CBG MEB

Public Assessment Report

Scientific discussion

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

(etoricoxib)

NL/H/3780/001-004/DC

Date: 6 November 2017

This module reflects the scientific discussion for the approval of Etoricoxib Bristol 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets. The procedure was finalised on 19 April 2017. 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
EDQM	European Directorate for the Quality of Medicines
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 Bristol 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets from Bristol Laboratories 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 Bristol 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, Ireland 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 Bristol is a film-coated tablet:

- 30 mg: bluish green, round, biconvex, film-coated tablets debossed with ‘443’ on one side and ‘L’ on the other side.
- 60 mg: green, round, biconvex, film-coated tablets debossed with ‘444’ on one side and ‘L’ on the other side.
- 90 mg: white to off-white, round, biconvex, film-coated tablets debossed with ‘445’ on one side and ‘L’ on the other side.
- 120 mg: pale-green, round, biconvex, film-coated tablets debossed with ‘446’ on one side and ‘L’ 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 OPA/Alu/PVC-Alu blister, PVC/PVDC blister, Triplex (PVC/PE/PVDC), and white opaque HDPE round bottle sealed with induction seal and with white polypropylene screw cap containing two one gram desiccant containers.

The excipients are:
Tablet core - calcium phosphate dibasic anhydrous, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and silica.
Tablet coat – hypromellose, lactose monohydrate, titanium dioxide (E171), triacetin, indigo carmine aluminium lake (E132) (only in 30 mg, 60 mg and 120 mg) and iron oxide yellow (E172) (only in 30 mg, 60 mg and 120 mg).

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 yellow powder. The active substance is practically insoluble in water. It has no chiral centre 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 manufacturing process is performed at four manufacturing sites in several steps. Sufficient details on the process have been provided. The specifications of the starting materials are acceptable and etoricoxib has been adequately characterised.

Quality control of drug substance
The active substance specification has been established in-house and contains tests for description, identification, polymorphic form, loss on drying, heavy metals, residue on ignition, related substances, assay, residual solvents, genotoxic impurities and particle size limits. It is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for one production scale batch. In addition, batch results are provided by the ASMF-holder for several production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for several commercial batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Based on the currently submitted data the retest period of 24 months with the storage restriction "do not store above 25°C" can be granted. The storage temperature restriction is not necessary but no objection will be made.

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 wet granulation method, lubrication time, compression and the effect of hardness.

The MAH demonstrated the similarity of the 120 mg drug product versus the reference product used in a bioequivalence study. A biowaiver was requested for the lower strengths. Comparative dissolution testing was performed at three pH conditions. The profiles of the 30 mg, 60 mg and 90 mg test products are considered similar to that of the 120 mg test product, either as >85% is dissolved in 15 min or f_2 values were between 50 and 100.

Manufacturing process
The manufacture process consists of wet granulation, lubrication and compression followed by coating. The process is a standard process and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients are all in compliance with the Ph.Eur. or in-house (Opadry coating materials). 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, identification of colourant, average weight, dissolution, uniformity of dosage units, organic impurities, assay, XRD and microbiological testing. The release and shelf-life specifications are identical. 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 several 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 has been provided on several batches per strength packed in the proposed packaging. The batches are stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). A shelf-life of 36 months with no specific storage restrictions is acceptable. In-use stability data is provided for the product stored in HDPE bottles for up to three months and the proposed in-use period of 90 days can be granted. Photostability has been adequately demonstrated.

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. 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 Etoricoxib Bristol 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 Bristol 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 Bristol 120 film-coated tablets (Bristol Laboratories Limited, United Kingdom) is compared with the pharmacokinetic profile of the reference product Arcoxia 120 mg film-coated tablets (Merck, Sharp & Dohme Limited, Germany).

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

A biowaiver for the lower strengths is justified based on the following:

- the pharmaceutical products are manufactured by the same manufacturing process.
- the qualitative composition of the different strengths is the same.
- the ratio between amounts of active substance and excipients is the same.
- the *in vitro* dissolution profile is similar under identical conditions for all strengths. Comparative dissolution testing was performed at three pH conditions. Similarity between the 120 mg biobatch and the 30 mg, 60 mg and 90 mg strengths was shown at pH 1.2 as more than 85% of the drug was dissolved within 15 minutes. At pH 4.5 and 6.8, similarity was proven as f_2>50.

Design

An open-label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (120 mg) of one of the two etoricoxib formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable. The wash-out period was 21 days which was more than 5 half-lives of etoricoxib (half-life is 22 hours), which is long enough to prevent carry-over effects. 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 did not report for dosing in period 2, one subject misbehaved towards medical staff and was withdrawn from the study in period 2, three subjects were found positive in an urine-scan for drug of abuse during period 2 check-in and were therefore not included in the statistical analysis. Therefore, 23 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=23	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	45063 ± 11912	2668 ± 489	1.84 (1.0 - 4.0)
Reference	44803 ± 11482	2610 ± 670	1.78 (1.0 - 3.5)
***Ratio (90% CI)**	1.01 (0.96 - 1.05)	1.05 (0.92-1.19)	--

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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Etoricoxib Bristol 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 Bristol.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity-related events and serious skin reactions • Serious gastrointestinal events • Thrombotic cardiovascular events • Renovascular events: oedema, hypertension and congestive heart failure
Important potential risks	None
Missing information	• Use in pregnancy and lactating women • Use in patients less than 16 years of age • Use in patients with renal insufficiency • Use in patients with hepatic impairment

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 120 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Etoricoxib Bristol 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Bristol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 April 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse