COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Etoricoxib Abiogen 30 mg, 60 mg, 90 mg and 120 mg, tablets

(etoricoxib)

NL/H/5493/001-004/MR

Date: 3 May 2022

This module reflects the scientific discussion for the approval of Etoricoxib Abiogen. The procedure was finalised at 10 January 2022. 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
CEP	Certificate of Suitability to the monographs of the European 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 Abiogen 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets, from Abiogen S.p.A.

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.

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

This mutual recognition 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 RVG 34279) which has been registered in the Netherlands by MSD since July 2002 (original product). The initial registration concerns a NL national procedure, the product has been registered in The Netherlands since 26 March 2016. With the current Mutual Recognition procedure CMS Italy is included.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Etoricoxib Abiogen 30 mg, film-coated tablets
White round biconvex film-coated tablet debossed with “E9OX” on one side and “30” on the other side.

Etoricoxib Abiogen 60 mg, film-coated tablets
White round biconvex film-coated tablet debossed with “E9OX” on one side and “60” on the other side.

Etoricoxib Abiogen 90 mg, film-coated tablets
White round biconvex film-coated tablet debossed with “E9OX” on one side and “90” on the other side.

Etoricoxib Abiogen 120 mg, film-coated tablets

White round biconvex film-coated tablet debossed with “E9OX” on one side and “120” on the other side.

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

The film-coated tablets are packed in oPA/Al/PVC/aluminium blisters.

The excipients are:

Tablet core - calcium hydrogen phosphate (E341), cellulose - microcrystalline (E460), croscarmellose - sodium (E468) and magnesium stearate (E572).

Tablet coating - Lactose monohydrate, hypromellose (E464), titanium dioxide (E171) and triacetin (E1518).

II.2 Drug Substance

The active substance is etoricoxib, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water. It has no chiral centra 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 consists of three chemical steps followed by a purification and recrystallization step. No class 1 solvents or heavy metal catalysts are used in the synthesis.
The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for six commercial batches.

Stability of drug substance

Stability data on the active substance has been provided for three batches stored at 25°C/60% RH (60 months), 30°C/75% RH (60 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months with no special storage conditions.

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 development of the proposed generic product is strongly based on the qualitative composition of the innovator product. The MAH demonstrated the similarity of the drug product versus the reference product used in the bioequivalence study. The batch size of the 120 mg test bio-batch is considered acceptable. Comparative dissolution testing was performed and the biowaiver of strengths has been sufficiently justified.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches per strength for manufacturer I and two batches (30 mg and 120 mg strength) or one batch (60 mg and 90 mg strength) for manufacturer II in accordance with the relevant European guidelines. The manufacturing process is divided into the following steps: mixing, compaction, milling, mixing, blending, lubrication, compression, film-coating and packaging.

Control of excipients

The excipients are all in compliance with the Ph. Eur. Specifications for Opadry coating material have been provided. The Opadry coating material is well known and the specifications are accepted. CoAs have been provided for all excipients.. 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 colorant, 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 from seven batches for the 30 mg and 120 mg strengths and four batches for the 60 mg and 90 mg strengths from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for at least one batch per manufacturing site per strength packed in the proposed Al-Al blister stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life was granted of 36 months without special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose and magnesium stearate 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 Abiogen 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 Abiogen 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Etoricoxib 120 mg film-coated tablets (Synthon Hispania S.L., Spain) is compared with the pharmacokinetic profile of the reference product Arcoxia (Etoricoxib) 120 mg film-coated tablets (MSD, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A single bioequivalence study was conducted using 120 mg tablets and a biowaiver to 30 mg, 60 mg and 90 mg tablets strengths is requested. According to the MAH, a biowaiver 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.

The different tablets strengths were found to be manufactured by the same manufacturing process, they contain the same excipients and they are dose-proportional to each other. In conclusion, for the dissolution testing of both Arcoxia and Etoricoxib film-coated tablets, the speed rate was found unsuitable as it led to cone formation at the bottom of the dissolution vessels. Comparison between Etoricoxib 120 mg film-coated tablets and Arcoxia 120 mg at these experimental conditions showed that the obtained results did not reflect the in vivo behaviour of the test product (i.e. bioequivalence to the reference product). A higher stirring speed was previously shown to be suitable to overcome the coning effect. In addition, the bio-waiver was further justified as described in the EMA Guideline for the investigation of bioequivalence.

Therefore, the listed points were confirmed by scientific data and were found to be acceptable. A biowaiver for the 30 mg, 60 mg and 90 mg strengths can be granted.

Bioequivalence studies

Design

A single dose, two-treatment, two-period, crossover, oral bioequivalence study was carried out under fasted conditions in 36 healthy male/female subjects, aged 21-72 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. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre dose and 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.

Etoricoxib may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of etoricoxib. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
Out of a total of 36, 35 subjects were eligible for pharmacokinetic analysis. One subject withdrew due to clinical events.

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

Treatment N=35	**AUC_{0-72h} (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)**	100.38 (97.59 – 103.24)	102.87 (95.81 – 110.45)	--

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

**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 Abiogen 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 Abiogen.

Table 2. 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 skin 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 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets (PT/H/2299/004). 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 Abiogen 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 concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Etoricoxib with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 10 January 2022.

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