Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Liothyronine Sodium 5 micrograms Tablets
Liothyronine Sodium 20 micrograms Tablets
liothyronine sodium

PL 50888/0001-0002

Sigmapharm Laboratories International, Limited

LAY SUMMARY

Liothyronine Sodium 5 micrograms Tablets
Liothyronine Sodium 20 micrograms Tablets
liothyronine sodium

This is a summary of the Public Assessment Report (PAR) for Liothyronine Sodium 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 Liothyronine Sodium Tablets in this lay summary for ease of reading.

For practical information about using Liothyronine Sodium Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Liothyronine Sodium Tablets and what are they used for?
The application for Liothyronine Sodium 5 micrograms Tablets is for a hybrid medicine. This means that the medicine is similar to the reference medicine, Liothyronine Sodium BP 20 micrograms Tablets (Mercury Pharma Group Limited), albeit with certain differences. In this case Liothyronine Sodium 5 micrograms Tablets is a lower strength (of the active substance) to the reference product.

The application for Liothyronine Sodium 20 micrograms Tablets is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with the reference medicine already authorised in the United Kingdom (UK) called Liothyronine Sodium BP 20 micrograms Tablets (Mercury Pharma Group Limited).

Liothyronine Sodium Tablets are used to:
- treat some of the more severe conditions in which the thyroid does not produce enough thyroxine.
- balance the effect of medicines used to treat an overactive thyroid.

How do Liothyronine Sodium Tablets work?
Liothyronine Sodium Tablets are a form of thyroxine which is quick acting and long lasting. Thyroxine is a hormone produced by the thyroid gland in the neck which controls many body functions.

How are Liothyronine Sodium Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (taken by mouth).

Please note that the doctor will monitor their patient’s thyroid function regularly to make sure that the patient is given the right dose for their condition.

The tablets can be either swallowed whole or dissolved in water. To dissolve the tablet, the patient should follow the below instructions:
- Put the tablet in a glass with at least 20 ml water for each tablet.
- Either stir to dissolve or wait until the tablet is fully dissolved.

- Drink all the liquid.
- Add a little more water to the glass and drink that, to make sure no medicine is left in the glass.

The solubility of liothyronine in water enables this method of administration.

The recommended dose is:
Adults:
The dose will depend upon the patient's condition, ranging from 10 micrograms to 60 micrograms daily in divided doses, as directed by their doctor.

Use in children and elderly:
The dose may be started at 5 micrograms a day.

If a dose lower than 20 micrograms is required, an appropriate tablet strength should be used.

The 5 microgram tablets are not scored. The 20 microgram tablets are scored. The score line is not intended for breaking the tablet.

For further information on how Liothyronine Sodium Tablets are used, refer to the PIL 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 this medicine 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 Liothyronine Sodium Tablets have been shown in studies?
As Liothyronine Sodium Tablets are hybrid/generic medicines, studies in healthy volunteer consist of tests to determine that they are therapeutically equivalent/bioequivalent to the reference medicine.

What are the possible side effects of Liothyronine Sodium Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL 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 PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Liothyronine Sodium Tablets are hybrid/generic medicines and are bioequivalent to the reference medicine, their possible side effects are taken as being the same as the reference medicine.

Why are Liothyronine Sodium Tablets approved?
It was concluded that Liothyronine Sodium Tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicines, 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 Liothyronine Sodium Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Liothyronine Sodium Tablets The RMP details the important risks of Liothyronine Sodium Tablets, how these risks can be minimised, any uncertainties about Liothyronine Sodium Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Liothyronine Sodium Tablets:
Important identified risks: None
Important potential risks: Medical errors (e.g., under-dose, overdose)
Missing information: None

The information included in the SmPCs and the PIL 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 Liothyronine Sodium Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

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

Other information about Liothyronine Sodium Tablets
Marketing Authorisations for Liothyronine Sodium Tablets were granted in the UK on 17 December 2021.

The full PAR for Liothyronine Sodium Tablets follows this summary.

This summary was last updated in February 2022.

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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 applications for Liothyronine Sodium 5 micrograms and 20 micrograms Tablets (PL 50888/0001-0002) could be approved.

