Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Liothyronine sodium 5 micrograms Hard Capsules
Liothyronine sodium 10 micrograms Hard Capsules
Liothyronine sodium 20 micrograms Hard Capsules

(liothyronine sodium)

PL 49578/0018-0020

Roma Pharmaceuticals Limited

LAY SUMMARY

Liothyronine sodium 5, 10 and 20 micrograms Hard Capsules (liothyronine sodium)

This is a summary of the Public Assessment Report (PAR) for Liothyronine sodium 5, 10 and 20 micrograms Hard Capsules. 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 Capsules in this lay summary for ease of reading.

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

What are Liothyronine sodium Capsules and what are they used for?

For Liothyronine sodium 5 and 10 micrograms Hard Capsules

These applications are for hybrid medicines. This means that these medicines are similar to reference medicines already authorised in the United Kingdom (UK) called Liothyronine Sodium BP 20 micrograms Tablets / Tertroxin Tablets 20mcg, although with certain differences. In this case, Liothyronine sodium 5 and 10 micrograms Hard Capsules are for a change in strength.

For Liothyronine sodium 20 micrograms Hard Capsules

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 UK called Liothyronine Sodium BP 20 micrograms Tablets / Tertroxin Tablets 20mcg.

Liothyronine sodium Capsules 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 Capsules work?

The active substance of Liothyronine sodium Capsules is liothyronine sodium.

Liothyronine sodium Capsules 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 Capsules used?

The pharmaceutical form of these medicines is a hard capsule and the route of administration is oral (via the mouth). They should be swallowed with a glass of water.

If the patient has difficulty swallowing a whole capsule, they should empty the contents of a capsule into a minimum of 20 ml of water. Stir and drink the whole liquid to ensure they take the full dose. It is possible to do this with liothyronine because this substance is soluble in water.

If the patient has been prescribed a dose lower than 20 micrograms, Liothyronine sodium 5 micrograms Capsules and Liothyronine sodium 10 micrograms Capsules are also available.

Adults:
The dose will depend upon their condition, ranging from 10 micrograms to 60 micrograms daily in divided doses.

Use in children and elderly:
The dose may be started at 5 micrograms a day.
Please note that the patient's doctor will monitor their thyroid function regularly to make sure that they are given the right dose for their condition.

For further information on how Liothyronine sodium Capsules 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 Capsules have been shown in studies?
For Liothyronine sodium 5 and 10 micrograms Hard Capsules
Because Liothyronine sodium 5 and 10 micrograms Hard Capsules are hybrid medicines, studies in healthy volunteers consist of tests to support the difference compared to the reference medicine.

For Liothyronine sodium 20 micrograms Hard Capsules
Because Liothyronine sodium 20 micrograms Hard Capsules 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 Liothyronine sodium Capsules?
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.

Because Liothyronine sodium Capsules are generic / hybrid medicines and are bioequivalent / therapeutically equivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Liothyronine sodium Capsules approved?
It was concluded that, Liothyronine sodium Capsules have been shown to be comparable to and to be bioequivalent / therapeutically equivalent to the reference medicines. Therefore, the

MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Liothyronine sodium Capsules?

A Risk Management Plan (RMP) has been developed to ensure that Liothyronine sodium Capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, 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 Liothyronine sodium Capsules

Marketing Authorisations for Liothyronine sodium Capsules were granted in the United Kingdom (UK) on 15 July 2021.

Following approval, the Marketing Authorisations underwent a change of ownership procedure on 11 August 2021 from the company Colonis Pharma Limited (PL 41344/0061 - 0063) to Roma Pharmaceuticals Limited (PL 49578/0018 - 0020).

The full PAR for Liothyronine sodium Capsules follows this summary.

This summary was last updated in September 2021.

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 Liothyronine sodium 5, 10 and 20 micrograms Hard Capsules (PL 49578/0018-0020) could be approved.

The products are approved for the following indications:
Liothyronine is indicated in adults and children 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 can be used also in the treatment of thyrotoxicosis as an adjunct to carbimazole to prevent sub-clinical hypothyroidism developing during treatment.

Liothyronine sodium 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 is a naturally occurring thyroid hormone.
Liothyronine sodium 5, 10 and 20 micrograms Hard Capsules are qualitatively similar in biological action to thyroxine but the effect develops in a few hours and lasts for 24 to 48 hours after stopping the treatment.

