Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Iraksin 5 microgram Tablets
Liothyronine Sodium 5 microgram Tablets
Iraksin 10 microgram Tablets
Liothyronine Sodium 10 microgram Tablets

(liothyronine sodium)

PL 20117/0323-0324

Morningside Healthcare Limited

LAY SUMMARY
Iraksin 5 microgram Tablets
Liothyronine Sodium 5 microgram Tablets
(liothyronine sodium)

This is a summary of the Public Assessment Report (PAR) for Iraksin/ Liothyronine Sodium 5 & 10 microgram Tablets. It explains how these products were assessed and their authorisations 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 package leaflet or contact their doctor or pharmacist.

What are Liothyronine Sodium Tablets and what are they used for?
These applications are for a hybrid medicines. This means that these medicines are similar to a reference medicine already authorised in the European Union (EU) called Liothyronine Sodium BP 20 micrograms Tablets, albeit with certain differences. In this case, Liothyronine Sodium Tablets are both different strengths to the reference product.

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. 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 contain the active ingredient liothyronine sodium, which is 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 this medicine is tablets and the route of administration is oral by mouth.

Patients should swallow a whole tablet with a glass of water. If there is any difficulty in swallowing a whole tablet, then the tablet may be crushed and added to a glass with minimum of 20 ml of water and swirl for 5 minutes until completely dissolved. Please ensure that the entire amount of water is consumed to ensure the full dose is taken. If the solution appears cloudy this is not an issue. Patients who are unsure of how to take the medicine correctly, should check with their doctor or pharmacist.

Recommended dose:
Adults:
The dose will depend upon the patient's condition, ranging from 10 micrograms to 60 micrograms daily in divided doses.

Children below 12 years of age:
The dose may be started at 5 micrograms a day.

Adolescents (Children 12 -17 years of age):
Initially 10 - 20 micrograms daily; increased to 60 micrograms daily in 2-3 divided doses.

Elderly:
The dose may be started at 5 micrograms a day. Please note that doctor will monitor their patient's thyroid function regularly to make sure that the right dose for is given for their patient's condition.

For further information on how Liothyronine Sodium Tablets are used, refer to the package leaflet and Summaries 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/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of liothyronine have been shown in studies?
Because Liothyronine Sodium Tablets are a hybrid medicines, studies in healthy volunteers consist of tests to determine that they are therapeutically equivalent to the reference medicine.

What are the possible side effects of Liothyronine Sodium Tablets?
Because Liothyronine Sodium Tablets are a hybrid medicines and are therapeutically equivalent to the reference medicine, their benefits and possible side effects are taken as being 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 Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Liothyronine Sodium Tablets approved?
It was concluded that, in accordance with EU requirements, Liothyronine Sodium Tablets have been shown to be therapeutically equivalent 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.

It was concluded that Liothyronine Sodium Tablets have been shown to be effective in the treatment of some of the more severe conditions in which the thyroid does not produce enough thyroxine, it is also used to balance the effect of medicines used to treat an overactive thyroid. Further, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that 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?

A Risk Management Plan (RMP) has been developed to ensure that Liothyronine Sodium Tablets are 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 Liothyronine Sodium Tablets

Marketing Authorisations for Liothyronine Sodium Tablets were granted in the UK on 22 August 2019.

The full PAR for Liothyronine Sodium Tablets follows this summary.

This summary was last updated in September 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 applications for Iraksin/ Liothyronine Sodium 5 & 10 microgram Tablets (PL 20117/0323-0324) could be approved.

The products are approved for the following indications:

- 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.

- These products can also be used as an adjunct to carbimazole to prevent sub-clinical hypothyroidism developing during carbimazole treatment of thyrotoxicosis.

- 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. 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.

These applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal products of a suitable originator products, Liothyronine Sodium BP 20 micrograms Tablets 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 based on being a hybrid medicinal product of a reference product that has been licensed for over 10 years.

Data from a pharmacokinetic dosage form proportionality study was submitted with these applications. This 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.

National marketing authorisations were granted in the UK on 22 August 2019.

II QUALITY ASPECTS

II.1 Introduction

These products consist of either 5 micrograms of liothyronine sodium or 10 micrograms of liothyronine sodium. The other excipients are as follows lactose monohydrate, partially pregelatinized maize starch, spray dried acacia, sodium chloride, and magnesium stearate.

The finished products are packaged in Aluminium foil (ALU/ALU) blisters containing 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, or 112 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.

