Public Assessment Report

Decentralised Procedure

Levothyroxine 25 micrograms/5ml Oral Solution
Levothyroxine 50 micrograms/5ml Oral Solution
Levothyroxine 100 micrograms/5ml Oral Solution
(levothyroxine sodium)

Procedure No: UK/H/6468/001-003/DC

UK Licence No: PL 34777/0003-0005

BCM SPECIALS LIMITED
LAY SUMMARY

Levothyroxine 25 micrograms/5ml Oral Solution
Levothyroxine 50 micrograms/5ml Oral Solution
Levothyroxine 100 micrograms/5ml Oral Solution
(Levothyroxine sodium)

This is a summary of the Public Assessment Report (PAR) for Levothyroxine 25 micrograms/5ml Oral Solution (PL 34777/0003; UK/H/6468/001/DC), Levothyroxine 50 micrograms/5ml Oral Solution (PL 34777/0004; UK/H/6468/002/DC) and Levothyroxine 100 micrograms/5ml Oral Solution (PL 34777/0005; UK/H/6468/003/DC). It explains how the applications for Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution 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 Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution.

For practical information about using Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

These products will be referred to as Levothyroxine Oral Solution in the remainder of this summary, for ease of reading.

What is Levothyroxine Oral Solution and what is it used for?

Levothyroxine Oral Solution are ‘generic medicines’. This means Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution are similar to ‘reference medicines’ already authorised in the European Union (EU) called Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions.

Levothyroxine Oral Solution is used to treat hypothyroidism, a condition in which the thyroid gland is underactive and so does not make enough thyroxine for the body's needs.

Levothyroxine Oral Solution is also used to treat thyroid cancer and diffuse non-toxic goitre or Hashimoto's thyroiditis, conditions in which the thyroid gland becomes enlarged causing a swelling in the front of the neck.

How does Levothyroxine Oral Solution work?

These medicines contain the active ingredient levothyroxine sodium, which is a synthetic form of thyroxine (T4) which is produced by the thyroid gland.

Thyroid hormones are responsible for maintaining a normal rate of metabolism in the body and are required for normal growth and development of the body, especially the nervous system. When the thyroid gland is underactive it is unable to produce normal amounts of thyroxine and levels of these hormones in the body decrease, causing hypothyroidism. Symptoms of hypothyroidism include weight gain, intolerance to cold and tiredness.

How is Levothyroxine Oral Solution used?

This medicinal product can only be obtained with a prescription.

Levothyroxine Oral Solution should be taken on an empty stomach, usually before breakfast.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.
What benefits of Levothyroxine Oral Solution have been shown in studies?
The company provided data from the published literature on levothyroxine sodium. No additional studies were needed as Levothyroxine Oral Solution are generic medicines that are given as aqueous oral solutions and contain the same active substance, in the same concentration, as the reference medicines, Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions.

What are the possible side effects of Levothyroxine Oral Solution?
As Levothyroxine Oral Solution are generic medicines, their possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Levothyroxine Oral Solution, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why was Levothyroxine Oral Solution approved?
It was concluded that, in accordance with EU requirements, Levothyroxine Oral Solution have been shown to have comparable quality and to be comparable to Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions. Therefore, the MHRA decided that, as for Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions, the benefits outweigh the identified risks and recommended that Levothyroxine Oral Solution can be approved for use.

What measures are being taken to ensure the safe and effective use of Levothyroxine Oral Solution?
A risk management plan (RMP) has been developed to ensure that Levothyroxine Oral Solution are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Levothyroxine Oral Solution, 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 Oral Solution
Malta, Ireland and the UK agreed to grant Marketing Authorisations for Levothyroxine Oral Solution on 20 April 2018. A Marketing Authorisation was granted in the UK on 21 May 2018.


The full PAR for Levothyroxine Oral Solution follows this summary. For more information about treatment with Levothyroxine Oral Solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2018.
## SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Levothyroxine 25 micrograms/5ml Oral Solution (PL 34777/0003; UK/H/6468/001/DC), Levothyroxine 50 micrograms/5ml Oral Solution (PL 34777/0004; UK/H/6468/002/DC), and Levothyroxine 100 micrograms/5ml Oral Solution (PL 34777/0005; UK/H/6468/003/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), Malta and Ireland were the Concerned Member States (CMS).

