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)

Urizetinax Modified Release Hard Gelatin Capsule

(Tamsulosin HCl 0.4 mg**)**

Date: March, 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for "Urizetinax (Tamsulosin HCl 0.4mg) Modified Release Hard Gelatin Capsules" from Zeta Pharma for Pharmaceutical Industries (Zeta Pharm).

The product is indicated to treat the symptoms of an enlarged prostate - a condition technically known as benign prostatic hyperplasia.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white crystalline powder. It is slightly soluble in water and anhydrous ethanol, sparingly soluble in methanol, freely soluble in dimethyl sulfoxide and formic acid, practically insoluble in ether, and it is non-hygroscopic. It has one chiral center and it is synthesized as R-isomer. It doesn't exhibit polymorphism.
- The synthesis of drug substance consists of four steps, with the formation of two intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, IR, UV Spectroscopy, Nuclear Magnetic Resonance (^{1}H and ^{13}C) and the structure is well characterized.
- The drug substance specifications include the following tests description, solubility, identification (IR, chloride test and HPLC), loss on drying, melting range, residue on ignition, related substances (HPLC), assay (HPLC), residual solvents (GC), and enantiomeric purity (chiral HPLC). 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.
- Tamsulosin HCl is packed in white high molecular high-density polyethylene (HM-HDPE) bag and tied with linear seals. The bag is then kept in the black LDPE bag and tied with liner seal. The black LDPE bag is then kept in the triple laminated high barrier bag, and sealed with heat sealer. Finally, the above triple laminated high barrier bag is packed in a HM-HDPE drum.
- 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 is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 25°C ± 2°C, RH 60% ±5%), and conclude the conformity of specifications during the retest period and storage conditions. The storage conditions for Tamsulosin HCl are "Preserve in tightly-closed container

at 25°C (Excursions between 15°C and 30°C are allowed). Keep away from excessive heat and moisture.”.

Medicinal Product

- **Product Description**
  - Urizetinax 0.4 mg modified release hard gelatin capsules are available as two pieces hard gelatin capsule size one, containing white to off white colored semi spherical shape pellets, with opaque blue cap / opaque blue body.
  - The product is packed in a carton box containing 1,2,3 (PA/Alu/PVC) /Alu strip(s), each strip containing 10 hard gelatin capsules.
  - The excipients for the **pellets** are: microcrystalline cellulose, hydroxypropyl methyl cellulose (HPMC), methacrylic acid-ethyl acrylate co-polymer dispersion liquid, talc, titanium Dioxide, polyethylene glycol-6000, polysorbate 80, sodium hydroxide.
  - **The capsule shell (Cap and Body)** consists of: gelatin, methyl paraben, propyl paraben, sodium lauryl sulfate, colloidal silicon dioxide, titanium dioxide, brilliant blue.
- **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 consists of manufacturing of drug pellets (drug solution preparation, wet mixing, extrusion, spheronization, enteric coating), The manufacturing process of finished product includes capsule filling, blistering and packaging.
- The manufacturing process of pellets was adequately validated by the manufacturer of pellets and includes 3 commercial batches.
- Control of excipients, all excipients comply with USP except for propyl paraben, sodium lauryl sulfate, silica colloidal anhydrous and brilliant blue which are in-house and the specifications of the excipients are acceptable.
- Product specification of the finished product includes the four universal tests as description, identification, assay, impurities and additional tests as mass uniformity, disintegration, content uniformity, dissolution, and microbiological examination. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three primary batches, demonstrating compliance with the release specifications.

- 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 (accelerated at 40°C ± 2°C/75% RH ± 5% RH) and long-term at 30°C ± 2°C/65% RH ± 5% RH) 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 provided for the gelatine present in the capsule shell.

Summary basis of opinion:

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

- The supplier of drug substance was asked to submit a control strategy of the possible genotoxic impurity as byproduct, likely to be formed during the manufacturing process of the active ingredient.

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

- The supplier submitted the risk assessment of the possible formation of the genotoxic impurity that included a justified control strategy acc. to ICH M7 guideline.