For Liothyronine sodium 5 and 10 micrograms Hard Capsules
These applications were approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be hybrid medicinal products of a suitable originator product, Liothyronine Sodium BP 20 micrograms Tablets / Tertroxin Tablets 20mcg, that has been licensed within the EU for a suitable time, in line with the legal requirements.

For Liothyronine sodium 20 micrograms Hard Capsules
This application was approved under Regulation 51B of The Human Medicines Regulation 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 / Tertroxin Tablets 20mcg that has been licensed within the EU for a suitable time, in line with the legal requirements.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic / hybrid medicinal products of a suitable reference product. The bioequivalence study was 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 21 February 2019 and as a result of its consideration was of the opinion that on the grounds relating to quality, safety and efficacy it may be unable to advise the licensing authority to grant the authorisations. In response, the Applicant submitted further quality, safety and efficacy data for these medicinal products addressing these concerns which were deemed acceptable and Marketing Authorisations were granted in the UK on 15 July 2021.

Following approval, the Marketing Authorisations underwent a change of ownership procedure on 11 August 2021 from the company Colonis Pharma Limited (PL 41344/0061 - 0063) to Roma Pharmaceuticals Limited (PL 49578/0018 - 0020).

II QUALITY ASPECTS

II.1 Introduction

Each hard capsule contains 5, 10 or 20 micrograms of liothyronine sodium.

In addition to liothyronine sodium, these products also contain the excipients:
Capsule contents:
Maize starch and magnesium stearate (E 572).

Capsule shell:
Gelatin (all product strengths), titanium dioxide (E 171) (10 and 20 micrograms strengths) and yellow iron oxide (20 micrograms strength only).

All strengths of the finished product are packaged in opaque PVC/PVDC/aluminium blisters. Each blister contains 7 or 10 capsules. The medicinal products are available in pack sizes of 28, 56, 100 and112 hard capsules. 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.

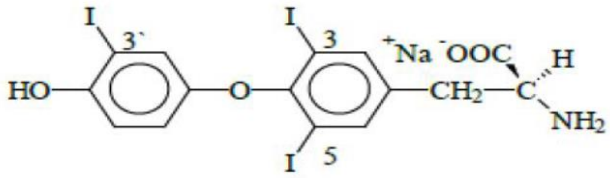
II.2 ACTIVE SUBSTANCE

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: White or slightly coloured, hygroscopic powder
Solubility: Slightly soluble in ethanol (96%) and dissolves in dilute solutions of alkali hydroxide.

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 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.

With the exception of gelatin, no excipients of animal or human origin are used in the final products. EDQM certificates have been provided for gelatin.

Confirmation has been given that the magnesium stearate used in the capsules 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 'Do not store above 25°C. Keep the blister in the outer carton 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 application(s).

III.5 Ecotoxicity/Environmental Risk Assessment
An Environmental Risk Assessment (ERA) has been provided. The $PEC_{surfacewater}$ has been calculated to be 0.0003 µg/L using the maximum daily dose of liothyronine (60 mg) and default values for $WasteW_{inhab}$, DILUTION and F_{Pen}. The $PEC_{surfacewater}$ value is below the threshold triggering a Phase II Environmental Risk Assessment.

The results of the ERA show that there is no risk of increased environmental exposure with the use of these products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of liothyronine sodium are well-known. With the exception of data from one 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 study is, thus, satisfactory.

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

STUDY
This study was a randomised, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study comparing the test product Liothyronine sodium 20 micrograms Hard Capsules versus the reference product Liothyronine Sodium BP 20 micrograms Tablets / Tertroxin Tablets 20mcg in subjects under fasted conditions.