The products are approved for the following indications:

- Used for the treatment of coma of myxoedema, the management of severe chronic thyroid deficiency and hypothyroid states occurring in the treatment of thyrotoxicosis.
- Liothyronine sodium 5 micrograms and 20 micrograms Tablets can be used also in the treatment of thyrotoxicosis as an adjunct to carbimazole to prevent sub-clinical hypothyroidism developing during treatment.
- Liothyronine sodium 5 micrograms and 20 micrograms Tablets may be preferred for treating severe and acute hypothyroid states because of its rapid and more potent effect, but thyroxine sodium is normally the drug of choice for routine replacement therapy.

Liothyronine sodium, the active substance, is a synthetic form of naturally occurring thyroid hormone. The biological action of liothyronine sodium is quantitatively similar to that of levothyroxine sodium, but the effects develop in a few hours and disappear within 24 to 48 hours of stopping treatment.

The application for Liothyronine Sodium 5 micrograms Tablets was approved under Regulation 52B of The Human Medicines Regulations 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, called Liothyronine Sodium BP 20 micrograms Tablets (Mercury Pharma Group Limited)), that has been licensed within the United Kingdom (UK) for a suitable time, in line with the legal requirements.

The application for Liothyronine Sodium 20 micrograms Tablets was approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Liothyronine Sodium BP 20 micrograms Tablets (Mercury Pharma Group Limited).

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

Data from two bioequivalence studies were submitted with these applications. These 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.

Advice was sought from the Commission of Human Medicines (CHM) on 08 November 2019 because major objections were raised with respect to quality and clinical aspects of the dossier. The Committee provisionally concluded that further information on quality and clinical aspects should be requested before the products could be approved. In response to the

CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the Marketing Authorisations was recommended.

National Marketing Authorisations were granted in the UK on 17 December 2021.

II QUALITY ASPECTS

II.1 Introduction

These products contain 5 micrograms or 20 micrograms of liothyronine sodium in each tablet.

In addition to liothyronine sodium, these products also contain the excipients calcium sulfate dihydrate, corn starch, gelatin, magnesium stearate and mannitol (E421).

The finished products are packaged in high-density polyethylene (HDPE) containers, each with a polypropylene child-resistant closure, with a 2 g canister containing silica gel and a cotton plug. The products are available in pack sizes of 28 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.

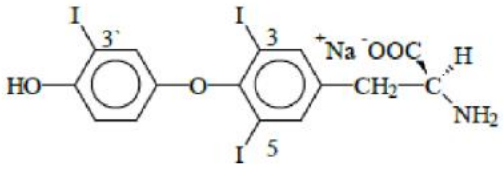
II.2 ACTIVE SUBSTANCE

rINN: Liothyronine sodium

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

Molecular Formula: $C_{15}H_{11}I_3NNaO_4$

Chemical Structure:



Molecular Weight: 673.0 g/mol (anhydrous)

Appearance: A ‘light tan’, odourless, crystalline, hygroscopic powder.

Solubility: Slightly soluble in alcohol, practically insoluble in water and most other organic solvents.

Liothyronine 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.

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, no excipients of animal or human origin are used in the final products. An EDQM certificate has been provided for the excipient gelatin.

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 2 years, with the storage conditions ‘Store in the original container in order to protect from light.’ , 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 is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of liothyronine 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 hybrid applications of an already authorised product 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 is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from two bioequivalence studies have been submitted with these applications. These studies were conducted in line with current Good Clinical Practice (GCP).

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

Bioequivalence study 1 (single-dose, fasting)
This study was an open-label, randomised, two-treatment, two-sequence, single-dose, two-way, crossover, bioequivalence study comparing the test product Liothyronine sodium 5 micrograms tablets versus the reference product Liothyronine sodium 20 microgram tablets in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least eight hours, subjects were administered a single supratheraputic dose (100 micrograms) of either the test (20 x 5 micrograms tablets) or reference product (5 x 20 micrograms tablets) with approximately 150 ml water. The study had a two-stage study design. Blood samples were taken pre-dose and up to 72 hours post-dose, with a washout period of 15 and 16 days (for the two stages) between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Primary analysis (baseline corrected values)

Summary of Bioequivalence Parameters of Baseline Corrected Total (free + bound) liothyronine					
Parameter	N	Geometric Least Square Mean (GLSM)		Ratio	90% CI
		Test Product (A)	Reference Product (B)		
C_{max} (ng/mL)	36	7.320	7.812	93.69	(90.39, 97.11)
AUC_{0-t} (ng.hr/mL)	36	81.043	86.907	93.25	(89.58, 97.08)

Table 2: Secondary analysis (baseline uncorrected values)

Summary of Bioequivalence Parameters of Baseline Uncorrected Total (free + bound) liothyronine					
Parameter	N	Geometric Least Square Mean (GLSM)		Ratio	90% CI
		Test Product (A)	Reference Product (B)		
C_{max} (ng/mL)	36	8.374	8.891	94.18	(91.17, 97.30)
AUC_{0-t} (ng.hr/mL)	36	150.375	159.923	94.03	(89.01, 99.33)

According to the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product (20 x 5 micrograms tablets) and the reference product (5 x 20 micrograms tablets).