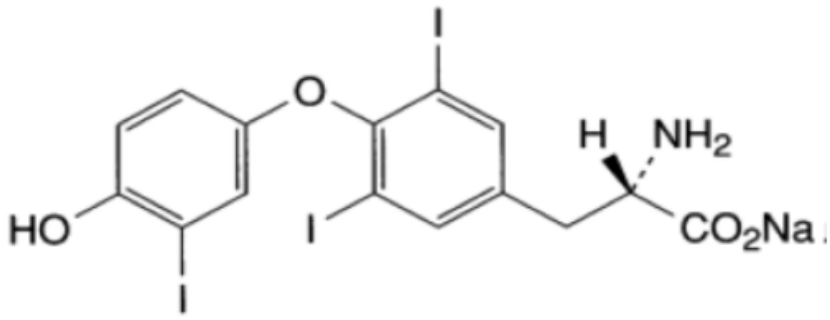
II.2 ACTIVE SUBSTANCES

rINN: Liothyronine sodium

Chemical Name: L-Tyrosine, *O* – (4 – hydroxy – 3 – iodophenyl) – 3, 5 – diiodo – , monosodium salt

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

Chemical Structure:



Molecular Weight: 673

Appearance: White or slightly coloured, hygroscopic crystalline powder

Solubility: Practically insoluble in water, slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

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.

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 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.

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

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 formulae 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 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 18 months, with the storage conditions “Do not store above 30°C. Store in the original package 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 a 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 a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from a pharmacokinetic dose proportionality study has been submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

A 20 mcg Liothyronine Sodium dosage strength, by the same manufacturer, was authorised in 2017. The application was supported by an acceptable bioequivalence study comparing the generic 20 mcg strength with the UK reference product Liothyronine Sodium BP 20 microgram Tablets, first authorised in 1993. The 90% confidence intervals for the ratios of the geometric least-squares means of the ln-transformed pharmacokinetic parameters AUC_{0-t} and C_{max} were within the predefined acceptance interval of 80.00 – 125.00% but would have met narrowed acceptance limits of 90.00 – 111.11%, had these been applied. Discussion is currently ongoing among regulatory authorities in Europe as to whether thyroid hormone replacement therapies including levothyroxine and liothyronine should be considered narrow therapeutic index drugs which would have implications for bioequivalence acceptance criteria.

The BE study was designed and conducted appropriately and bioequivalence between the now authorised 20 mcg liothyronine tablets of Morningside Healthcare Ltd and the UK reference product was concluded.

These applications are for new, lower strengths of liothyronine in 10 mcg and 5 mcg tablet presentations, in the same formulation as the authorised 20 mcg strength and manufactured using the same process. The qualitative composition of the different strengths is the same and although there is some deviation from quantitatively proportional composition, the amount of active substance is less than 5 % of the tablet core weight.

It is now understood that the higher intrinsic solubility of liothyronine poses fewer inherent pharmaceutical challenges for absorption from the gastrointestinal tract compared to levothyroxine. This is derived from published literature supporting the similarity of pharmacokinetic profiles following administration of oral solution compared with oral solid dosage forms of liothyronine.

Although the conditions for a waiver of strengths are recognised, on the basis of this further scientific understanding, to have been met in principle, the applicant supplied a clinical dosage form proportionality study to support the present applications for 10 mcg and 5 mcg tablet strengths; this provides assurance that liothyronine bioavailability following administration of the new tablet strengths is proportional to that following administration of

the already authorised 20 mcg strength. The study involved a three period, six sequence cross-over pharmacokinetic comparison of the generic formulation in strengths of 20 mcg, 10 mcg and 5 mcg, each administered at a supratherapeutic dose of 100 mcg. Comparisons were made between the extremes of the strength range as well as with the middle strength. Given that the aim of the study was to investigate proportional systemic availability across the proposed range of dosage strengths, and given that the study included comparison of the extremes of the strength range, pre-specified acceptance criteria for 90% confidence intervals of 80.00 – 125.00% are considered acceptable.

IV. 2 Pharmacokinetics

Dosage form proportionality study

A Randomized, Open-Label, 3-Way Crossover Study Evaluating the Pharmacokinetic Dosage strength proportionality of Liothyronine 5, 10, and 20 mcg Tablets Following a Single Oral Dose of 100 mcg In Healthy Subjects Under Fasting Conditions

Objective:

To evaluate the dosage form proportionality of three different strengths of liothyronine tablets (5 mcg, 10 mcg, and 20 mcg), administered as a single oral dose of 100 mcg under fasting conditions.

Study design:

A single centre, randomized, single-dose, open-label, dosage form proportionality, 3-way crossover comparative BA study to evaluate the dosage form proportionality of three different strengths of liothyronine tablets (5 mcg [Test 1], 10 mcg [Test 2], and 20 mcg [“Reference”]), administered as a single oral dose of 100 mcg under fasting conditions.

Study conduct

In each period, according to the randomization scheme, subjects were administered a single oral dose (total dose of 100 mcg) of either the Test 1 or Test 2 or Reference study medication as follows:

- Treatment A (Test 1): Liothyronine sodium 5 mcg tablet as a 20 x 5 mcg tablets
- Treatment B (Test 2): Liothyronine sodium 10 mcg tablet as a 10 x 10 mcg tablets
- Treatment C (Reference): Iraksin 20 mcg tablet as a 5 x 20 mcg tablets

The treatment phases were separated by a washout period of seven days.

