EDA Assessment Report for human medicinal product

(Scientific Discussion)

Gabimedra 2.5 mg ,5 mg, 10 mg and 15 mg Film Coated Tablet

(Mirogabalin "As Besylate")

Date: September 2026

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for "Gabimedra 2.5, 5, 10 and 15 mg" from Bio Med for Pharmaceutical Industries (BIOMED)

The product is indicated for the treatment of peripheral neuropathic pain, diabetic peripheral neuropathic pain, and post-herpetic neuralgia.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance off-white to white colour powder, soluble in methanol and dimethyl sulfoxide, insoluble in Cylohexane. Mirogabalin besylate has three chiral centers. The active form is R-isomer. Mirogabalin besylate exhibits polymorphism, the crystalline form resulting from the manufacturing process adopted by the supplier is form I.
- The synthesis of drug substance includes five stages with the formation of four intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via mass spectrometry (MS), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR) and elemental analysis. Moreover, the crystalline form of Mirogabalin besylate has been confirmed by X-ray powder diffraction (XRD) and Thermal Gravimetric Analysis (TGA).
- The drug substance specifications include description, solubility, identification (IR), identification (HPLC), water content (KF), loss on drying, residue on ignition, heavy metals, Benzene sulfonic acid content (poteniometry), S-isomer content (HPLC), dimer content (HPLC), related substances (HPLC), residual solvents (GC), Nickel content (ICP-MS), X-ray diffraction and particle size distribution.
- Analytical methods were adequately described and validated

- The supplier provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification
- The API is packed in double lined low-density food grade polyethylene bag (transparent inner and black outer) tie with plastic fastener and followed by HDPE drums.

. 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 24 months when stored below 25°C in the proposed container

Medicinal Product

- **Product Description**

  - For 2.5mg: Pale to deep green biconvex round non-scored film coated tablets with white to off white core.
  - For 5mg: Faint red to dark brick red Round biconvex non scored film coated tablet
  - with white to off white Core
  - For 10mg: Pale to deep yellow Round biconvex non scored film coated tablet with
  - white to off white Core
  - For 15mg: White to off white Round biconvex non scored film coated tablet with white to off white Core

  - The product is packed in carton box contain triplex (OPA/ AL/ PVC /AL) blister
  - The excipients areD-Mannitol, Microcrystalline Cellulose pH 102, Starch 1500, Povidone K30, Crospovidone, Citric acid monohydrate, Magnesium Aluminum Silicate, Magnesium Stearate, Purified Water, Hypromellose (HPMC E5), Macrogol (PEG 600), Purified Talc, Titanium dioxide (C.I: 77891).
    **For 2.5mg: Quinoline yellow (C.I: 47005) and Brilliant blue (C.I: 42090)
    **For 5mg: Iron Oxide red (C.I: 77491)
    **For 10mg: Iron Oxide yellow (C.I: 77492)

- **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 products of Mirogabalin besylate.
  - 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, granulation, drying, sieving, milling, mixing, lubrication, compression, coating and blistering.

  - The applicant submitted the process validation protocol of the manufacturing process in line with relevant guidelines and committed to provide the process validation report for the first three production batches.

- **Control of excipients**

  - All excipients comply with B.P and USP except for Quinoline yellow and Brilliant blue which comply with in-house specifications.

- **Control of Drug Product**

  - Product specifications include Description, colour of core, Disintegration, Mass Uniformity test, Water content (KF), Identification (HPLC & UV), Assay (HPLC), Dissolution, Uniformity of dosage units, Related Substances (HPLC) and Microbiological tests.
  - Analytical methods were revised and found to be suitable for the required testing.
  - Batch Analysis from the proposed production site were provided for two pilot scale batches for each concentration. The results of all tests are well within specification limits and batch data is acceptable

- **Container closure system**

-The drug product is packed in triplex (OPA/ AL/ PVC /AL) blister then further placed in a carton box with an inner leaflet.