Subjects were administered a single supratherapeutic oral dose [5 x 20 mcg tablet or capsule] of either test or the reference product under fasting conditions. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 36 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table: Pharmacokinetic parameters – baseline adjusted total (free + bound) liothyronine

Pharmacokinetic parameter	Arithmetic Means (± SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng*hr/mL)	84.854 ± 20.082	88.433 ± 20.119
$AUC_{(0-\infty)}$ (ng*hr/mL)	90.139 ± 21.257	94.811 ± 20.259
C_{max} (ng /mL)	7.644 ± 1.315	7.862 ± 1.552
t_{max}[1] (hrs)	2.250 (1.500, 5.000)	2.250 (1.250, 5.000)

[1]Median (min, max)

Table: Pharmacokinetic parameters – baseline unadjusted total (free + bound) liothyronine:

Pharmacokinetic parameter	Arithmetic Means (± SD)	
	Test product	Reference product
$AUC_{(0-t)}$ (ng*hr/mL)	157.261 ± 26.910	159.407 ± 24.985
$AUC_{(0-\infty)}$ (ng*hr/mL)	242.484 ± 44.898	253.871 ± 58.355
C_{max} (ng /mL)	8.662 ± 1.408	8.850 ± 1.607
t_{max}[1] (hrs)	2.250 (1.500, 5.000)	2.250 (1.250, 5.000)

[1]Median (min, max)

Table: The geometric mean and 90% confidence interval based on least squares mean obtained from ANOVA for the ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for baseline adjusted (corrected) data of total (free+bound) liothyronine

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV %[1]
$AUC_{(0-72)}$	95.8819 %	92.2972 % to 99.6057 %	9.1433 %
C_{max}	97.5257 %	94.7723 % to 100.3592 %	6.8662 %

[1]Estimated from the Residual Mean Squares

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 strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 20 micrograms product strength can be extrapolated to the other strengths.

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 were submitted with these applications 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 these applications.

The safety data from the bioequivalence study 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 is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application 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.

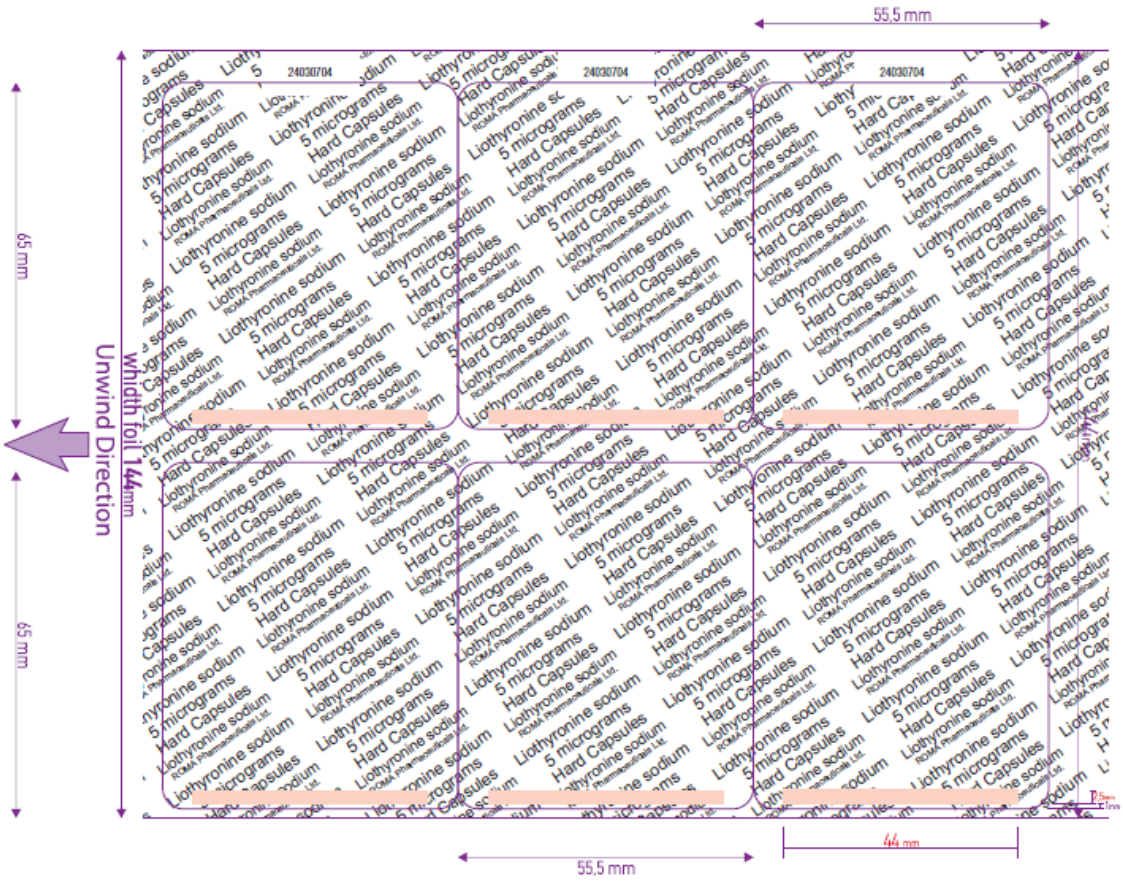
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