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

Tamsulosin Hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Tamsulosin (as Hydrochloride) is indicated for:

It reduces tension of the smooth muscles in the prostate and the urethra, enabling urine to pass more readily through the urethra and facilitating urination. In addition, it diminishes sensations of urge.

It is used in men for the treatment of the complaints of the lower urinary tract associated with an enlarged prostatic gland (benign prostatic hyperplasia). These complaints may include difficulty urinating (poor stream), dribbling, urgency and having to urinate frequently at night as well as during the day.

Mechanism of action:
Tamsulosin binds selectively and competitively to the postsynaptic α 1-adrenoceptors, in particular to subtypes α 1A and α 1D. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects
Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms.
It also improves the storage symptoms in which bladder instability plays an important role.
These effects on storage and voiding symptoms are maintained during long - term Therapy. The need for surgery or catheterization is significantly delayed. α 1-adrenoceptors antagonists can reduce blood pressure by lowering peripheral resistance.

Pharmacokinetics
Bioequivalence Study

The bioequivalence studies of Urizetinax 0.4mg Modified Release Hard Gelatin Capsule (Tamsulosin Hydrochloride) product of Zeta Pharma were done relative to Omnic 0.4mg Modified Release Hard Gelatin Capsule (Tamsulosin Hydrochloride) administered to healthy participants.

Design
This study was Randomized, Single Oral Dose, an Open Label, Open-Label, Four-Way, Four-Periods, Two Treatment, Two Sequence, Crossover study with a washout period 7 days between dosing under fast and fed conditions.

Biological Samples Collection;
Pre-dose, 1 hr., 2 hr., 2.5 hr., 3 hr., 3.5 hr., 4 hr., 4.5 hr., 5 hr., 5.5 hr., 6 hr., 6.5 hr., 7 hr., 8 hr., 9 hr., 10 hr., 12 hr., 24 hr., 48 hr. and 72 hours.

Sample Collection & Sample Processing:
- Twenty- (20) Blood samples were collected though indwelling cannula placed forearm vein with a suitable disposable syringe.
- On Labeled poly propylene tubes containing heparin as anti-coagulant five milliliters (5 ml) were collected from subjects as blood sampling interval schedule
- After blood sampling for all subjects at each sampling points, the tubes were centrifuged.
- After centrifugation plasma was separated from each sample and transferred into tubes.
- The polyethylene tubes containing plasma separated are stored at -70°C (±15°C) until analysis.
- The total volume of blood drawn for the purpose of this study was approximately (450 mL) from each subject.

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

CRO developed validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Tamsulosin HCl** under **fasting conditions**.

Treatment N=25	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	208.551 ± 92.422	225.485 ± 94.864	18.328 ± 4.868	5.5	------
Reference	200.633 ±101.673	220.918 ± 103.115	17.769 ± 4.696	5	------
*Ratio (90%) CI	106.7659% (96.77433-117.789)	104.4184% (96.23748-113.2947)	103.1502% (97.5576-109.0635)	------	------
CV (%)	---	-------	------	------	------

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Tamsulosin HCl** under **fed conditions**.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	196.29 ± 91.84	222.85 ± 112.11	12.74 ± 4.27	6	
Reference	201.24 ± 87.7	215.96 ± 87.71	13.05 ± 4.38	6.5	
*Ratio (90%) CI	96.26587% (89.74494-103.2606)	100.4305% (92.50925-109.0299)	97.8186% (88.13566-108.5654)	------	------
CV (%)	---	-------	------	------	------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC 0-t,, AUC0-∞ and C max are within the bioequivalence acceptance range of 80-125%.

Based on these studies demonstrated that the Active Pharmaceutical Ingredient Tamsulosin Hydrochloride in Urizetinax 0.4 mg Modified Release Hard Gelatin Capsule product of Zeta Pharma & Omnic 0.4mg Modified Release Hard Gelatin Capsule are bioequivalent after a single oral dose of test and reference administration under fasting on 25 participants & fed conditions on 24 participants.