These products are Prescription Only Medicines (legal classification POM).

The applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The reference product that has been authorised for not less than 10 years in the EEA is Eltroxin 100 micrograms Tablets (PL 10972/0032) authorised in the UK since 09 November 1993. The reference products named for the purpose of clinical interchangeability are Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions (PL 12762/0459, PL 12762/0461 and PL 1276/0462) marketed by Mercury Pharmaceuticals ltd. The comparative reference products submitted via the decentralised procedure under Article 10a as line extensions of the original product (i.e. Eltroxin tablets). No new data exclusivity attaches to the line extension and exclusivity is calculated by reference to the original product (i.e. Eltroxin tablets). The authorised article 10a oral solutions are considered part of the original Global Marketing Authorisation for Eltroxin tablets.

Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution are indicated for the treatment of:

- hypothyroidism (congenital or acquired)
- diffuse non-toxic goitre
- goitre associated with Hashimoto's thyroiditis
- suppression therapy in thyroid carcinoma.

These medicines contain the active ingredient levothyroxine sodium, which is a synthetic form of thyroxine (T4) which is produced by the thyroid gland.

Thyroid hormones are responsible for maintaining a normal rate of metabolism in the body and are required for normal growth and development of the body, especially the nervous system. When the thyroid gland is underactive it is unable to produce normal amounts of thyroxine and levels of these hormones in the body decrease, causing hypothyroidism. Symptoms of hypothyroidism include weight gain, intolerance to cold and tiredness.

No new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that has been licensed for over 10 years.

Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution are aqueous oral solutions at the time of administration and in line with the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS and CMS considered that the application could be approved at the end of procedure on 20 April 2018. After a subsequent national phase, Market Authorisations were granted in the UK on 21 May 2018.
II QUALITY ASPECTS

II.1 Introduction
Levothyroxine 25 micrograms/5ml Oral Solution is a clear, colourless to pale yellow, each 5 ml of oral solution contains levothyroxine equivalent to levothyroxine sodium 25 micrograms.

Levothyroxine 50 micrograms/5ml Oral Solution is a clear, colourless, to pale yellow solution, each 5 ml of oral solution contains levothyroxine equivalent to levothyroxine sodium 50 micrograms.

Levothyroxine 100 micrograms/5ml Oral Solution is a clear, colourless, to pale yellow, solution, each 5 ml of oral solution contains levothyroxine equivalent to levothyroxine sodium 100 micrograms.

The other ingredients are the pharmaceutical excipients, namely glycerol (E422), purified water, citric acid monohydrate (E330), sodium hydroxide (E524), sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217).

The finished products are packaged in 100 ml amber glass bottles with a tamper evident, child resistant screw cap with polyethylene liner. The bottle is packaged in a cardboard container which also includes a CE-marked 10 ml dosing pipette (with 0.25 ml graduations), and a separate ‘bung’ adaptor which is fitted to the neck of the bottle at first use (i.e. after opening), to ensure proper use of the pipette.

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 Drug substance
rINN: Levothyroxine sodium
Chemical name(s): Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate

Structure:

![Structure of Levothyroxine sodium]

Molecular formula: C_{15}H_{10}I_4NaNaO_4xH_2O (x≈5)
Molecular weight: 798.9 (anhydrous)
Appearance: Almost white or slightly brownish yellow, fine, slightly hygroscopic, crystalline powder
Solubility: Very slightly soluble in water, slightly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides

With the exception of the stability data, all aspects of the manufacture and control of the active substance levothyroxine sodium are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP).
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate generic and stable oral solution containing levothyroxine sodium as the active moiety, that could be considered generic medicinal products of the currently licensed products, Eltroxin 25 mcg, 50 mcg, 100 mcg per 5ml Oral Solutions (Mercury Pharmaceuticals Ltd).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. These products do not contain or consist of genetically modified organisms (GMO).

