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)

Seroloxetine Delayed release capsule containing enteric coated pellets

(Duloxetine 30mg & 60mg (as Hydrochloride))

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 Seroloxetine Delayed release capsule containing enteric coated pellets from P and C Labs (Pellets and CR Products).

The product contains Duloxetine which is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of the following conditions:
• Major depressive disorder (MDD) in adults.
• Generalized anxiety disorder (GAD) in adults and pediatric patients 7 years of age and older.
• Diabetic peripheral neuropathic pain (DPNP) in adults.
• Fibromyalgia (FM) in adults and pediatric patients 13 years of age and older.
• Chronic musculoskeletal pain in adults.

II. Quality Aspect

Drug Substance

- A CEP has been submitted for evaluation.
- The drug substance is white or almost white powder. Duloxetine is sparingly soluble in water, freely soluble in methanol and practically insoluble in hexane. Duloxetine exhibits polymorphism. The polymorphic form produced by the manufacturing process adopted by the supplier is form A. Duloxetine has one chiral centre, the active form is S-duloxetine.
- The drug substance specifications are as follow: Appearance, Solubility, Identification (HPLC, IR, test for chlorides, XRD), Loss on drying, Specific optical rotation, Sulfated ash, Enantiomeric purity (HPLC), Related substances (HPLC), Assay (HPLC) and Residual solvents (GC). Particle size distribution of Duloxetine has been found to be critical for the performance characteristics of the finished pharmaceutical product, therefore PSD analysis of duloxetine is included in the specifications.
- Analytical methods are according to the current version of European pharmacopeia monograph of Duloxetine except for the analytical method for determination of residual solvents which has been adequately described and validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- Duloxetine HCl is packed in double polyethylene bag (outer black), placed in a polyethylene drum.
- Re-test period of the drug substance is 5 years according to the certificate of suitability.

Medicinal Product

Product Description

- **30 mg Capsules:**

  - Transparent violet Cap / transparent pink Body containing white to off white pellets.

- **60 mg Capsules:**

  -Opaque yellow Cap / Opaque yellow Body containing white to off white pellets.

- **The excipients used in manufacture of pellets are**: Sugar Sphere (20#25) used as core material, Hydroxy propyl methylcellulose, Hydroxypropyl cellulose, Crospovidone Type B, Polysorbate 80, Talc, Triethyl citrate, Titanium dioxide "used for drug loading stage and barrier coating" and Hydroxy propyl methylcellulose Phthalate, Triethyl citrate, Talc (Micronized) & Titanium dioxide "used for enteric coating stage".
- **Capsule shell composition (30 mg)**: Gelatin, Methyl paraben, Propyl paraben, Sodium lauryl sulfate, Colloidal silicon dioxide, Erythrosine red and Brilliant Blue.
- **Capsule shell composition (60 mg)**: Gelatin, Methyl paraben, Propyl paraben, Sodium lauryl sulfate, Colloidal silicon dioxide, Titanium dioxide, Quinoline Yellow and Ponceau red.
- The product is packed in Aluminum (OPA/ALU/PVC) / Aluminum Blister placed in Carton box containing 1,2 or 3 blisters.

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 of the enteric coated pellets consists of Drug loading, Barrier Coating & Enteric Coating. The manufacturing process of Seroloxetine capsules includes capsule filling, blistering and packaging.
- The manufacturing process of enteric coated pellets was adequately validated by the manufacturer of enteric coated pellets and includes 3 commercial batches.

Control of excipients

- All excipients used in manufacture of pellets comply with BP.
- All excipients used in the manufacture of capsule shell comply with BP/USP except for Erythrosine red, Brilliant Blue, Quinoline Yellow, & Ponceau red which have in-house specifications.

Control of Drug product:

- Product specifications includes the four universal tests for description, identification, assay, impurities, and additional tests of uniformity of mass, disintegration, water content, uniformity of dosage units by content uniformity, dissolution and microbiological analysis.
- Analytical methods used for testing of Duloxetine pellets were adequately described and well validated by the enteric coated pellets manufacturer. Additionally, the analytical methods used for testing seroloxetine were adequately described and well validated by the finished pharmaceutical product manufacturer.
- Batch Analysis from the proposed production site of seroloxetine capsules were provided provided for 3 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 accelerated storage conditions at (40°C±2°C /75±5%RH) and long-term storage conditions at (30°C±2°C/65±5%RH) and concluded the conformity of specifications during the shelf-life and storage conditions. Seroloxetine capsules should be stored at a temperature not exceeding 30°C in dry place.

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:

For the drug substance:
-Clarification of the polymorphic form of duloxetine resulting from the manufacturing process is required from the supplier of drug substance.

For the drug product:
-The specification limit of total impurities in the set of specifications, used for control of Duloxetine pellets by the enteric coated pellets manufacturer, exceeded the limit specified in the USP monograph.

-The risk assessment of elemental impurities provided by the finished pharmaceutical product manufacturer had to be revised to include the elements of class 2A (Co, V & Ni).

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

-The supplier of drug substance clarified that the polymorphic form of duloxetine resulting from the manufacturing process is Form A
-The enteric coated pellets manufacturer revised the specification limit of total impurities to comply with USP monograph.
-The finished pharmaceutical product manufacturer provided results of class 2A elements for 3 batches of seroloxetine capsules and the results of class 2A were found below their control threshold.

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

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

Duloxetine (as Hydrochloride) is indicated for:
- Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain.
- Treatment of generalized anxiety disorder.

Mechanism of action:

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Pharmacodynamic effects

Duloxetine normalized pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behavior in a model of persistent pain. The pain inhibitory action of duloxetine is

believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Seroloxetine 60mg Delayed Release Capsule containing enteric coated pellets Manufactured by: P&C Labs (Pellets & CR Products) was done relative to Cymbalta ® 60mg Hard Gastro - Resistant Capsule administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strength Seroloxetine 30mg Delayed release capsule containing enteric coated pellets based on the following arguments:

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

Design

This Study Was an Open Label, Randomized, Fasting, Single Oral Dose, Two Treatments, Two Sequences and Two Periods, Crossover study with a washout interval of one week between dosing in healthy participants.

Biological Samples Collection:
Before dosing Pre-dose, 1 hr. ,2 hr. ,3 hr. ,4 hr. ,5 hr. ,5.5 hr. ,6 hr.,6.5 hr.,7 hr.,7.5 hr.,8 hr.,8.5 hr.,9 hr.,9.5 hr.,10 hr.,10.5 hr.,11 hr.,11.5 hr., 12 hr., 24 hr., 48 hr., and 72 hr. post dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Duloxetin 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 Duloxetine HCl under fasting conditions.

Treatment N=27	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	869 ± 920.34	925.11 ± 979.37	47.86±39.55	7	12.24±4.22
Reference	896.06± 858.14	945.37 ± 900.45	50.05± 40.87	6	11.16± 3.82
*Ratio (90%) CI	100.96% (87.43-116.58)	99.65% (87.98-112.87)	95.66% (86.38-105.93)	------	------
CV (%)	---	-------	------	------	------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} are within the bioequivalence acceptance range of 80-125%

Based on this study demonstrated that the active pharmaceutical ingredient Duloxetin HCl in Seroloxetine 60mg Delayed Release Capsule Contain Enteric Coated Pellets Manufactured by (P & C Labs pellets and CR products) & Cymbalta ® 60 mg Hard Gastro- Resistant Capsule are bioequivalent after a single oral dose of test and reference administration under fasting conditions on 27 participants.