Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Levothyroxine 12.5 micrograms Tablets
Levothyroxine 25 micrograms Tablets
Levothyroxine 50 micrograms Tablets
Levothyroxine 75 micrograms Tablets
Levothyroxine 100 micrograms Tablets

levothyroxine sodium anhydrous

PL 29831/0756, 0757, 0550, 0570, 0551

Wockhardt UK Limited

LAY SUMMARY

Levothyroxine 12.5 micrograms Tablets
Levothyroxine 25 micrograms Tablets
Levothyroxine 50 micrograms Tablets
Levothyroxine 75 micrograms Tablets
Levothyroxine 100 micrograms Tablets
levothyroxine sodium anhydrous

This is a summary of the Public Assessment Report (PAR) for Levothyroxine 12.5 micrograms, 25 micrograms, 50 micrograms, 75 micrograms, and 100 micrograms Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Levothyroxine Tablets in this lay summary for ease of reading.

For practical information about using Levothyroxine Tablets, patients should read the Patient Information Leaflets (PILs) or contact their doctor or pharmacist.

What are Levothyroxine Tablets and what are they used for?
The applications for Levothyroxine 25 micrograms, 50 micrograms, and 100 micrograms Tablets are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, the reference medicines already authorised in the United Kingdom (UK) called Eltroxin 25 mcg, 50 mcg, 100 mcg tablets/Levothyroxine 25 mcg, 50 mcg, 100 mcg tablets (PL 12762/0016, PL 10972/0031 – 0032).

The applications for Levothyroxine 12.5 micrograms and 75 micrograms Tablets are for hybrid medicines. This means that these medicines are similar to the reference medicine, Eltroxin 100 mcg tablets/Levothyroxine 100 mcg tablets, albeit with certain differences. In this case, Levothyroxine 12.5 micrograms and 75 micrograms Tablets, are lower strengths (of the active substance), than the reference product.

Levothyroxine Tablets are used to replace the thyroxine that the patient's thyroid gland cannot produce and prevent the symptoms of hypothyroidism. Before starting the treatment, their doctor will carry out a blood test to work out how much levothyroxine the patient needs.

How do Levothyroxine Tablets work?
Levothyroxine Tablets contains the active substance, levothyroxine which is a synthetic version of thyroxine, a hormone that is produced naturally in the body by the thyroid gland. Thyroxine controls how much energy the body uses. When the thyroid gland does not produce enough thyroxine (a condition known as hypothyroidism), many of the body's functions slow down.

Some of the most common symptoms of hypothyroidism are:
- Tiredness
- weight gain
- feeling depressed.

How are Levothyroxine Tablets used?

The pharmaceutical form of these medicines is a tablet, and the route of administration is oral (by mouth).

The patient may be taking this medicine for the rest of their life.

The dose will be decided by the patient's doctor and will depend on the results of their blood tests. The dose they should take will be on the label attached by their pharmacist.

The patient should swallow the tablets with plenty of water. They should usually take their tablets before breakfast or their first meal of the day.

Adults

The recommended starting dose is 50 – 100 micrograms every day.

The patient's doctor may increase the dose they take every 3 – 4 weeks by 50 micrograms until their thyroxine levels are correct. The final daily dose may be up to 100 – 200 micrograms daily.

Patients over 50 years of age

The recommended starting dose will be no more than 50 micrograms every day. The dose may then be increased by 50 micrograms every 3 – 4 weeks until the patient's thyroxine levels are correct. The final daily dose will be between 50 – 200 micrograms daily.

Patients over 50 years of age with heart problems

The recommended starting dose will be 25 micrograms every day or 50 micrograms every other day. The dose may be increased by 25 micrograms every 4 weeks until the patient's thyroxine levels are correct. The final daily dose will usually be between 50 – 200 micrograms daily.

Use in children and adolescents

For young children, the patient's doctor is likely to prescribe Levothyroxine Oral Solution instead of tablets.

Congenital hypothyroidism in infants

This is a condition where the baby has been born with a thyroid gland that does not produce enough thyroxine. The starting dose is 10 -15 micrograms/kg body weight per day for the first three months. The dose will then be adjusted depending on how the baby responds to the treatment.

Acquired hypothyroidism in children

This is a condition where the child's thyroid gland stops working properly because it has been attacked by their immune system, e.g. in children with an autoimmune disease or following a viral infection. The starting dose is 12.5 – 50 micrograms per day. The dose will then be increased every 2 – 4 weeks depending on how the child responds to the medicine.

Juvenile myxoedema

This is a condition where children and adolescents develop severe hypothyroidism (produce very low levels of thyroid hormones). The starting dose is 25 micrograms every day. The

dose will then be increased by 25 micrograms every 2 – 4 weeks until the child shows mild symptoms of hyperthyroidism (a condition where the thyroid gland produces too much thyroxine). The dose will then be reduced slightly.