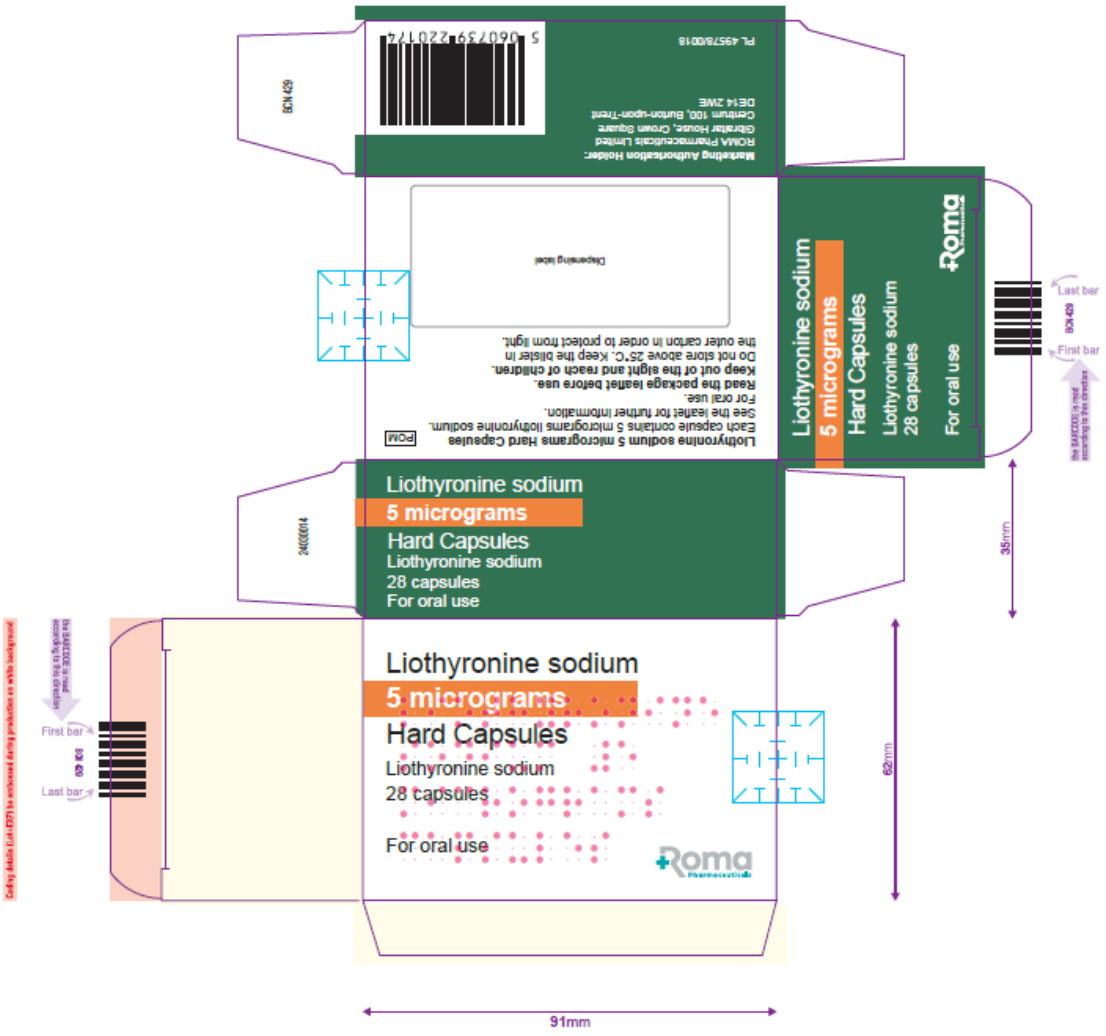
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with liothyronine sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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

