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)

Sonismapex tablets

(Carbidopa 25 mg (as monohydrate) + Levodopa 250 mg)

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: Sonismapex tablets (Carbidopa 25 mg (as monohydrate), Levodopa 250 mg) from Apex Pharma.

The product is indicated for the treatment of symptoms of idiopathic Parkinson's disease (paralysis agitans), post-encephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

II. Quality Aspect

Drug Substance

1. Levodopa:

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is a white to off-white crystalline powder, freely soluble in 3N Hydrochloric acid, slightly soluble in water, and insoluble in alcohol. No polymorphic forms of this molecule are reported and the asymmetric center of the molecule has the 'S' absolute configuration.
- The synthesis of drug substance includes two steps with the formation of one intermediate. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, NMR (^{1}H & ^{13}C), mass spectrometry& elemental analysis and the structure is well characterized.
- The drug substance specifications are in accordance with USP and include the following tests, description, solubility, identification (by IR and HPLC), specific rotation, loss on drying, residue on ignition, organic impurities, assay, residual solvents and microbial limits. 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.

2. Carbidopa

- APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is a white to creamy-white powder, slightly soluble in water and in methanol, practically insoluble in alcohol, in acetone, in chloroform and in ether, freely soluble in 3N hydrochloric acid. The compound crystallizes as a monohydrate and it has one chiral center. The substance is slightly hygroscopic.

- The synthesis of drug substance includes four steps with the formation of three intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via IR, NMR (^{1}H & ^{13}C), mass spectrometry& elemental analysis and the structure is well characterized.
- The drug substance specifications are in accordance with USP and include the following tests, description, solubility, identification (by IR and HPLC), specific rotation, loss on drying, residue on ignition, related substances, assay, residual solvents, para toluene sulphonic acid content (by HPLC), methyl para toluene sulphonate and ethyl para toluene sulphonate (by LC-MS), hydrazine (by TLC) and microbial limit. 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**
- White to off-white round biconvex scored tablet, engraved A, M from one side & plain from other side.
- The product is packed in Carton Box containing 1, 2, 3 opaque PVDC/ALU blister containing 10 tablets and insert leaflet.
- The excipients are: Maize starch, Pregelatinized starch, Microcrystalline Cellulose and Magnesium Stearate.
- 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 sieving & mixing, granulation, drying & milling, final blending and lubrication & compression.
- The manufacturing process was adequately validated according to relevant guidelines for three proposed commercial batches.
- Control of excipients, all excipients comply with BP & USP and the specifications of the excipients are justified.

- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests uniformity of mass, hardness, friability, disintegration, sub division test, water content, uniformity of dosage unit, dissolution and microbiological test. All limits are acceptable.
- Analytical methods were adequately described and validated.
- Batch Analysis from the proposed production site were provided for three proposed commercial 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, 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.

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
Carbidopa & Levodopa are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Levodopa is the metabolic precursor of dopamine. Carbidopa is a peripheral dopa decarboxylase inhibitor, it is used as an adjunct with levodopa to prevent levodopa degradation to dopamine in extracerebral tissue, thereby decreasing the peripheral side effects of Levodopa.

Carbidopa /Levodopa is indicated for the treatment of the symptoms of idiopathic Parkinson's disease (Paralysis Agitans), post encephalitic Parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of test product "Sonismapex 25/250mg tablet" (Carbidopa 25mg/ Levodopa 250mg) manufactured by: Apex Pharma, Egypt relative to reference product "Sinemet 25/250mg tablet" (Carbidopa 25mg/ Levodopa 250mg) produced by: Merck Sharp & Dohme B.V., The Netherlands administered to healthy participants.

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Three Sequence, Three Period, partially replicated crossover bioequivalence study with a washout period of one week between periods in 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).

Analytical Methods

All procedures used to perform the bio-analyses of Carbidopa /Levodopa 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 Carbidopa 25mg under fast conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	543.61 ± 278.24	551.11 ± 281.51	107.40 ± 48.85	3.00	2.18 ± 0.81
Reference	536.76 ± 245.89	554.17 ± 272.93	105.72 ± 51.20	2.66	2.23 ± 1.41
***Ratio (90%) CI**	101.31 (91.50-112.17)	100.13 (90.62-110.63)	102.82 (91.20-115.92)	--------	-------
CV (%)	-------	-------	25.76	-------	-------

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of Levodopa 250mg under fast conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
Test	4738.84 ± 1319.12	4780.48 ± 1317.90	2029.21 ± 754.36	1.33	1.76 ± 0.44
Reference	4960.73 ± 1304.25	5003.78± 1298.85	2046.17 ± 632.84	1.33	1.75 ± 0.37
*Ratio (90%) CI	95.27 (91.52-99.17)	95.25 (91.55-99.1)	96.53 (88.35-105.48)	------	------
CV (%)	------	------	19.87	--------	--------

- Thirty-three (33) subjects from the general population were planned to be enrolled in this study.
- One subject withdrew before dosing of period I for personal reason.
- One subject was excluded after dosing of period I due to selection criteria (vomiting).
- One subject was excluded after dosing of period I due to selection criteria (vomiting), but attended the study period II & III.
- One subject withdrew before dosing of period III for 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 Carbidopa 25mg / Levodopa 250mg in product dosage form of the test product “Sonismapex 25/250mg tablet” manufactured by: Apex Pharma, Egypt & reference product “Sinemet 25/250mg tablet” (Carbidopa 25mg/ Levodopa 250mg) produced by: Merck Sharp & Dohme B.V., The Netherlands are bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 29 participants.