For further information on how Levothyroxine Tablets are used, refer to the PILs and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Levothyroxine Tablets have been shown in studies?
As Levothyroxine Tablets are generic/hybrid medicines, studies in healthy volunteers have been limited to tests to determine that these are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Levothyroxine Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PILs or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PILs that comes with the medicines. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Because Levothyroxine Tablets are generic/hybrid medicines, and are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

Why were Levothyroxine Tablets approved?
It was concluded that Levothyroxine Tablets have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and authorised that these can be approved for use.

What measures are being taken to ensure the safe and effective use of Levothyroxine Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Levothyroxine Tablets. The RMP details the important risks of Levothyroxine Tablets, how these risks can be minimised, any uncertainties about Levothyroxine Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Levothyroxine Tablets:

Summary of safety concerns	
Important identified risks	•Embrotoxicity (hypothyroidism of fetus) •Circulatory collapse in preterm neonates
Important potential risks	•Product substitution issue •Off label use for weight reduction •Under or over dosage due to medication error (multiple tablet)
Missing information	• None

The information included in the SmPCs and the PILs is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Levothyroxine Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Levothyroxine Tablets
Marketing Authorisations for Levothyroxine Tablets were granted in the United Kingdom (UK) on 29 October 2024.

The full PAR for Levothyroxine Tablets follows this summary.

This summary was last updated in December 2024.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Levothyroxine 12.5 micrograms, 25 micrograms, 50 micrograms, 75 micrograms, and 100 micrograms Tablets (PL 29831/0756, 0757, 0550, 0570, 0551) could be approved.

The products are approved for the following indications:
Control of hypothyroidism, congenital hypothyroidism in infants, acquired hypothyroidism in children and juvenile myxoedema.

Levothyroxine 12.5 micrograms, 25 micrograms, 50 micrograms, 75 micrograms, and 100 micrograms Tablets contain levothyroxine sodium used for the treatment of hypothyroidism. The thyroid gland is dependent upon 2 active principles for its main hormone activity these are levothyroxine (tetraiodothyronine) and tri-iodothyronine. These closely related iodine containing amino acids are incorporated into the glycoprotein thyroglobulin. The chief action of levothyroxine is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form tri-iodothyronine which is thought to be the active tissue form of thyroid hormone.

The applications for Levothyroxine 25 micrograms, 50 micrograms, and 100 micrograms Tablets were approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Eltroxin 25 mcg, 50 mcg, 100 mcg tablets/Levothyroxine 25 mcg, 50 mcg, 100 mcg tablets, that have been licensed within the UK for a suitable time, in line with the legal requirements.

The applications for Levothyroxine 12.5 micrograms and 75 micrograms Tablets were approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), as hybrid medicinal product of suitable originator product, Eltroxin 100 mcg tablets/Levothyroxine 100 mcg tablets.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic/hybrid medicinal products of suitable reference products.

With the exception of two bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications are for generic/hybrid medicinal products of suitable reference product. The bioequivalence studies were conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 29 October 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is anhydrous levothyroxine sodium.
Five different strengths of tablets are available.
Each 12.5 micrograms tablet contains 12.5 micrograms of anhydrous levothyroxine sodium, each 25 micrograms tablet contains 25 micrograms of anhydrous levothyroxine sodium, each 50 micrograms tablet contains 50 micrograms of anhydrous levothyroxine sodium, each 75 micrograms tablet contains 75 micrograms of anhydrous levothyroxine sodium, and each 100 micrograms tablet contains 100 micrograms of anhydrous levothyroxine sodium.

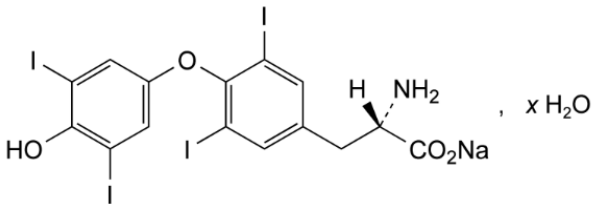
In addition to anhydrous levothyroxine sodium, these products also contain the following excipients:
lactose monohydrate, maize starch, croscarmellose sodium, gelatin, and magnesium stearate.

