EDA Assessment Report for human medicinal product

(Scientific Discussion)

Euthyrox 75 mcg Tablets

(Levothyroxine Sodium)

Date: September 2024

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Euthyrox 75 mcg Tablets from Merck Ltd Scientific office.

-The product is indicated for Hypothyroidism & Pituitary TSH Suppression.

II. Quality Aspect

Drug Substance

- A CEP has been submitted for evaluation.
- The drug substance is almost white or slightly brownish-yellow, fine, slightly hygroscopic, crystalline powder, very slightly soluble in water, slightly soluble in ethanol (96 per cent). it dissolves in dilute solutions of alkali hydroxides.
- The drug substance specifications are appearance, solubility, identification, appearance of solution, specific optical rotation, related substances, assay, residual solvents, inorganic iodide, particle size and microbial purity.
- Analytical methods are in line with the current version of the European pharmacopeia monograph and the certificate of suitability (CEP).
- The applicant provided batch analysis results of 3 batches. The results of all tests were well within specification limits and batch data was found acceptable.
- Container closure system is double polyethylene bags (outer black), placed in a plastic transparent box.
- As per the CEP issued by the EDQM, the retest period of the drug substance is 36 months if stored in double polyethylene bags (outer black), placed in a plastic transparent box.

Medicinal Product

- **Product Description**

- Uncoated, off-white, round tablet which is flat on both sides, has a beveled edge, a dividing score on both sides and an inscription on one side
- The product is packed in aluminum/aluminum blister (“Alu/Alu blister”) packs.
- The excipients are Mannitol, Maize starch / corn starch, Gelatin, Croscarmellose sodium, Citric acid, anhydrous and Magnesium stearate.

- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. The development focused on the new formulation in which lactose monohydrate was replaced with mannitol to avoid the formation of impurity (maillard reaction product). Although, citric acid anhydrous used as a pH modifier was observed to form a condensation product with the drug substance, its use has been justified by controlling the reaction product in the release and shelf life specifications of the drug 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 preparation of granulation solution, Granulation, Drying, Sieving, Blending, Compression and Packaging.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included validation of specific operating parameters for each step of manufacturing where applicable.
- Control of excipients, all excipients comply with USP/Ph.Eur.
- Product specification includes appearance, resistance to crushing, water content, dissolution, divisibility, identity, uniformity of dosage units, assay, chemical purity and microbial purity.
- Analytical methods were revised and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided for 3 commercial batches. The results of all tests are well within specification limits and batch data is acceptable.
- Container closure system is blister formed using an aluminum forming foil “Cold-formable aluminum foil with soft-tempered aluminum, layered with PVC (polyvinychloride) inside and OPA (oriented polyamide) outside” and an aluminum lidding foil then placed in Printed cardboard boxes with package insert
- Stability of finished pharmaceutical product is submitted and conclude the conformity of specifications during the shelf life and storage conditions. The finished pharmaceutical product is stable for 36 months if stored below 30°C.

- There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product except gelatine. A declaration of TSE/BSE free is submitted for gelatine used in the manufacture of Euthyrox tablets.

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

-The most recent revision of the CEP as well as a summary of changes between the 2 revisions should be submitted.

For the Drug product:

- The results of NDELA impurity (N-Nitrosodiethanolamine) should be submitted in three consecutive commercial batches.
- Results of elemental impurities should be submitted for three consecutive batches of Euthyrox tablets.

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

-The applicant submitted and updated revision of CEP with a summary of changes made to the previous revision.

-The applicant provided results of NDELA in 3 batches of different strengths of Euthyrox tablets, the results were significantly below 10% of the Acceptable Intake (AI) which was found acceptable.

-The applicant submitted the results of elemental impurities for 3 batches of the highest strengths of Euthyrox tablets and none of the elemental impurities could be found above levels considering a 30% permitted daily intake (PDE) limit for orally administered drug products.

Recommendation:

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

Introduction

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

Levothyroxine Sodium is used for:

- Treatment of benign euthyroid goitre, especially in adults where iodine is not indicated
- Prophylaxis of relapse after surgery for euthyroid goitre, depending on the post-operative hormone status
- Substitution therapy in hypothyroidism
- Suppression therapy in thyroid cancer
- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

Summary of the clinical studies submitted to EDA:

1- Study Design: Phase I, open label, randomized, two-period, two sequence Type of Control: 600 µg of formulation of levothyroxine old formulation (Marketed levothyroxine sodium tablets) given as single oral dose of 3 tablets of 200 ug in healthy subjects, 216 subjects were randomized to treatment sequence.

2- Study Design: Phase I, open label, randomized, three period, six sequence crossover, single center trial. 42 subjects were randomized to treatment sequence. A total of 37 subject completed the trial.

-Based on the clinical study of Euthyrox Tablets submitted to EDA, found to recommend the approval of the marketing authorization of product.