The excipient composition of the proposed products is qualitatively the same as that of the reference product with the exception of sodium propyl 4-hydroxybenzoate (propylparaben), present in the proposed generic but not in the reference product. In addition, sodium methyl 4-hydroxybenzoate (methylparaben) exists at a concentration of which exceeds the concentration of methylparaben in the reference product.

Acceptable justifications were provided for the inclusion of propylparaben, and the greater concentration of methylparaben with reference to permitted daily exposure limits, the reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use (EMA/CHMP/SWP/272921/2012) and data showing preservation over the proposed shelf life.

The current levels of methylparaben and propylparaben in all formulation strengths are considered to be acceptable for the proposed posology and age range. The Applicant has implemented an excipient warning for para-hydroxybenzoates in the SmPC. A similar warning has been implemented in the patient information leaflet, in line with the latest Annex to the European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ EMA/CHMP/302620/2017 which specifies the inclusion of such a warning in the package leaflet for any medicine that contains parahydroxybenzoates at any concentration.

Sodium content
According to the recommended posology, the sodium content of levothyroxine 25, 50 & 100 micrograms/5ml Oral Solution, exceeds the 1 mmol per single dose threshold for implementation of a warning in the package leaflet. The sodium warning in the package leaflet has been updated in line with the Annex to the EC guideline ‘Excipients in the labelling and package leaflet of medicinal products for human use’ (SANTE-2017-11668) EMA/CHMP/302620/2017 9 October 2017. In addition, appropriate amendments have been implemented in the SmPC. The warnings in relation to sodium content are considered acceptable.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on three commercial scale batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have
been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the product**

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 15 months, with the special storage conditions of “Store in the original package in order to protect from light”, “Do not store above 25°C”, and “Do not freeze”. Once opened the product should be used within 28 days.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

It is recommended that Marketing Authorisations are granted for Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**

The pharmacodynamic, pharmacokinetic and toxicological properties of levothyroxine sodium are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

**III.2 Pharmacology**

No new pharmacology data are required for these applications and none have been submitted.

**III.3 Pharmacokinetics**

No new pharmacokinetic data are required for these applications and none have been submitted.

**III.4 Toxicology**

No new toxicology data are required for these applications and none have been submitted.

**III.5 Ecotoxicity/Environmental risk Assessment (ERA)**

As these products are intended for generic substitution of products that are already marketed, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion of the non-clinical aspects**

It is recommended that Marketing Authorisations are granted for Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution.

**IV. CLINICAL ASPECTS**

**IV.1 Introduction**

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of levothyroxine sodium. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

**IV.2 Pharmacokinetics**

A bioequivalence study was not submitted as the product meets the criteria specified in the *Notes for
Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference product and the excipients for the proposed and reference products are qualitatively similar and would not be expected to affect gastrointestinal transit, in the amounts administered, or absorption of the active substance. The drug product contains glycerol, which has the potential to affect gastrointestinal transit when taken in large amounts. However, based on the maximum dose administered there is expected to be no significant effect on GI transit rate, and therefore absorption or bioavailability of the active.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted an RMP, 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 Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Table 1. Summary of safety concerns

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<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
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<tr>
<td></td>
<td>• Hypersensitivity to the active substance or to any of the excipients.</td>
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<td></td>
<td>• Excessive dosage of levothyroxine</td>
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<td>• Use in patients with adrenal insufficiency</td>
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<td></td>
<td>• Myocardial ischaemia and arrhythmias</td>
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<td>• Use in patients with cardiovascular disorders</td>
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<td>• Use in elderly patients and patients with a long term history of hypothyroidism</td>
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<td>• Use in patients with diabetes</td>
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<td></td>
<td>• Sub-clinical hyperthyroidism associated with bone loss</td>
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<td>• Hair loss in children</td>
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<td></td>
<td>• Use in patients with thyrotoxicosis</td>
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<tr>
<td>Important potential risks</td>
<td>• Medication errors including unintentional overdose</td>
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<td></td>
<td>• Use during pregnancy and lactation</td>
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<tr>
<td>Missing information</td>
<td>None</td>
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IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted for Levothyroxine 25, 50, and 100 micrograms/5ml Oral Solution.

V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with levothyroxine sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Annex 1  Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

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<thead>
<tr>
<th>Scope</th>
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<th>Product Information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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