Public Assessment Report
Scientific discussion

Etoricoxib Gobens 30, 60, 90 and 120 mg Film-coated Tablets

Etoricoxib

ES/H/0415/001-004/DC

Applicant: Laboratorios Normon, S.A.

Registration number in Spain:xxx

This module reflects the scientific discussion for the approval of **Etoricoxib Gobens 30 mg, 60 mg, 90 mg and 120 mg film-coated tablets.** The procedure was finalised on February 2017. For information on changes after this date please refer to the module ôUpdateô.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Arcoxia film-coated tablets by Merck Sharp & Dohme, Ltd. Arcoxia film-coated tablets have been registered since February 13th, 2002 through.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member State involved in this procedure is PT.

The efficacy and security of etoricoxib has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Etoricoxib Gobens 30, 60, 90 and 120 mg film-coated tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, security and efficacy has been carried out besides the bioequivalence studies against the reference product.

Etoricoxib is indicated for symptomatic pain relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis and for the short-term treatment of moderate pain associated with dental surgery.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Etoricoxib Gobens 30, 60, 90 and 120 mg film-coated tablets** for Laboratorios Normon S.A.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE

Etoricoxib is an active substance that is not described in Ph.Eur. There is one supplier of active substance, an Active Substance Master File (ASMF) has been submitted to support the quality of the active ingredient. Re-test period is included in the ASMF

DRUG PRODUCT

Description of the product

30 mg: blue-green, round-shaped, biconvex film-coated tablets.

60 mg: dark green, round-shaped, biconvex film coated tablets.

90 mg: white, round-shaped, biconvex film-coated tablets.

120 mg: pale-green, round-shaped, biconvex film-coated tablets.

The qualitative composition of the film-coated tablets is as follows:
Core:
Etoricoxib
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Glycerol triacetate
The 30, 60 and 120 mg tablets also contain yellow ferric oxide (E172) and indigo carmine lake (E132).

Etoricoxib film-coated tablets are packed in:
Aluminium/aluminium-polyamide-PVC blisters
Aluminium/PVC-PVDC blisters
Aluminium/PVDC-PE blisters

Pharmaceutical development

The pharmaceutical development has been properly described. The function of the excipientes has been discussed. The manufacturing process is described in detail.

The validation studies show that the manufacturing process for the product is suitable for routine production of the medicinal product.

Excipients

The information provided is adequate. These excipients, an exception colourant excipients, are described in European Pharmacopoeia and they are analysed according to the corresponding monographs. The composition of Yellow iron oxide and Indigo carmin is properly described.

Product specification

Specifications proposed are adequate. The product specifications cover appropriate parameters for this dosage form. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly validated following the ICH Q2 (R1) Guideline.

Container closure system

Information about container closure system is correct. Etoricoxib film-coated tablets are packed in:
Aluminium/aluminium-polyamide-PVC blisters
Aluminium/PVC-PVDC blisters
Aluminium/PVDC-PE blisters

Stability

Stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life (*24 months with no storage conditions*).

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns film coated tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Etoricoxib is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

Biowaiver

The bioequivalence of test and reference products has been demonstrated for 120 mg strength (please refer to section of results). These data can be extrapolated (i.e., 30 mg, 60 mg and 90 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

To support the application, the Applicant has submitted the bioequivalence study (Study Protocol Code: N-ETO-15-211) ña phase I clinical trial, single oral dose, randomised, open label, two treatments, two periods, two sequences, cross-over to determine the bioequivalence of Etoricoxib 120 mg film-coated tablet (Laboratorios Normon, S.A.) and Arcoxia 120 mg film-coated tablet (Merck Sharp & Dohme Ltd.), after oral administration to healthy adult male volunteers under fasting conditionsò.

The clinical part was performed from October 01st, 2015 to November 12th, 2015 at Clinical Trials Unit, Hospital Universitario de la Princesa. C/ Diego de León, nº 62. Madrid, Spain.

The analytical portion was conducted at Anapharm Europe S.L.U., C/ Encuny 22 - 08038 Barcelona (Spain) from November 23rd, 2015 to December 03th, 2015.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

A comparative randomized, open label, single dose, two-treatment, two-sequence, two-period crossover study to determine the bioequivalence of Etoricoxib 120 mg film-coated tablet (Laboratorios Normon, S.A.) and Arcoxia 120 mg film-coated tablet (Merck Sharp & Dohme Ltd.), after oral administration to healthy adult volunteers under fasting conditions with a washout period of 14 days.

This approach is acceptable as the application concerns an oral immediate release formulation (film-coated tablets) and according to the SmPC the reference product may be taken with or without food, therefore, a single dose study under fasting conditions with the highest strength is considered acceptable to demonstrate bioequivalence with the reference product.

The wash-out period of 14 days is considered adequate since the drug has a half-life of approximately 22 hours and this wash-out exceeds 5 elimination half-lives and no pre-dose levels were detected.

Considering the elimination half-life of etoricoxib, the sampling schedule and the sampling time period of 72 hours seems long enough to estimate PK parameters. Sampling after 72 hours is unnecessary for immediate release formulations.

Test product: Etoricoxib 120 mg film-coated tablets manufactured by Laboratorios Normon, S.A., Spain. Batch number: G315. Batch size: 100,000 film-coated tablets. Expiry date (re-test date): December 2015. Assay (content): 99.0 % of label claim.

Reference product: Arcoxia 120 mg tablets, manufactured by Merck Sharp & Dohme, Ltd. (from the Spanish market). Batch number: 1016080. Expiry date: January 2017. Assay (content): 97.0% of label claim.

The reference product is adequate with regards to expiry date, content and it was obtained from Spanish market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

36 subjects (20 men and 16 women) as planned in the protocol, were randomised and 34 of them completed the study and therefore, 36 volunteers were considered for pharmacokinetics and 34 for statistical analysis.

Two volunteers (number 13 and 17) were excluded from the bioequivalence analysis because they did not complete the study. The volunteer 13 did not carry out period 2 because of adverse events (tonsillitis and cough) and the volunteer 17 due to personnel reasons.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples..

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the WinNonLin version 6.3 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic

parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.

Following EMA criteria, the two formulations were classified as bioequivalent if the standard 90% confidence intervals of the pharmacokinetic parameters (AUC_{0-72} and C_{max}) with log transformation are within the 80.00-125.00 range.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=34:

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%[1]
C_{max}	112.57	104.27	121.54	18.61
AUC_{0-72}	102.96	99.10	106.97	9.29

[1] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for etoricoxib the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-72} are within the acceptance range of 80-125%.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substances etoricoxib are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown to be in compliance with the requirements of European Union guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in February 2017.