IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Levothyroxine Sodium 100 microgram tablets
Levothyroxine sodium
PA22865/017/004

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Levothyroxine Sodium 25mcg, 75mcg & 100mcg Tablets, from Renata Pharmaceuticals (Ireland) Limited, on 10th August 2026 for

Levothyroxine Sodium 25, 75 & 100 microgram Tablets
- Treatment of euthyroid goitre, especially in adults, if iodine is not indicated.
- Recurrent prophylaxis after goitre resection, depending on postoperative hormone status.
- Substitution with hypothyroidism.
- Suppression treatment in thyroid carcinoma.
- Substitution during concomitant treatment with thyreostatic agents in hyperthyroidism.

Levothyroxine Sodium 100 microgram Tablets
- Diagnostic use in thyroid suppression examinations.

With IE as RMS in this decentralised procedure, Renata Pharmaceuticals (Ireland) Limited applied for the Marketing Authorisations for Levothyroxine Sodium in DE, IT, MT, PL, and PT.

A European Reference Product is used in the RMS and CMSs: Euthyrox 25 microgram, 75 microgram, 100 microgram tablets, MAH: Merck B.V., registered in NL.

The proposed legal supply status is that of a medicinal product subject to prescription that may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Levothyroxine Sodium 100 mcg Tablets
Name(s) of the active substance(s) (INN)	Levothyroxine Sodium
Pharmacotherapeutic classification (ATC code)	H03AA01
Pharmaceutical form and strength(s)	100 mcg Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/017/004
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1275/004/DC
Reference Member State	IE
Concerned Member State	DE, IT, MT, PL, PT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Levothyroxine Sodium 25mcg Tablets.

II.2 Drug substance

The active substance Levothyroxine Sodium is an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

25 microgram:
Each tablet contains 25 micrograms levothyroxine sodium.

75 microgram:
Each tablet contains 75 micrograms levothyroxine sodium.

100 microgram:
Each tablet contains 100 micrograms levothyroxine sodium.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. and are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and EU legislation for use with foodstuffs==> requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Levothyroxine Sodium 25 microgram, 75 microgram and 100 microgram Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Euthyrox (25 microgram, 75 microgram, 100 microgram) tablets on the European market. No new nonclinical data have been submitted. The overview provided based on literature review is thus appropriate. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Levothyroxine Sodium 25mcg, 75mcg & 100mcg Tablets is a generic product, and levothyroxine is an analogue of an endogenous substance used as replacement therapy to restore the endogenous thyroid level in human only, which will not lead to increased consumption. Therefore, further environmental risk assessment is not considered necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Levothyroxine are well known. As Levothyroxine is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Euthyrox marketed by Merck B.V.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Euthyrox.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Levothyroxine Sodium 100 mcg Tablets (6 × 100 mcg) (Test) of Renata Limited, Bangladesh was compared to the reference product Euthyrox (Levothyroxine sodium) tablets 100 mcg (6 × 100 mcg) of Merck BV, Netherlands in healthy adult subjects under fasting conditions.

On the basis of results from that study, the applicant has proposed a biowaiver for the two lower tablet strengths (25 and 75 microgram tablets).

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

In line with current EMA product-specific bioequivalence guidance (EMA/CHMP/176098/2020), the applicant has conducted one bioequivalence study, under fasting conditions, between a single supra-therapeutic dose (600 micrograms) of test and reference product (6 x 100 microgram tablets).

An open label, balanced, randomised, two-treatment, two sequence, two-period, cross-over, single-dose, oral bioequivalence study of Levothyroxine Sodium 100 mcg Tablets (6 × 100 mcg) (Test) of Renata Limited, Bangladesh and Euthyrox (Levothyroxine sodium) tablets 100 mcg (6 × 100 mcg) (Reference) of Merck BV, Netherlands in healthy adult subjects under fasting conditions.

As levothyroxine is an endogenous substance, plasma levothyroxine values for pharmacokinetic analysis were corrected for endogenous thyroxine by subtraction of the mean of three pre-dose plasma thyroxine concentrations (e.g. at 0.5 h, 0.25 h, and 0 h pre-dose) from the values obtained post-dose.

The following results were obtained for baseline corrected levothyroxine:

Parameters (units)	Ln-transformed Data					
	Geometric Least square Mean		(T/R) Ratio %	90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test-T	Reference-R				
C_{max} (ng/mL)	80.5522	74.1735	108.60	103.58-113.86	11.9	100
AUC_{0-72} (hr. ng/mL)	2893.3563	2901.2881	99.73	96.18-103.41	9.1	100

Conclusion on bioequivalence:
The test to reference ratio of geometric least squares means and corresponding 90% confidence interval for ln-transformed Cmax and AUC0-72 were within the pre-defined acceptance ranges of 80.00 to 125.00% and 90.00 to 111.11%, respectively, for baseline corrected levothryroxine. Bioequivalence between the test and reference 100 microgram tablets was demonstrated.

Proposed biowaiver:
At this time, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, results from Study 227-21 with the 100-microgram formulation can be extrapolated to other proposed strengths (25 and 75 microgram tablets). The biowaiver is accepted.

IV.3 Pharmacodynamics

No new efficacy data have been submitted as part of this application, and none are expected.

IV.4 Clinical Efficacy

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. No new efficacy data have been submitted as part of this application, and none are expected.

IV.5 Clinical Safety

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. Only safety data arising from the bioequivalence study have been submitted as part of this application. Both test and reference products were equally well tolerated. No safety concerns were identified.

Risk Management Plan (RMP)

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the above-mentioned sildenafil containing products.

Safety Specification

Important identified risks	None
Important potential risks	Circulatory collapse in very low birth weight preterm neonates
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. No new clinical studies were conducted.

It was demonstrated through the bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

On the basis of results from that study for the 100 microgram tablets, a biowaiver for the two lower tablet strengths (25 and 75 microgram tablets) has been established. Dissolution similarity between strengths has been sufficiently demonstrated using an appropriate method. The justification for a biowaiver is acceptable in view of the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*.

V. OVERALL CONCLUSIONS

Levothyroxine Sodium 25mcg, 75mcg & 100mcg Tablets is a generic form of Euthyrox 25 microgram, 75 microgram, 100 microgram tablets. Levothyroxine is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents.

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Levothyroxine Sodium demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

23.06.2031