LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Etoricoxib Orion
(etoricoxib)

SE/H/1554/01-04/DC

This module reflects the scientific discussion for the approval of Etoricoxib Orion. The procedure was finalised on 2016-10-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Etoricoxib Orion, 30 mg, 60 mg, 90 mg, 120 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Arcoxia, 60 mg, 90 mg, 120 mg, film-coated tablet authorised in UK since 2002, with Merck Sharp & Dohme Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Arcoxia, 120 mg, film-coated tablet from UK with Merck Sharp & Dohme Limited as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Etoricoxib has an oral bioavailability of approximately 100 %. Following an oral dose of etoricoxib maximal plasma concentrations occur at approximately 1 hour. The pharmacokinetics of etoricoxib is not affected by food to a clinically relevant extent (the rate of absorption is decreased but the extent of absorption is not affected), and therefore there are no restrictions with respect to food in the SmPC of the originator. The pharmacokinetics of etoricoxib is linear within the clinical dose range. The terminal half-life is 22 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Etoricoxib, 120 mg, tablets with Arcoxia, 120 mg, tablets under fasting conditions. The study was conducted at Alembic Research Centre, Gujarat, India between 14th November and 9th December 2013. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of etoricoxib were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for etoricoxib, n=23.

Treatment	**AUC_{0-72h}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**45063±11912**	**2668±489**	**1.50 (1.00-4.00)**
Reference	**44803±11482**	**2610±670**	**2.00 (1.00-3.50)**
***Ratio (90% CI)**	**100.82 (96.54-105.29)**	**104.82 (92.36-118.97)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

From a pharmacokinetic point of view, absence of studies with the additional strengths is acceptable, as the pharmacokinetics of etoricoxib is linear within the clinical dose range.

Based on the submitted bioequivalence study, etoricoxib 120 mg tablets are considered bioequivalent with Arcoxia, 120 mg, tablets.

The results of the study with 120 mg formulation CAN be extrapolated to other strengths 30, 60 and 90 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Orion.

Safety specification

The applicant has submitted the version 1.2 RMP dated 07.10.2016 with the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	• Serious gastrointestinal (GI) events • Thrombotic cardiovascular events • Renovascular events: Oedema, hypertension and congestive heart failure (CHF) • Hypersensitivity-related events and serious skin reactions
Important potential risk	• None identified
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

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

RMS recommendation

RMP is approvable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Arcoxia, UK/H/0532-5/004/DC (content) and Topiramat Orion, DE/H/1325/001-004/DC as well as Venlafaxine Orion DE/H/1420/001-003/DC (layout). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Etoricoxib Orion, is found adequate. There are no objections to approval of Etoricoxib Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Etoricoxib Orion, 30 mg, 60 mg, 90 mg, 120 mg, film-coated tablet was positively finalised on 2016-10-13.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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