Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Levothyroxine Kappler 100 micrograms tablets

(levothyroxine sodium anhydrous)

PL 22363/0016

Kappler Pharma Consult GmbH

LAY SUMMARY

Levothyroxine Kappler 100 micrograms tablets (levothyroxine sodium)

This is a summary of the Public Assessment Report (PAR) for Levothyroxine Kappler 100 micrograms tablets. It explains how Levothyroxine Kappler 100 micrograms tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Levothyroxine Kappler 100 micrograms tablets.

This product will be referred to as Levothyroxine 100 mcg tablets in this lay summary for ease of reading.

For practical information about using Levothyroxine 100 mcg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What is Levothyroxine 100 mcg tablets and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Eltroxin 100 mcg tablets.

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

How does Levothyroxine 100 mcg tablets work?
Thyroxine is a hormone which is produced naturally in the body by the thyroid gland. Levothyroxine is a synthetic version of this hormone. Thyroxine controls how much energy your 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 is Levothyroxine 100 mcg tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is by mouth (oral).

This medicine should be used exactly as the patient's doctor or pharmacist told their patient. If unsure the patient should check with their doctor or pharmacist. 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 the patient's blood tests. The dose to be taken will be on the label attached by the pharmacist.

The tablets should be swallowed with plenty of water and the tablets should be taken at least half an hour before breakfast, or the first meal of the day.

Adults
The recommended starting dose is 50-100 micrograms every day. The doctor may increase the dose taken every 3-4 weeks by 50 micrograms until their patient's 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 their 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 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 their patient's thyroxine levels are correct. The final daily dose will usually be between 50-200 micrograms daily.

Use in children
The dose for children depends on their age, weight and the condition being treated. The child will be monitored to make sure that they get the right dose. If necessary, the tablets can be divided.

Levothyroxine is also available as an oral solution.

Congenital hypothyroidism in infants
This is a condition where a baby has been born with a thyroid gland that does not produce enough thyroxine. The starting dose is 10-15 micrograms/kg bodyweight 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 a 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 100 mcg tablets is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Levothyroxine 100 mcg tablets have been shown in studies?
Because Levothyroxine 100 mcg tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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 100 mcg tablets?
Because Levothyroxine 100 mcg tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Levothyroxine 100 mcg tablets approved?
It was concluded that, in accordance with EU requirements, Levothyroxine 100 mcg tablets has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levothyroxine 100 mcg tablets?
A Risk Management Plan (RMP) has been developed to ensure that Levothyroxine 100 mcg tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Levothyroxine 100 mcg tablets
A Marketing Authorisation for Levothyroxine 100 mcg tablets was granted in the UK on 8 July 2019.

The full PAR for Levothyroxine 100 mcg tablets follows this summary.

This summary was last updated in August 2019.

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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 application for Levothyroxine Kappler 100 mg micrograms tablets (PL 22363/0016) could be approved.

The product is indicated for the treatment of the following:

- control of hypothyroidism
- congenital hypothyroidism in infants
- acquired hypothyroidism in children
- juvenile myxoedema.

Levothyroxine sodium is a synthetic thyroid hormone which used for the treatment of hypothyroidism. The thyroid gland is dependent upon two active principles for its main hormone activity. These are levothyroxine (tetraiodothyronine) and tri-iodothyronine which areclosely related iodine containing amino acids are incorporated into the glycoprotein thyroglobulin. The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form tri-iodothyronine which is thought to be active tissue form of thyroid hormone. Tri-iodothyronine is certainly more rapid acting and has shorter duration of action than levothyroxine

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines. The reference medicinal product is Eltroxin 100 microgram tablets (PL 10972/0032) which was granted a Marketing Authorisation in the UK to Mercury Pharma Group Ltd on 09 November 1993

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

With the exception of the pilot and pivotal bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. 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 this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

Advice was sought from the Commission of Human Medicines (CHM) on 7-8th December 2017 and 21st-22nd February 2019, to consider quality and clinical issues. At the meeting in February, CHM considered that the issues were resolved and approval of the product could be recommended.