- Stability

- Stability of finished pharmaceutical product is submitted in accelerated (40°C ± 2 °C /75% RH ± 5% RH) and long-term (30°C ± 2 °C /65% RH ± 5% 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 finished pharmaceutical product is stable for 24 months if stored below 30°C in a dry place.

- 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.
- A declaration/certificate of TSE/BSE free is submitted for Magnesium Stearate

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:

-Specifications of the API on applicant letterhead including the test particle size distribution should be submitted.

- Despite the produced isomer is R-Isomer while in conclusion "Based on the submitted data it is demonstrated that Mirogabalin besylate produced by the supplier is optically active S-Isomer "clarify the difference between them.

-Stability data for more recent batches covering the proposed retest period (24 months) should be submitted.

For the Drug product:

- Regarding the related substances test kindly note that the following impurities are degradation products:

* Clarify the lactam impurity which is also classified as a metabolite & a major degradation product according to literature & a specified impurity according to the reference product patent JP7744908B2 & summary of product information in pmda.go.jp (designated as A204-4455 which is the oxidized metabolite & degradation product of Mirogabalin).

- A 2nd identification test for Mirogabalin besylate should be considered as identification by a single chromatographic retention time procedure is not specific according to ICH Q6A guideline

The Quality of the drug product has been found satisfactory after

-The applicant has submitted the specifications of the API including the test for particle size distribution.

- The supplier demonstrated that Mirogabalin besylate produced by it is optically active R-Isomer and S-Isomer is controlled as an impurity in API specifications.

-Stability data for more recent batches covering the proposed retest period (24 months) was submitted

- The applicant mentioned that the supplier method mentioned in the DMF for impurities was applied and complete validation study was performed for the three impurities and accordingly updated finished product specifications controlling the three impurities submitted

- The applicant has revised the specifications of the drug product to include 2nd identification tests for both APIs by UV spectroscopy.

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

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

Mirogabalin is indicated for diabetic peripheral neuropathic pain (DPNP) and postherpetic neuralgia (PHN), for the indication of peripheral neuropathic pain (PNP).

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Gabimedra 15 mg F.C.Tablets Man. by: P&C Labs for Bio Med for Pharmaceutical industries (BIOMED), Egypt relative to Tarlige 15 mg Tablets by Daiichi Sankyo Co., Limited, Japan administered to healthy subjects.

Biowaiver

The EDA was granted a biowaiver for the lower strength Gabimedra 2.5, 5, and 10 mg Film Coated Tablets based on the following arguments;

All tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

Comparative randomized, single dose, two-way crossover bioequivalence study to determine the bioequivalence of Mirogabalin from Gabimedra 15 mg F.C.T. (Man. by: P&C Labs for Bio Med for Pharmaceutical industries (BIOMED), Egypt versus Tarlige 15 mg Tablets (Daiichi Sankyo Co., Limited, Japan in Healthy Human Volunteers Under Fasting Condition with a Washout Period of 7 days Between periods in 28 healthy subjects.

Analytical Methods

All procedures used to perform the bio-analyses of Mirogabalin 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 Gabimedra 15 mg F.C.Tablets under fasting conditions.

Treatment N=28	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	941.99±315.36	953.09±322.57	219.64±81.73	1.35±0.66 (0.75-2.50)	3.78±0.58
Reference	911.26±307.62	926.62±309.85	202.39±77.72	1.54±0.68 (0.75-3.00)	3.65±0.72
***Ratio (90%) CI**	104.07 (99.45-108.92)	103.39 (98.92-108.07)	108.86 (99.87-118.66)	------	-------
CV (%)	--------	------	-------	-------	---

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC $_{0\text{-}t}$ and C $_{max}$ are within the bioequivalence acceptance range of 80-125%

Based on this study demonstrated that Mirogabalin in Gabimedra 15 mg F.C.Tablets Man. by: P&C Labs for Bio Med for Pharmaceutical industries (BIOMED), Egypt of & reference product, Tarlige 15 mg Tablets by Daiichi Sankyo Co., Limited, Japan , are Bioequivalent after a single oral dose of test and reference administration under Fasting conditions on 28 subjects.