EDA Assessment Report for human medicinal product

(Scientific Discussion)

Veozah 45 mg Film Coated Tablet

(Fezolinetant)

Date: October 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Veozah 45 Film Coated Tablet from Astellas Pharma International B.V.

The product is indicated to reduce the frequency and severity of moderate to severe Vasomotor symptoms (VMS) due to menopause.

II. Quality Aspect

Drug Substance

- Full details of the S part have been submitted for evaluation.

The drug substance is a white powder. It is highly soluble in aqueous media. Fezolinetant is classified as highly permeable. Therefore, it can be classified as a Biopharmaceutics Classification System (BCS) Class 1 drug. It shows polymorph and Form I is consistently produced by the API manufacturer.

- The synthesis of drug substance consists of five steps with the formation of two intermediates was revised and found to comply with ICH Q11 (Development and Manufacture of Drug Substances).
- The drug substance is elucidated via Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (H^1 NMR, C^{13} NMR), Mass spectroscopy, elemental analysis and X-ray powder diffraction (XRPD).
- The drug substance specifications are Description, Identification (IR & XRPD), Assay, Related Substances, Enantiomer, Residual Solvent, Benzene Content and Residue on Ignition.
- Analytical methods were adequately described and validated. They were revised and found to be suitable for the required testing.
- The applicant provided batch analysis results of nineteen batches total from both suppliers. The results of all tests were well within the specification limits and batch data was found acceptable.
- Container closure system is double polyethylene bags that is then placed in a rigid container. The specifications of the primary packaging component are provided including appropriate identification test for the primary packaging in contact with the drug substance. All these specifications are revised and found to be satisfactory.
- Stability of API is submitted in accelerated 40°C±2°C /75% ± 5% RH and long-term storage conditions 25°C ±2°C /60% ± 5% RH and conclude the conformity of specifications during the shelf life and storage conditions. The retest period of the API is 36 months when stored below 30°C in the proposed container.

Medicinal Product

- **Product Description**

- Fezolinetant Tablets 45 mg are round light red film-coated tablets (approximately 7.1 mm diameter) containing 45 mg active ingredient. The tablets are debossed with the company logo (graphic presentation ‘ ’) and ‘645’ on the same side.
- The product is packed in in aluminum/aluminum blister. The blister consists of a unit dose cavity formed from polyamide/aluminum/polyvinyl chloride laminated forming foil sealed with an aluminum foil/heat-seal coated lidding foil.
- The excipients are: Mannitol, Hydroxypropyl cellulose, Purified Water, Hydroxypropyl cellulose (Low-Substituted), Microcrystalline Cellulose, and Magnesium Stearate.
- The film coat composition consists of: OPADRY™ 03F440031 and Purified water.
- Pharmaceutical development, the development of the product has been described, the choice of excipients is justified and their functions explained. The formulation design focused on the development of a formulation which would preserve the chemical and physical stability of Fezolinetant during manufacture and for the shelf-life of the product while maintaining the kinetic solubility advantage imparted during dissolution which is essential to achieve the desired in vivo bioavailability.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process consists of pulverizing, dissolving, granulating, blending, compressing, dispersing, coating, bulk packaging and packaging.
- The manufacturing process has been adequately validated on three full production scale batches per manufacturer. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.
- Control of excipients, all excipients comply with Ph. Eur except for OPADRY™ 03F440031 that follows In House specifications.
- Product specification includes Description, Identification, Assay, Related Substances, Dissolution and Uniformity of dosage units, and Microbial Limits.
- Analytical methods were used in testing the finished pharmaceutical product were presented in the dossier. They were reviewed and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided from the proposed production sites were provided for clinical, primary stability and process validation batches. The results of all tests were well within specification limits and batch data was found acceptable.

- Container closure system is aluminum/aluminum blister. The blister consists of a unit dose cavity formed from polyamide/aluminum/polyvinyl chloride laminated forming foil sealed with an aluminum foil/heat-seal coated lidding foil. Each blister cavity contains a single tablet. The blisters are packed in carton boxes.

- Stability of finished pharmaceutical product is submitted in accelerated (40°C/75% RH) and long-term (25°C/60% RH & 30°C/75% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The provided stability study supports the proposed shelf life of 36 months when stored in aluminum/aluminum blister below 30°C.

- Additionally, the manufacturer submitted stability study to support the holding time of 24 months applied to Fezolinetant tablet 45 mg in the bulk pack (PE bag in Al bag in HDPE closure) when in suitable warehouse 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.

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

III. Non-Clinical &Clinical Aspects

Fezolinetant is a well-known active substance with established efficacy and tolerability.

The product Veozah containing Fezolinetant is used for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Mechanism of action Fezolinetant is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron, which is postulated to restore the balance in KNDy neuronal activity in the thermoregulatory centre of the hypothalamus. Pharmacodynamic effects In postmenopausal women, with fezolinetant treatment, a transient decrease of luteinizing hormone (LH) levels was observed. No clear trends or clinically relevant changes in sex hormones measured (follicle-stimulating hormone (FSH), testosterone, oestrogen, and dehydroepiandrosterone sulphate) in postmenopausal women were observed.

Pharmacokinetics
-Dose proportionality in healthy women, fezolinetant Cmax and AUC increased proportionally with doses between 20 and 60 mg once daily.
-Accumulation After once-a-day dosing, steady-state plasma concentrations of fezolinetant were generally reached by day 2, with minimal fezolinetant accumulation. The pharmacokinetics of fezolinetant do not change over time.
-Absorption Fezolinetant Cmax is usually achieved at 1 to 4 hours post-dose. No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie,

high-fat meal. Veozah may be administered with or without food.

-Elimination The apparent clearance at steady-state of fezolinetant is 10.8 l/h. Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in faeces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. The effective half-life (t1/2) of fezolinetant is 9.6 hours in women with VMS.

Summary of Listing of Clinical Studies:

-Safety and Tolerability Study: Single center, phase 1, double-blind, randomized, placebo-controlled, single- and multiple ascending dose escalation study in healthy male and female participants. The study consisted of 3 parts (parts 1, 2 and 3).

- PK. Study: Single center, phase 1, open-label absorption, metabolism and excretion study in healthy menopausal female participants.

-Based on the clinical study of Veozah 45 mg Film Coated Tablet submitted to EDA, found to recommend the approval of the marketing authorization of product.