EDA Assessment Report for human medicinal product

(Scientific Discussion)

Rocoxar 60 mg, 90 mg ,120 mg 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 Rocoxar 60mg, 90mg and 120mg from El Delta for Pharmaceutical industries (Delta Pharma).

The product is indicated for symptomatic treatment of the signs and symptoms of osteoarthritis (OA), treatment of acute gouty arthritis, treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures.

II. Quality Aspect

Drug Substance

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is an off-white to creamy colored powder, freely soluble in tetrahydrofuran, dimethyl sulfoxide and in dimethyl formamide, soluble in acetone and methanol, sparingly soluble in ethanol. Etoricoxib shows polymorphism and the produced polymorph was **form-1**.
- The synthesis of drug substance includes three steps with the formation of two intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, ^{1}H-NMR, ^{13}C-NMR, Mass Spectrometry, X-Ray Diffraction, DSC and the structure is well characterized.
- The drug substance specifications are in accordance with in house and include the following tests description, solubility, identification (by IR & HPLC), assay (by HPLC), related substances, residual solvent, heavy metal, sulphated ash, loss on drying, X-Ray Diffraction and particle size distribution test. 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:** Green to dark green round biconvex film coated tablets with white to off-white core.
- **90mg:** White to off-white round biconvex film coated tablets with white to off-white core.
- **120mg:** Olive green to green round biconvex film coated tablets with white to off-white core.

- The product is packed in "Carton box containing AL/AL strips each of 7 film coated tablets".

- **The excipients are:**

Core:

Microcrystalline cellulose, calcium phosphate dibasic anhydrous, croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, isopropyl alcohol and purified water.

Coating ingredients:

Hydroxypropyl methyl cellulose, diethyl phthalate, ethyl cellulose, talc, titanium dioxide, colorants (for 60 & 120mg strengths), isopropyl alcohol and purified water.

- **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 except for the coating material (In-house) 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 weight, uniformity of dosage unit, residual solvent, disintegration time 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 3 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 120mg is 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 rheumatoid arthritis, chronic low back pain, acute pain, and gout.
Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conduct on Rocoxar 120mg film coated tablets (Etoricoxib 120mg) Manufactured by: El Delta for Pharmaceutical industries (Delta Pharma), relative to the reference product Arcoxia 120 mg film coated tablets (Etoricoxib 120mg) produced by: Merck Sharp & Dohme Limited, UK administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Rocoxar 60mg&90mg film-coated tablets based on the following arguments:

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

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Two Period, crossover bioequivalence study with a washout period of one week between periods under fasting conditions in healthy participants.
On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240 ml water after overnight fasting (at least 8-10 hours in fasting) according to the randomization sheet.
Blood Sampling: pre-dose blood sample were withdrawn at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hrs. after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Etoricoxib 120mg 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 **Etoricoxib 120mg** under fasting conditions.

Treatment N=34	**AUC0-t (ng.h/ml)**	**Cmax (ng/ml)**	**tmax (h)**	**$T_{1/2}$ (h)**
Test	38071.19	2312.39	1.35	31.54
Reference	40405.21	2226.31	1.35	36.41
***Ratio (90%) CI**	94.51 (88.93-100.44)	102.41 (92.94-112.85)	--------	-------
CV (%)	-------	--------	-------	-------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC $_{0\text{-t and}}$ AUC $_{0\text{-inf}}$ are within the bioequivalence acceptance range of 80 % - 125 %.

Based on this study demonstrated that Etoricoxib 120mg in product dosage form of the test product Rocoxar 120mg film coated tablets manufactured by: El Delta for Pharmaceutical industries (Delta Pharma), & reference product Arcoxia 120 mg film coated tablets (Etoricoxib 120mg) Produced by: Merck Sharp & Dohme Limited, UK are bioequivalent after a single oral dose of test and reference administration under fasting conditions on 34 participants.