Bioequivalence study 2 (single-dose, fasting)
This study was an open-label, randomised, two-treatment, two-sequence, single-dose, two-way, crossover, bioequivalence study comparing the test product Liothyronine sodium 20 micrograms tablets versus the reference product Liothyronine sodium 20 microgram tablets in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least eight hours, subjects were administered a single supratheraputic dose (100 micrograms; 5 x 20 micrograms tablets) of either the test or reference product with approximately 150 ml water. Blood samples were taken pre dose and up to 72 hours post-dose, with a washout period of 15 between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 3: Primary analysis (baseline corrected values)

Summary of Bioequivalence Parameters of Baseline Corrected Total (free + bound) liothyronine					
Parameter	N	Geometric Least Square Mean (GLSM)		Ratio	90% CI
		Test Product (A)	Reference Product (B)		
C_{max} (ng/mL)	38	7.203	7.754	92.90	(89.20, 96.74)
AUC_{0-t} (ng.hr/mL)	38	81.200	87.269	93.05	(88.29, 98.06)

Table 4: Secondary analysis (baseline uncorrected values)

Summary of Bioequivalence Parameters of Baseline Uncorrected Total (free + bound) liothyronine					
Parameter	N	Geometric Least Square Mean (GLSM)		Ratio	90% CI
		Test Product (A)	Reference Product (B)		
C_{max} (ng/mL)	38	8.305	8.829	94.07	(90.70, 97.56)
AUC_{0-t} (ng.hr/mL)	38	149.519	156.441	95.58	(88.46, 103.26)

According to the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product (5 x 20 micrograms tablets) and the reference product (5 x 20 micrograms tablets).

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 from the clinical studies submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)
The applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 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 is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the applications, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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 products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with liothyronine sodium is considered to have demonstrated the therapeutic value of the products.

The benefit/risk is, therefore, considered to be positive.

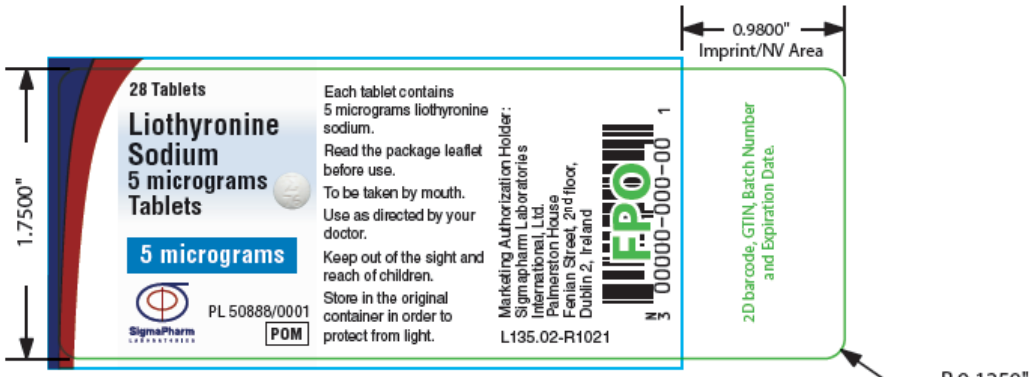
The Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