A Marketing authorisation was granted for this product on 8 July 2019.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 100 micrograms levothyroxine sodium anhydrous. In addition to levothyroxine sodium this product also contains the excipients microcrystalline cellulose, maize starch, magnesium oxide (heavy), sodium starch glycolate type A, and magnesium stearate.

The finished product is packaged in the tablets are packed in PVC/Aluminium blister in pack sizes of 28 tablets.

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

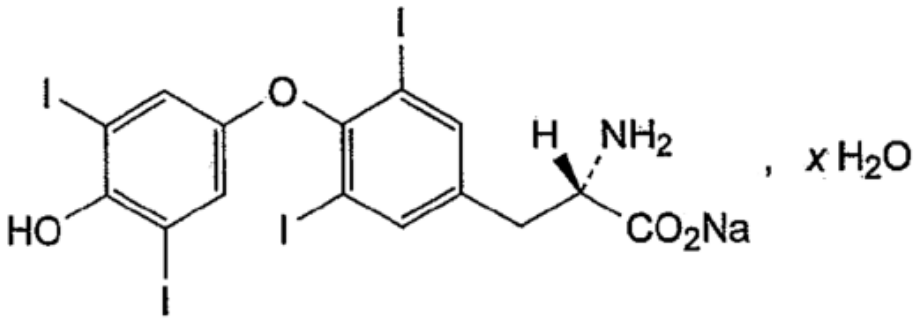
II.2 ACTIVE SUBSTANCE

rINN: Levothyroxine Sodium

Chemical Name: Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl] propanoate

Molecular Formula: $C_{15}H_{10}I_4NNaO_4 \times H_2O$

Chemical Structure:



Molecular Weight: 799.0

Appearance: An 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.

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.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.
Comparative in vitro dissolution and impurity 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.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

A satisfactory batch formula has been provided for the manufacture of the product, 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 are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. 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 2 years with the storage condition “Do not store above 30 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 a marketing authorisation is 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 this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is 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 a pilot bioequivalence study and a pivotal bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following:

Pilot study
To preliminary assess the potential for bioequivalence of levothyroxine 100microgram tablets formulation given as 600 microgram dose (six tablets) vs Equal dose of reference formulation (6 x levothyroxine 100microgram tablets) in male and female, healthy volunteers under fasting conditions. The other aims were to determine the sample size with the secondary objective to assess safety and tolerability. 14 subjects were planned to be enrolled and 13 were analysed.

A single supra-therapeutic oral dose of test or reference product was administered on two occasions, at the start of period I and period II, separated by a washout period of 41 days. Blood samples were taken pre-dose and up to 72 hours post dose.

Results
Although the test formulation and the reference formulation in the pilot study were bioequivalent regarding the peak plasma concentration (Cmax), they were not bioequivalent regarding the extent of absorption (AUC) in fasting conditions. The pilot study was not powered to demonstrate bioequivalence and therefore the sample size was subsequently adjusted for the pivotal study. There were no adverse events in the study and the dose was well tolerated by the subjects.

Pivotal study
A pivotal open label, two period, two sequence, cross-over, block-randomised, single dose study to assess the bioequivalence of levothyroxine 100microgram tablets (test formulation) given as 600 mcg dose (six tablets) vs Equal dose of reference formulation (6 x levothyroxine 100 microgram tablets) in male and female healthy volunteers under fasting conditions.

Subjects were randomised to receive a single oral dose [6 x 100micrograms tablets] of either Test or Reference product in each study period. Blood samples were taken pre-dose and up to 72 hours post dose, a washout period of 44 days was maintained between dosing periods.

A summary of the pharmacokinetic results are presented below:

Test name	Parameter	Point estimate (T/R %)	Lower 90% CL	Upper 90% CL	Acceptance range	Equivalence criteria met?
Classic 90% CI	net-C_{max}	93.51	90.68	96.42	80.00 – 125.00 %	YES
Classic 90% CI	net-AUC_{0-72}	101.55	98.54	104.64	90.00 – 111.11 %	YES

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios for the critical parameters Cmax and AUC and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference product 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 Directive 2001/83/EC, 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 a marketing authorisation is recommended for this application.

V USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

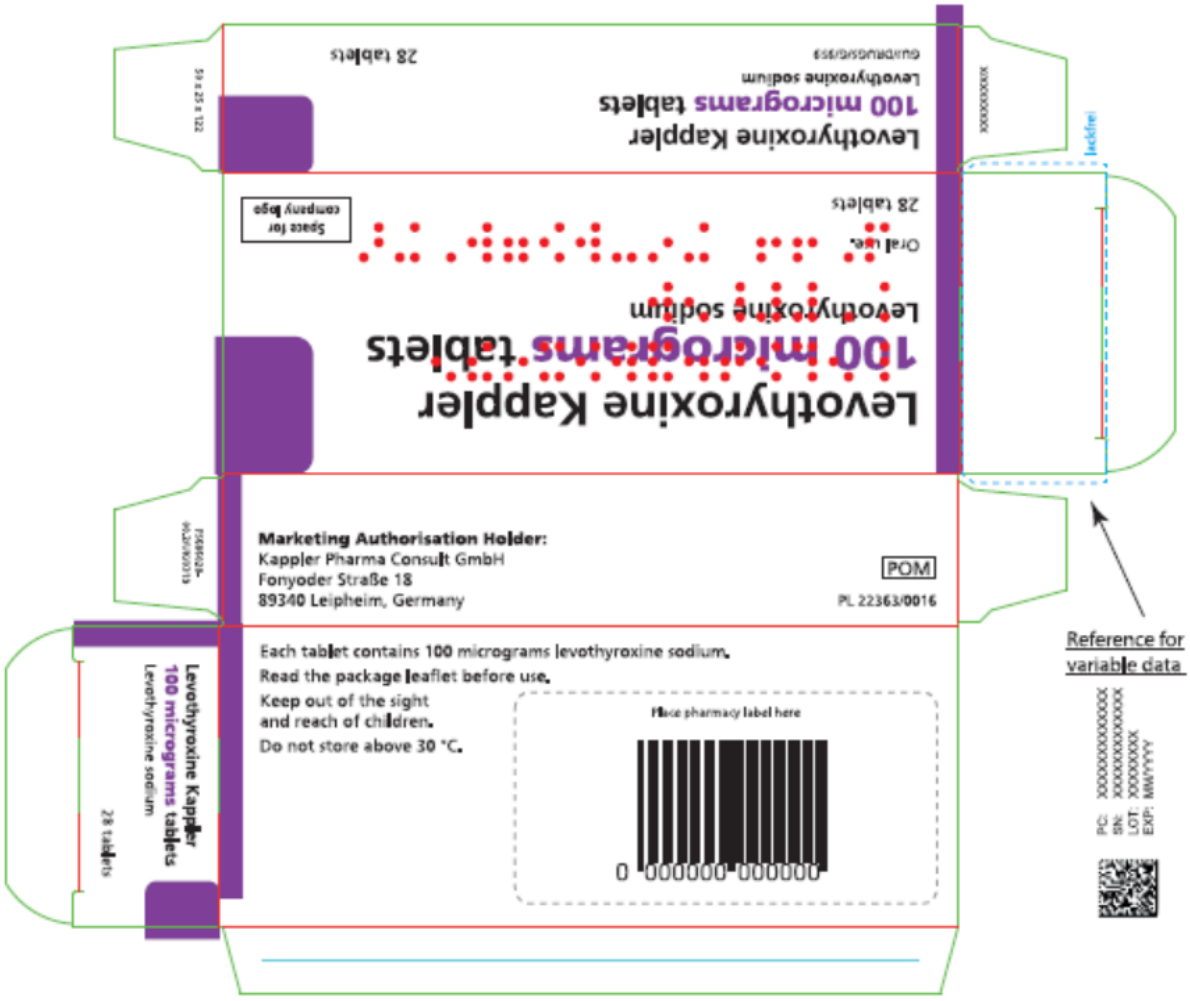
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product 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 compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.




Levothyroxine Kappler
100 micrograms
tablets
Kappler Pharma Consult GmbH
LOT:/EXP: see Impress

TABLE OF CONTENT 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 product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Outcome**	**Assessment report attached Y/N**