EDA Assessment Report for human medicinal product

(Scientific Discussion)

Atcocoxib 60mg & 90mg film coated tablets

(Etoricoxib)

Date: September 2023

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Atcocoxib 60mg & 90mg Film Coated Tablets from ATCO pharma for pharmaceutical industries.
- The product contains the active substance "Etoricoxib" which belongs to a group of medicines called "Selective COX-2 inhibitors". These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It 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 and the short-term treatment of moderate pain after dental surgery.

II. Quality Aspect

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is "off white to creamy white powder", freely soluble in tetrahydrofuran, dimethyl formamide & dimethyl sulfoxide, soluble in methanol and acetone, sparingly soluble in ethanol, practically insoluble in water. It shows polymorphism.
- The synthesis of drug substance includes 2 steps with the formation of 1 intermediate. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, ^{1}H-NMR,^{13}C-NMR, Mass Spectrometry & elemental analysis and the structure is well characterized. The polymorphic form of the drug substance is confirmed via XRPD as **form 1**.
- The drug substance specifications are in accordance with In-house specifications and include the following tests: description, solubility, identification (by IR & HPLC), related substances, heavy metals, sulphated ash, loss on drying, assay (by HPLC) and residual solvents. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.
- Stability of API is submitted and conclude the conformity of specifications during the shelf life and storage conditions.

Medicinal Product

- **Product Description**
- **60mg:** Off white to pale yellow round biconvex unscored film coated tablets.
- **90mg:** Off white to pale yellow round biconvex unscored film coated tablets.

- The product is packed in "Carton box containing 1,2 or 3 AL/AL strips each of 10 film coated tablets and insert leaflet".

- **The excipients are:**

Core:
Microcrystalline crystalline, croscarmellose sodium, dicalcium phosphate anhydrous, magnesium stearate and Purified water.

Coating ingredients:
Hydroxypropyl methyl cellulose, polyethylene glycol 6000, talc, titanium dioxide, iron oxide yellow, purified water and ethyl alcohol.

- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process is done by mixing, wet granulation, drying, sieving, compression and film coating. *The potential of polymorphic conversion of Etoricoxib during wet granulation was raised by the authority and justification has been submitted.*
- The manufacturing process was adequately validated according to relevant guidelines for three primary sized batches of each strength.
- Control of excipients, all excipients comply with USP and the specifications of the excipients are acceptable.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests uniformity of mass, uniformity of dosage unit, water content, residual solvent, disintegration test, dissolution test and microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three primary batches of each strength, demonstrating compliance with the release specification.
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of finished pharmaceutical product is submitted and conclude the conformity of specifications during the shelf life and storage conditions.
- There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

Conclusion:
Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

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.

Etoricoxib is indicated for the treatment of symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis & the pain and signs of inflammation associated with acute gouty arthritis.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Atcocoxib 90mg film coated tablet (Manufactured by: ATCO Pharma for Pharmaceutical Industries, Egypt) relative to the reference product Arcoxia® 90mg film coated tablet (Manufactured by Merck Sharp & Dohme LTD, United Kingdom) administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Atcocoxib 60mg film-coated tablets based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- Both strengths of Atcocoxib are manufactured by the same process.
- Atcocoxib has linear pharmacokinetics over the therapeutic dose range.
- Both tablet strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

A comparative, Open-Label, single dose, randomized, Two-Treatment, Two-Sequence, Two-Period, crossover bioequivalence study under fasting conditions with a washout period of one week between each study period in healthy participants.

Analytical Methods

All procedures used to perform the bio-analyses of Etoricoxib in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses. The bioequivalence study accordance with

acceptable standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of Atcocoxib 90mg Film Coated Tablet (Etoricoxib 90mg) under fasting conditions.

Treatment N=26	C_{max} ng/ml	T_{max} (hr)	AUC_{0-t} (ng.hr/ml)	AUC_{0-inf} (ng.hr/ml)	K_{el} (hr^{-1})	$t_{1/2}$ (hr)
Test	1801.10 ±449.86	1.63	27600.38435 ±5865.343	32580.80927 ±9447.455	0.03102 ±0.010	25.22 ±10.44
Reference	1786.88 ±647.44	1.38	25273.64408 ±3991.341	28775.37604 ±5869.634	0.03358 ±0.009	22.58 ±7.58
***Ratio (90%) CI**	102.5 (94.11-111.64)	---------	108.34 (103.24-113.7)	111.23 (104.18-118.74)	---------	---------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80% - 125%.

Based on this study demonstrated that the active pharmaceutical ingredient of Etoricoxib in film coated tablet of the test product, Atcocoxib 90mg film coated tablet (Manufactured by: ATCO Pharma for Pharmaceutical Industries, Egypt) & reference product, Arcoxia® 90mg film coated tablet (Manufactured by Merck Sharp & Dohme LTD, United Kingdom) are Bioequivalent after a single an oral dose of test and reference administration under fasting conditions on 26 participants.