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

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

Liothyronine Sodium 5 micrograms Tablets

Flat Label



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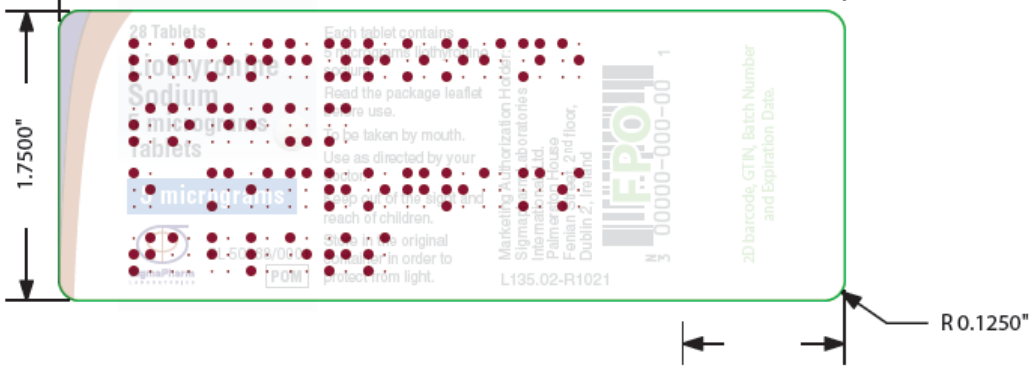

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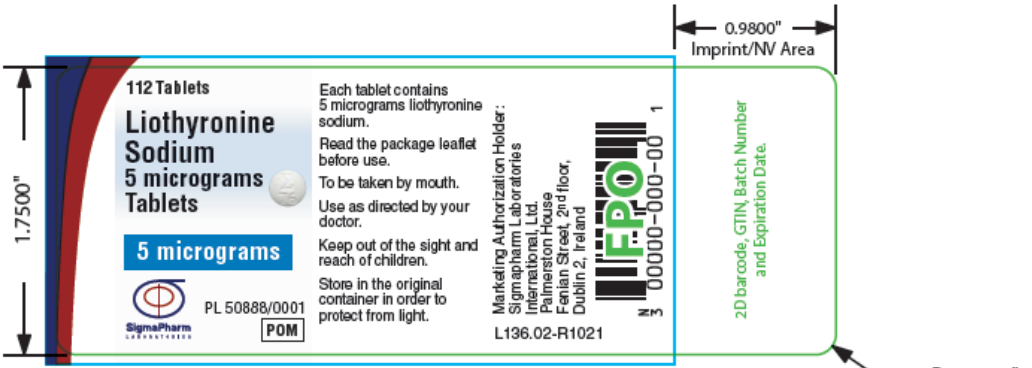

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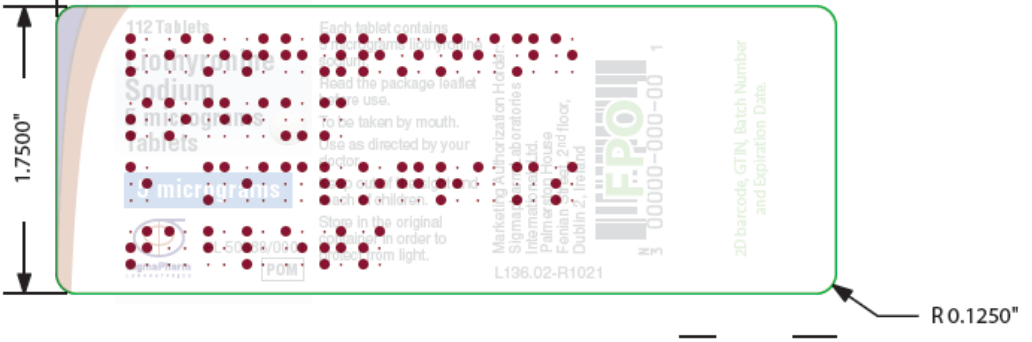
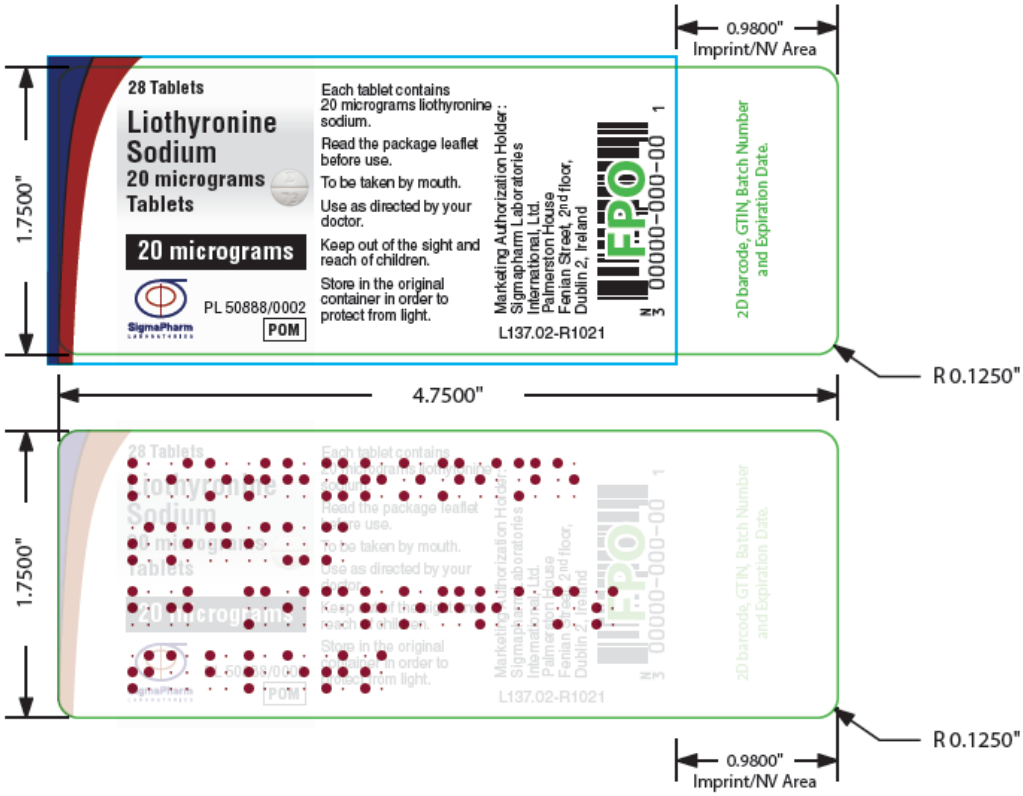