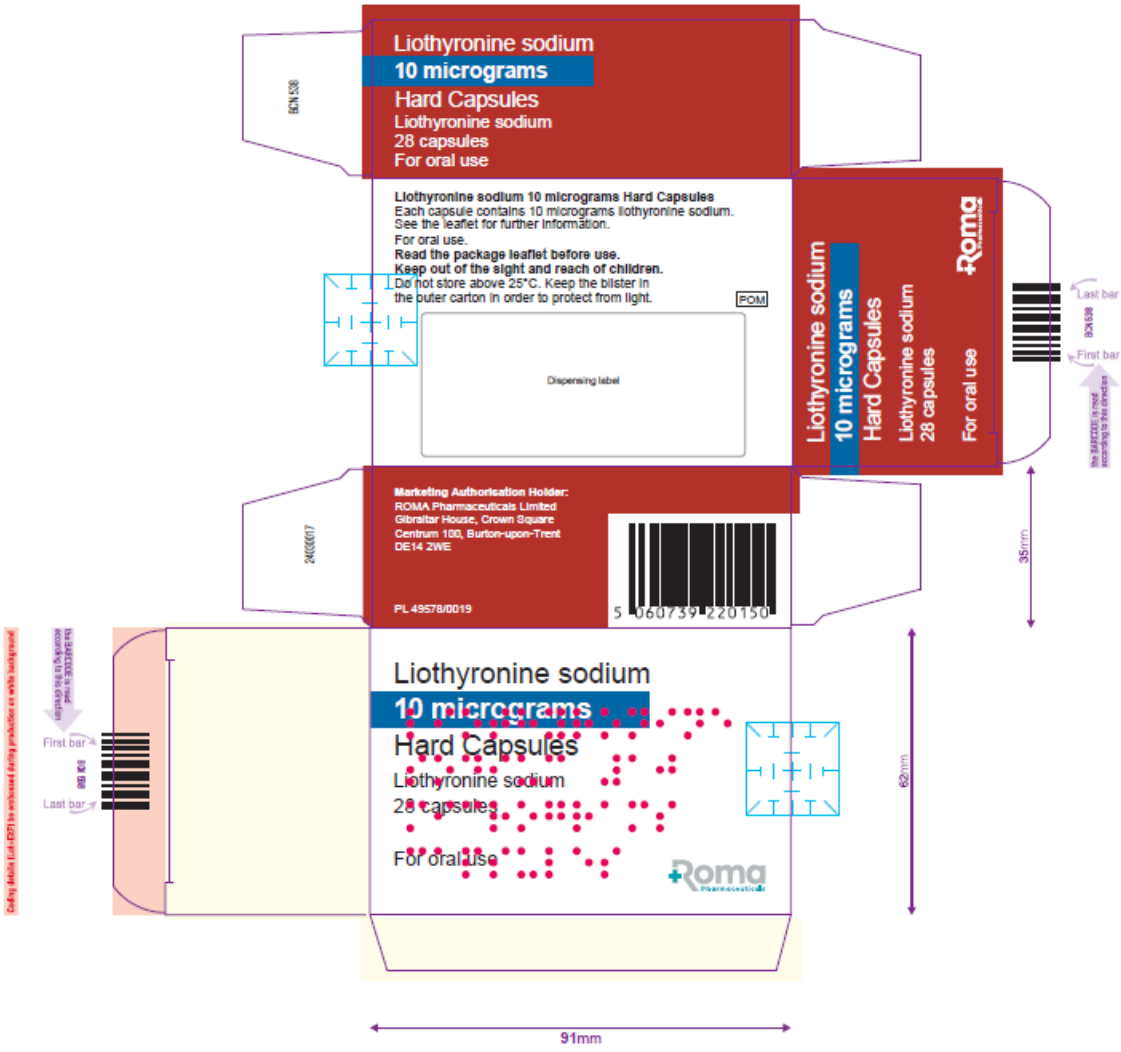
In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

