Arab Republic of Egypt
Egyptian Drug Authority
CAPP

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الصيدلية

EDA Assessment Report for Human Medicinal Product

(Scientific Discussion)

Averosomnia 3 mg film coated tablets

(Eszopiclone)

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 Eszopiclone 3mg from Averroes Pharma for Pharmaceutical Industries.

The product is indicated for Insomnia.

II. Quality Aspect

Drug Substance

- APIMF (applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or light yellow crystalline solid powder, soluble in methylene chloride and diluted HCl, practically insoluble in water and slightly soluble in 95% ethanol, non-hygroscopic, photo labile and exhibit polymorphism.
- The synthesis of drug substance includes four steps. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via UV, FT-IR, ^{1}HNMR, ^{13}CNMR, Mass spectroscopy, Elemental analysis & XRPD and the structure is well characterized.
- The drug substance specifications are in accordance with USP and In-house specifications and include the following tests description, solubility, identification (using IR, HPLC & XRPD), loss on drying, residue on ignition, related substance, assay, chiral purity 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**
  - Averosomnia 3mg film coated tablet is pale blue to blue round biconvex tablet plain from one side and “AVS” symbol from the other side.
  - The product is packed in aluminum foil/ white opaque triplex (PVC/PE/PVDC) strip of 10 tablets.
  - **The excipients are:** Anhydrous calcium hydrogen phosphate, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, colloidal silicon dioxide & magnesium stearate (for tablet core) and hypromellose, polyethylene glycol 6000, titanium dioxide, talc powder, brilliant blue and purified water (for 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 mixing, sieving, blending, compression and coating.
- The manufacturing process was adequately validated according to relevant guidelines. Process validation included three primary sized batches.
- Control of excipients, all excipients comply with USP except for brilliant blue is following In-house specifications and the specifications of the excipients are justified.
- Product specifications include the four universal tests for description, identification, assay, impurities and additional tests: uniformity of mass, disintegration, dissolution, uniformity of dosage unit and microbial tests. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch analysis from the proposed production site were provided 3 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 is submitted and conclude the conformity of specifications during the shelf-life and storage conditions.
- 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.

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

Eszopiclone 3mg is well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Eszopiclone is indicated for the treatment of insomnia as it has shown to decrease sleep latency and improve sleep maintenance.

The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Eszopiclone is a nonbenzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conduct on the test product Averosomnia 3mg film coated tablets (Eszopiclone 3mg) manufactured by: Averroes Pharma for Pharmaceutical Industries, Egypt relative to the reference product Lunesta® 3mg Tablets (Eszopiclone 3 mg) produced by: Sunovion pharmaceuticals Inc, U.S.A. administered to healthy participants.

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, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 hours after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Eszopiclone 3mg 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 **Eszopiclone 3mg** under fasting conditions.

Treatment N=23	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	366.65	382.61	49.60	1	7.38±1.43
Reference	355.89	374.41	51.04	0.75	7.53±1.95
***Ratio (90%) CI**	104.06 (97.30- 111.29)	103.32 (96.75- 110.32)	99.16 (86.78- 113.30)	--------	-------
CV (%)	-------	-------	--------	-------	-------

*ln-transformed values

* Twenty- four (24) volunteers were enrolled & participated in the study, twenty-three (23) who completed all study periods and included in pharmacokinetics and statistical analysis, as Volunteer no. 11 withdrawn from the study due to personal reason

Conclusion

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

Based on this study demonstrated that Eszopiclone 3mg in product dosage form of the test product Averosomnia 3mg film coated tablets manufactured by: Averroes Pharma for Pharmaceutical Industries & reference product Lunesta® 3 mg Tablets (Eszopiclone 3 mg) produced by: Sunovion Pharmaceuticals Inc, USA are bioequivalent after a single oral dose of test and reference administration under fasting conditions on 23 participants.