Liothyronine Sodium 20 micrograms Tablets

Flat Label



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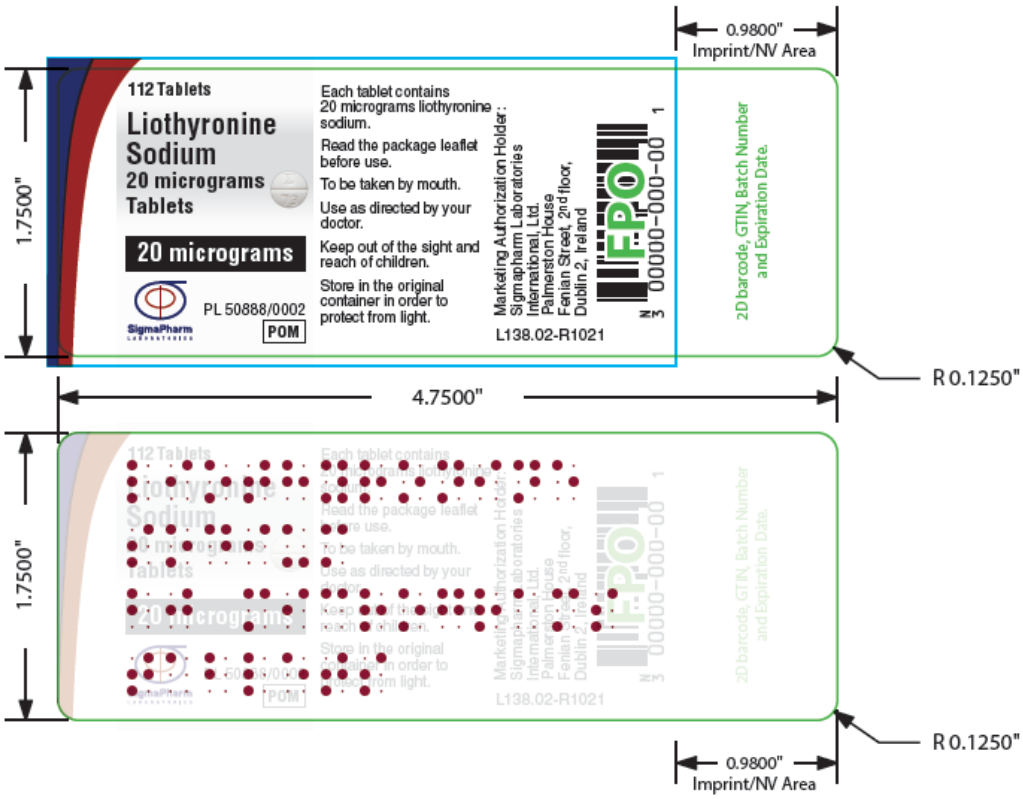
Flat Label



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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 SmPC and/or PIL available on the MHRA website.

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