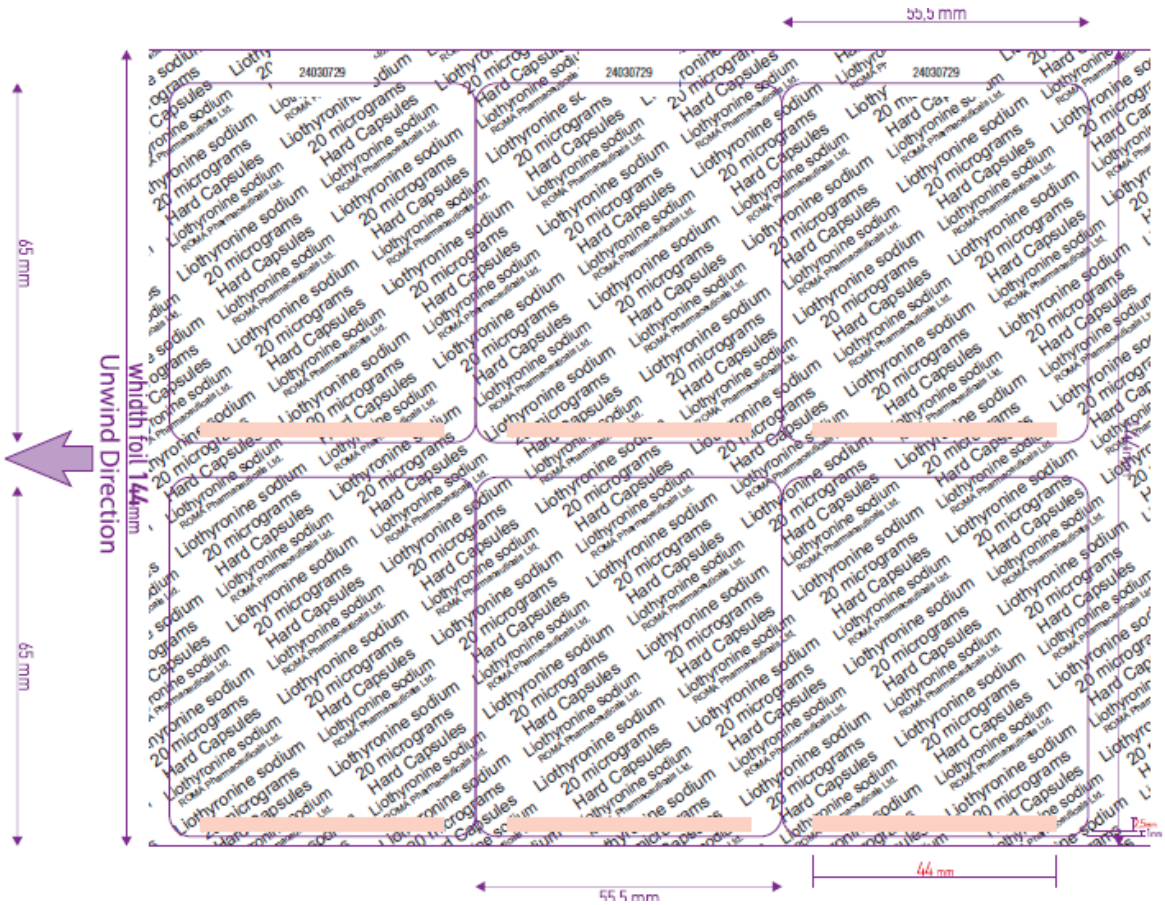
Representative copies of the labels at the time of licensing are provided below:

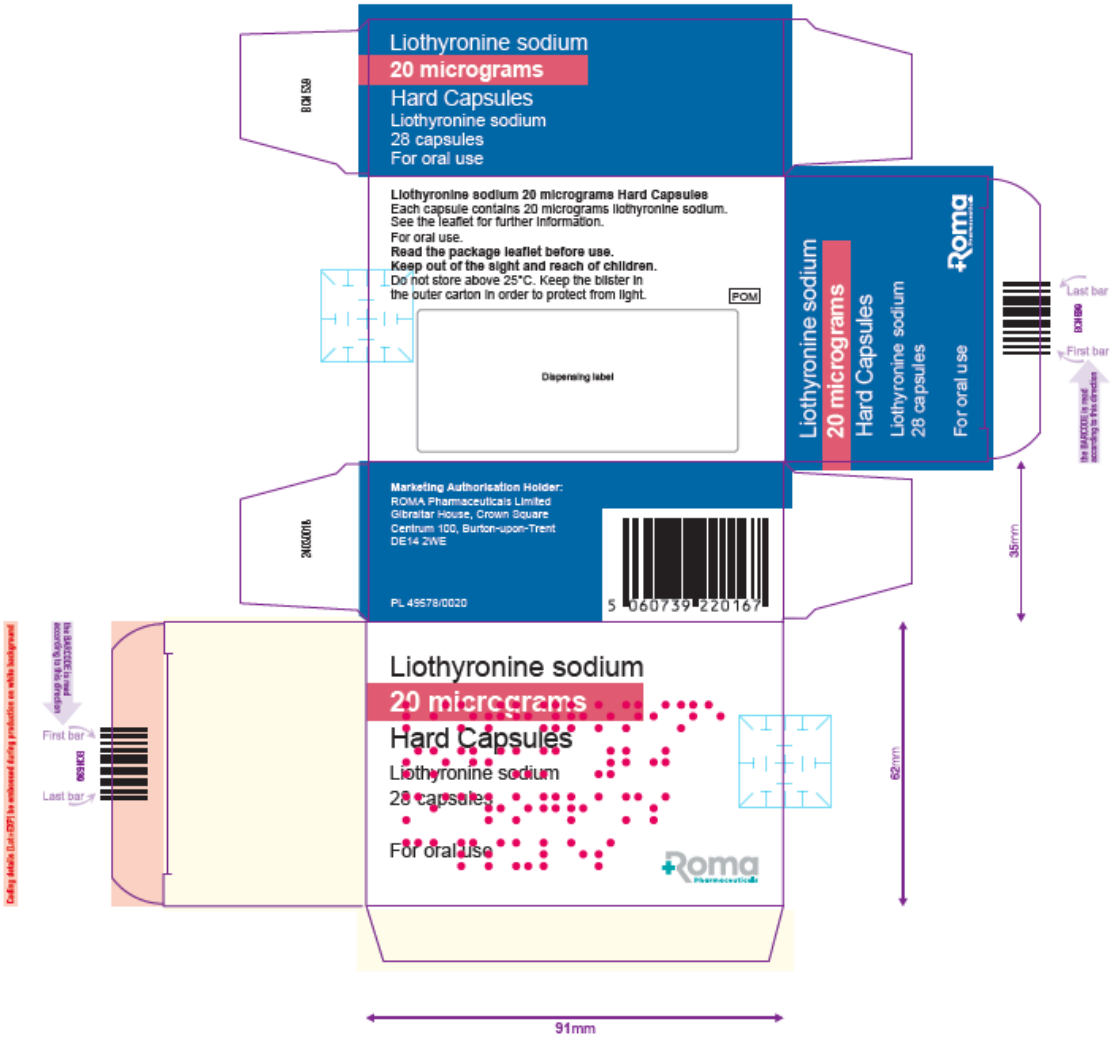

55,5 mm
65 mm
65 mm
Unwind Direction
whidth foil 144mm
24030704
44 mm
55,5 mm


Liothyronine sodium
5 micrograms
Hard Capsules
Liothyronine sodium
28 capsules
For oral use
Roma
Last bar
First bar
35mm
62mm
91mm


55,5 mm
65 mm
65 mm
Unwind Direction
whidth foil 144mm
24030717
24030717
24030717
44 mm
55,5 mm


Liothyronine sodium
10 micrograms
Hard Capsules
Liothyronine sodium
28 capsules
For oral use
Liothyronine sodium 10 micrograms Hard Capsules
Each capsule contains 10 micrograms liothyronine sodium.
See the leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Keep the blister in the outer carton in order to protect from light.
POM
Dispensing label
Marketing Authorisation Holder:
ROMA Pharmaceuticals Limited
Gibraltar House, Crown Square
Centrum 100, Burton-upon-Trent
DE14 2WE
PL 49578/0019
5 060739 220150
Roma
Last bar
First bar
35mm
62mm
91mm


55,5 mm
65 mm
Unwind Direction
Whidth foil 144mm
65 mm
55,5 mm
44 mm


Liothyronine sodium
20 micrograms
Hard Capsules
Liothyronine sodium
28 capsules
For oral use
Liothyronine sodium 20 micrograms Hard Capsules
Each capsule contains 20 micrograms liothyronine sodium.
See the leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C. Keep the blister in the outer carton in order to protect from light.
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PL 49578/0020
5 060739 220167
Roma
Last bar
First bar
35mm
62mm
91mm

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 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**