-004/DC

Date: 7 July 2016

This module reflects the scientific discussion for the approval of Etoricoxib Mylan 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets. The procedure was finalised on 22 July 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 Etoricoxib Mylan 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets from Mylan 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.

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 Belgium, Germany, Spain, Finland, France (only 30 and 60 mg), Ireland, Luxemburg, Portugal and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Etoricoxib Mylan is a film-coated tablet.

- 30 mg tablets: Blue green, film-coated, round, biconvex, bevelled edge tablet debossed with ‘M’ on one side and ‘EC1’ on the other side.
- 60 mg tablets: Green, film-coated, round, biconvex, bevelled edge tablet debossed with ‘M’ on one side and ‘EC2’ on the other side.
- 90 mg tablets: White, film-coated, round, biconvex, bevelled edge tablet debossed with ‘M’ on one side and ‘EC3’ on the other side.
- 120 mg tablets: Pale green, film-coated, round, biconvex, bevelled edge tablet debossed with ‘M’ on one side and ‘EC4’ on the other side.

The film-coated tablet contains as active substance 30 mg, 60 mg, 90 mg or 120 mg of etoricoxib.

The film-coated tablet is packed in:

- Cold form blister pack comprising of cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on other side i.e. OPA/Al/PVC) on one side and hard tempered aluminium foil (coated with VMCH heat seal lacquer) on the other side.
- PVC/PVdC blister pack comprising of clear, transparent PVC laminated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on other side (PVdC/PVC/Al).
- HDPE bottle pack comprises of round wide mouth white high density polyethylene (HDPE) bottle with polypropylene (PP) screw closure with induction sealing liner along with wad.

The excipients are:

Core:

- Calcium hydrogen phosphate, anhydrous

- Cellulose, microcrystalline
- Croscarmellose sodium
- Silica, colloidal anhydrous
- Magnesium stearate

Tablet coating:
All strengths
- Hypromellose
- Lactose monohydrate
- Titanium dioxide (E171)
- Triacetin
- Carnauba wax

30 mg
- Brilliant blue FCF (E133)
- Iron oxide black (E172)
- Iron oxide yellow (E172)

60 mg and 120 mg
- Iron oxide yellow (E172)
- Indigo carmine (E132)

The four 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. and BP). The active substance is practically insoluble in water. It has no chiral centres and is manufactured as crystalline form I. The drug substance is not hygroscopic.

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 three steps to get the desired polymorphic form Form-I. Sufficient details of the manufacturing process have been presented.

Quality control of drug substance
The drug substance specification has been established in-house by the ASMF-holder. 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 consecutive production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three consecutive production scaled batches stored at 25°C/60% RH (9 months) and 40°C/75% RH (6 months). No changes were observed at long term or accelerated conditions. Based on the stability data the proposed retest period of 12 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 excipients are well known and usual for the product. The formulation of Etoricoxib Mylan film-coated tablets is based on literature research and characterisation of reference product. The composition has been optimised based on dissolution profiles compared to the reference product.

The 120 mg drug product batch used in the bioequivalence study is manufactured with the same manufacturing process and composition as described. The similarity of the drug product versus the reference product used in the bioequivalence study has been adequately demonstrated.

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.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: pre-blending, granulation, sifting, blending, compression, film-coating and packaging. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches. All three pilot scaled batches are manufactured from one pilot scaled common blend batch. This is justified.

Control of excipients
The excipients comply with the Ph.Eur. or Directive 2008/128/EC. 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 and the colour, dissolution, uniformity of dosage units, related substances, 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 on three consecutive production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches per strength packed in the proposed packagings in accordance with applicable The batches were 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. At all conditions an increase in water content was observed in the PVC/PVdC-Al blister pack. In the Al-Al blister packs and the HDPE bottle packaging no trends were observed. The drug product is considered to be photostable.
The proposed shelf life of 24 months can be granted based on the provided stability data and the decision tree for data evaluation for retest period or shelf life estimation for active substances or finished products. The proposed packaging and storage conditions ‘Store in the original container, in order to protect from moisture’, are acceptable.

The MAH has performed an in-use stability study on one batch of highest and lowest strength (120 mg and 30 mg) of Etoricoxib Mylan film-coated tablets in 100’s HDPE bottle pack. Every bottle has been opened for 2 minutes per day for a duration of 100 days. The same trend was observed as during the long term stability studies. Based on the results it is not necessary to state an in-use shelf life in the SmPC.

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, and lactose is prepared without the use of other ruminant materials than milk and calf rennet. Magnesium stearate is of vegetable origin. All the excipients used in the manufacturing of the finished product are free from the risk of TSE/BSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Etoricoxib Mylan 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 Mylan 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 Mylan 120 mg (Mylan B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Arcoxia 120 mg (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
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 at two different rotation speeds at three pH conditions. At pH 1.2, the dissolution of the 120 mg biobatch and the additional 30 mg, 60 mg and 90 mg strengths was very rapid, i.e. more than 85% of the drug was dissolved within 15 min. At pH 4.5 and pH 6.8 dissolution was slower and thus the similarity was demonstrated between the biobatch and all concerned tablet strengths with the mathematical calculation of f2 (f2 between 50 and 100).
Both rotation speeds demonstrated similarity. A biowaiver was granted for the additional strengths.

Design
A open-label, randomised, two period, two treatment, two sequence, crossover, single dose comparative bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 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. Fasting was continued for 4 hours after drug administration. Drinking water restriction was maintained one hour before dosing to one hour after dosing and all the subjects were refrained from taking water during this period.There were 2 dosing periods, separated by a washout period of 16 days.

Blood samples were collected at pre-dose (0 hour) and post-dose at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 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 16 days which was more than 5 half-lives of etoricoxib (half-life is 22 hours). Furthermore, the sampling schedule is considered adequate to estimate the expected T_{max} around 2 hours. In addition, considering the elimination half-life of 22 hours, the sampling duration was long enough to adequately estimate AUC.

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
All 28 subjects finished the two study periods and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 120 mg etoricoxib under fasted conditions.

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	62276 ±16431	67920 ± 21991	3336 ± 725	1.5 (0.5-3.0)
Reference	60388 ± 14925	66193 ± 20573	3113 ± 569	1.0 (0.5-4.0)
***Ratio (90% CI)**	1.03 (0.99-1.06)	1.02 (0.98-1.06)	1.06 (0.98-1.15)	--

$AUC_{0-\infty}$ 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

**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 Mylan 120 mg is considered bioequivalent with Arcoxia 120 mg.

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 Mylan.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Thrombotic cardiovascular complications • Gastrointestinal complications • Cardia-renal risk including 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 the PLs for Celecoxib 100 mg and 200 mg capsules, hard (NL/H/2794/DC) and another Etoricoxib product. The only differences between the leaflets are related to section 6 of the PIL, with no impact on the readability (content of the pack). Furthermore, the layout of the two leaflets, as well as the font type, font size and dimensions are identical. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Etoricoxib Mylan 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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 Etoricoxib Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 July 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
Registration/update of the Pharmacovigilance System Master File (PSMF)	NL/H/3151/IA/001/G	IA/G	7-1-12016	6-2-2016	Approval	No