EDA Assessment Report for human medicinal product

(Scientific Discussion)

Flamoconsult 90mg Film Coated Tablets

(Etoricoxib)

Date: February 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Flamoconsult 90mg Film Coated Tablets from Pharmaconsult 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.
- Etoricoxib is an off - white powder. It is soluble in methanol, chloroform, methylene chloride and in acetone. It showed polymorphism and the produced polymorph by the API manufacturer is form I.
- The synthesis of drug substance includes one step without the formation of intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Infrared Absorption spectrophotometry, Ultra-violet spectrophotometry, Nuclear Magnetic Resonance (^{1}H, ^{13}C and DEPT-135) spectrometry, Mass spectrometry, Powder X-ray Diffraction (P-XRD), Differential Scanning Calorimeter (DSC) & Thermo Gravimetric Analyzer (TGA) and the structure is well characterized.
- The drug substance specifications are are in accordance with in-house specifications and include the following tests, description, identification (by IR), solubility, water content, residue on ignition, heavy metals, related substances, assay, residual solvent, particle size distribution, XRPD and microbial test, all limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of three drug substance batches demonstrating compliance with the current drug substance specification.
- Etoricoxib is packed in white LDPE bag twisted and tied. It is inserted in black LDPE bag twisted and tied (primary pack) then placed in an HDPE drum (secondary pack).
- Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable.

- Stability of drug substance have been performed on 3 drug substances batches for long-term at (25°C/ 60 RH% simulated commercial packaging) and for accelerated stability study at (40°C / 75 RH% - simulated commercial packaging) and conclude the conformity of specifications during the retest period.
- The storage conditions for Etoricoxib are "Preserve in well closed, light-resistant containers and Store at 25°C, excursions permitted between 15°C and 30°C".

Medicinal Product

- **Product Description**
- White to off-white round biconvex film coated tablets containing 90mg of Etoricoxib.
- The product is packed in (OPA/Alu/PVC)/Aluminum strip containing 10 tablets.
- The excipients are: Microcrystalline Cellulose (Avicel PH 102), Croscarmellose Sodium, Magnesium stearate, Colloidal silicon dioxide (Aerosol 200) & Calcium hydrogen Phosphate (Anhydrous) for "tablet core" and "Hypromellose E5 (HPMC E5), Titanium dioxide, Lactose monohydrate & Triacetin for "tablet coating".
- **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 sieving, mixing, compacting (dry granulation), milling, mixing, lubrication, compression and film coating.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary sized batches.
- Control of excipients, all excipients comply with with B.P and the specifications of the excipients are acceptable.
- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests mass uniformity, water content, uniformity of the dosage unit by weight variation, disintegration, dissolution and microbial limit, all limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided three primary batches, 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 have been performed on 3 primary batches for long-term at (30 º C ± 2 º C / RH 65 % ±5%) and for accelerated stability study at (40 º C ± 2 º C / RH 75 % ±5%) and conclude the conformity of specifications.

- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration/certificate of TSE/BSE free is submitted for substances of animal origin.

Summary basis of opinion:

From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process was as follow:

-The supplier of drug substance was asked to submit updated specification by adding (XRPD, PSD, and microbiological analysis tests) & tighten the limit of maximum single impurity to comply with ICH Q3A guidelines.

-The applicant was asked to tighten the limit of dissolution of the finished product based on the results of its comparative in-vitro dissolution testing against the reference product.

The Quality of the drug product has been found satisfactory after:

- The supplier of drug substance updated its specification by adding (XRPD, PSD, and microbiological analysis tests) & tightened the limit of maximum single impurity to be 0.1%.
- The applicant tightened the limit of dissolution of the finished product to be NLT 80% (Q) released after 30 min.

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 treatment of rheumatoid arthritis, chronic low back pain, acute pain, and gout.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Flamoconsult 90 mg film coated tablets (Pharmaconsult for Pharmaceuticals, Egypt) relative to Arcoxia 90mg film coated tablets administered to healthy participants.

Design

William's Design for three treatments, three periods (3 x3) in six sequences crossover trial; fasting; single dose one-week wash-out period; sampling for 72 hrs. due to drugs' long half-life in healthy participants. Blood samples will be collected Based on drug pharmacokinetics, collected at the following intervals: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12 ,24 ,48 and 72 hrs.

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 Etoricoxib under fasting condition.

Treatment N= 35	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**T_{max} h**	**t1/2 h**
Test	25996.311	1864.8877	0.97907739	22.533407
Reference	25439.699	1927.1081	1.0077331	21.485215
***Ratio (90%) CI**	102.18797 (96.125716- 108.63254)	96.771305 (88.36342 -105.97921)	---	---
CV (%)				

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC_{0-72} 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 product dosage form of the Flamoconsult 90mg film coated tablets (Pharmaconsult for Pharmaceuticals, Egypt) & Arcoxia 90mg film coated tablets are bioequivalent after a single oral dose of test and reference administration under fasting condition on 35 participants.