The finished products are packaged in clear transparent PVC/PVDC film with aluminium lidding foil blister pack and are available in pack-size of 28, 30 and 112 tablets.
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: anhydrous levothyroxine sodium
Chemical Name: Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate.
Molecular Formula: $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$ ($x \approx 5$)
Chemical Structure:



Molecular Weight: 799
Appearance: Almost white or slightly brownish-yellow, fine, slightly hygroscopic, crystalline powder.
Solubility: Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Anhydrous levothyroxine sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin and lactose monohydrate, no excipients of animal or human origin are used in the final products. The suppliers of gelatin have provided Certificates of Suitability from EDQM, confirming that the gelatin used complies with the TSE and BSE requirements.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions ‘Do not store above 25°C’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of levothyroxine sodium are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these are generic/hybrid applications of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of levothyroxine sodium are well-known. With the exception of data from two bioequivalence studies, no new clinical data are provided or are required for these applications. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics

In support of the applications, the applicant submitted the following bioequivalence studies:

Bioequivalence Study 1

This study was an open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing the test product, Levothyroxine 100 micrograms (μg) Tablets, versus the reference product, Eltroxin 100 micrograms tablets, in healthy, adult human subjects under fasting conditions.

After an overnight fast of at least 08 hours, subjects were administered six tablets of 100 μg (6 x 100 μg) either test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 40 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1. Summary of Pharmacokinetic Data for Baseline Corrected Levothyroxine (n=18) Dose: 6 × 100 µg (micrograms)

Parameter	Test Product: Levothyroxine Sodium Tablets BP 100 µg		Reference Product: Eltroxin® Levothyroxine Sodium Tablets 100 µg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (ng/mL)	18	88.567 ± 12.935 (14.605)	18	85.793 ± 13.317 (15.522)
AUC72 (ng/mL)*(hr)	18	3035.661 ± 493.969 (16.272)	18	3110.050 ± 665.947 (21.413)
Tmax (hr)^	18	2.000 (1.500 - 3.000)	18	2.125 (1.000 - 4.500)
(^) Tmax is presented as Median (Range)				

Table 2. Summary of Statistical Analysis of Baseline Corrected Levothyroxine

PARAMETER	Unit	REFERENCE LEAST SQUARE MEANS Ln DATA	TEST LEAST SQUARE MEANS Ln DATA	REFERENCE GEOMETRIC MEANS	TEST GEOMETRIC MEANS	INTRA-SUBJECT CV(%)
Cmax	(ng/mL)	4.440	4.473	84.782	87.658	6.682
AUC72	(ng/mL)*(hr)	8.022	8.005	3046.252	2995.375	9.253

PARAMETER	Unit	RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL	POWER	Bioequivalence
Cmax	(ng/mL)	103.39%	(99.45%;107.49%)	1.0000	Yes
AUC72	(ng/mL)*(hr)	98.33%	(93.19%;103.76%)	1.0000	Yes

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

Bioequivalence Study 2

This study was an open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing the test product, Levothyroxine 25 micrograms Tablets, versus the reference product, Eltroxin 25 micrograms tablets, in healthy, adult, human subjects under fasting condition.

After an overnight fast of at least 11 hours, subjects were administered a single oral dose of either test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 41 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 3. Summary statistics of all pharmacokinetic parameters – Baseline-corrected

Formulation	Parameter	N	Mean	SD	CV
Reference	C_{max} (ng/mL)	33	108.4348	38.2516	35.2761
	AUC_{0-72} (ng.h/mL)	33	3270.0026	898.7927	27.4860
	t_{max} (h)	33	3.4167	3.3276	97.3931
	K_{el} (h^{-1})	33	0.0125	0.0061	48.6925
	$t_{1/2}$(h)	33	77.7199	61.8755	79.6135
Test	C_{max} (ng/mL)	33	94.2103	28.4905	30.2414
	AUC_{0-72} (ng.h/mL)	33	3144.2293	913.9367	29.0671
	tmax (h)	33	3.5770	2.1260	59.4346
	K_{el} (h^{-1})	33	0.0094	0.0040	42.1209
	$t_{1/2}$ (h)	33	88.1452	42.4267	48.1327

Table 4. Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Baseline Corrected Levothyroxine (n=33)

Pharmacokinetics Parameter	Geometric mean		Ratio (%)
	Test	Reference	
LnC_{max}	91.7544	104.6212	87.70
$LnAUC_{0-72}$	3054.8234	3183.6180	95.95
Pharmacokinetics Parameter	**90% Confidence Intervals**	**Acceptance Criteria**	**Outcome of BE result**
LnC_{max}	(81.64 - 94.21%)	80.00% - 125.00%	Bioequivalent
$LnAUC_{0-72}$	(88.17-104.43%)	80.00% - 125.00%	

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional 12.5 micrograms, 50 micrograms, and 75 micrograms strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence studies on the 100 mg product strength can be extrapolated to the other products.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflets (PILs) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levothyroxine sodium is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPCs and PILs for these products are available on the MHRA website.

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PILs available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**