Product designated as “Reference” is the previously authorised 20 mcg liothyronine tablets in the generic formulation

Blood samples were collected at pre-dose (0.000) and up to 72.0 hours post-dose in each period.

The study design is acceptable. Administration of a supratherapeutic dose is appropriate for investigation of bioequivalence where the substance being studied is endogenous and is consistent with the published EMA guidance on bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**). The conduct of the study under fasting conditions is acceptable as liothyronine can be taken without food and the investigation of bioequivalence under fasting conditions increases sensitivity of the method to detect formulation differences.

In line with the EMA guideline, a sampling duration of 72 hours is considered long enough to capture more than 80% of total plasma exposure, regardless of elimination half-life.

Dosage form proportionality analysis:

Ratios (A/C, B/C and A/B), 90% Geometric Confidence Intervals, Intra- and Inter-Subjects CV (%) and p-values for Baseline Corrected Liothyronine

Comparison A/C :

Parameter (Unit)	Treatment Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric C.I.[2]		Intra-Subject CV (%)	Inter Subject CV (%)	p-values		
		Treatment A	Treatment C		Lower (%)	Upper (%)			Sequence	Period	Treatment
AUC_{0-t} (h*pg/mL)	Treatment A - Treatment C	66876.01	65328.65	102.37	88.49	118.42	24.38	52.36	0.6191	0.9950	0.7813
AUC_{0-inf} (h*pg/mL)	Treatment A - Treatment C	75114.91	79257.25	94.77	87.36	102.82	12.90	16.28	0.3873	0.3569	0.2642
C_{max} (pg/mL)	Treatment A - Treatment C	7304.36	7073.58	103.26	93.80	113.67	15.94	47.04	0.5868	0.5231	0.5655

Comparison B/C :

Parameter (Unit)	Treatment Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric C.I.[2]		Intra-Subject CV (%)	Inter Subject CV (%)	p-values		
		Treatment B	Treatment C		Lower (%)	Upper (%)			Sequence	Period	Treatment
AUC_{0-t} (h*pg/mL)	Treatment B - Treatment C	68050.01	65527.17	103.85	93.50	115.35	17.44	59.16	0.7226	0.2011	0.5364
AUC_{0-inf} (h*pg/mL)	Treatment B - Treatment C	77323.22	79219.41	97.61	92.55	102.93	8.50	17.16	0.4073	0.4855	0.4340
C_{max} (pg/mL)	Treatment B - Treatment C	7358.71	7072.67	104.04	95.95	112.82	13.42	57.79	0.5841	0.8764	0.4031

Comparison A/B :

Parameter (Unit)	Treatment Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric C.I.[2]		Intra-Subject CV (%)	Inter Subject CV (%)	p-values		
		Treatment A	Treatment B		Lower (%)	Upper (%)			Sequence	Period	Treatment
AUC_{0-t} (h*pg/mL)	Treatment A - Treatment B	66719.77	68335.48	97.64	91.01	104.74	11.62	41.08	0.5443	0.5702	0.5580
AUC_{0-inf} (h*pg/mL)	Treatment A - Treatment B	75180.64	77118.51	97.49	91.22	104.18	10.50	15.52	0.4543	0.3270	0.5093
C_{max} (pg/mL)	Treatment A - Treatment B	7311.64	7336.29	99.66	90.38	109.90	16.23	46.18	0.4804	0.1545	0.9525

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
LSM= Least squares mean.
Test-1 (A) = Morningside Healthcare Ltd, United Kingdom, liothyronine sodium 20 x 5 mcg tablets.
Test-2 (B) = Morningside Healthcare Ltd, United Kingdom, liothyronine sodium 10 x 10 mcg tablets.
Reference (C) = Morningside Healthcare Ltd, United Kingdom (Iraksin), liothyronine sodium 5 x 20 mcg tablets.
Probability (p) values are derived from Type III sums of squares
p-value for the Sequence effect is tested using the Subject(Sequence) effect as the error term

Conclusion:
The 90% confidence intervals for the A/C, B/C and A/B ratios for AUC $_{0-72}$ and Cmax lie within the pre-specified acceptance limits of 80.00 – 125.00%. These are considered acceptable limits for a dosage strength proportionality study given the existing recommendations in the product information for cautious dose escalation in susceptible populations and the contraindication of liothyronine in patients with established ischaemic heart disease.

It can be concluded that Liothyronine 20 mcg, 10 mcg and 5 mcg tablets (Morningside Healthcare Limited) are dosage strength proportional.

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

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.

This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisations is recommended for these applications.

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Liothyronine Sodium 20 micrograms Tablets (PL 20117/0270; Morningside Healthcare Limited). The bridging report submitted by the applicant is acceptable.

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.

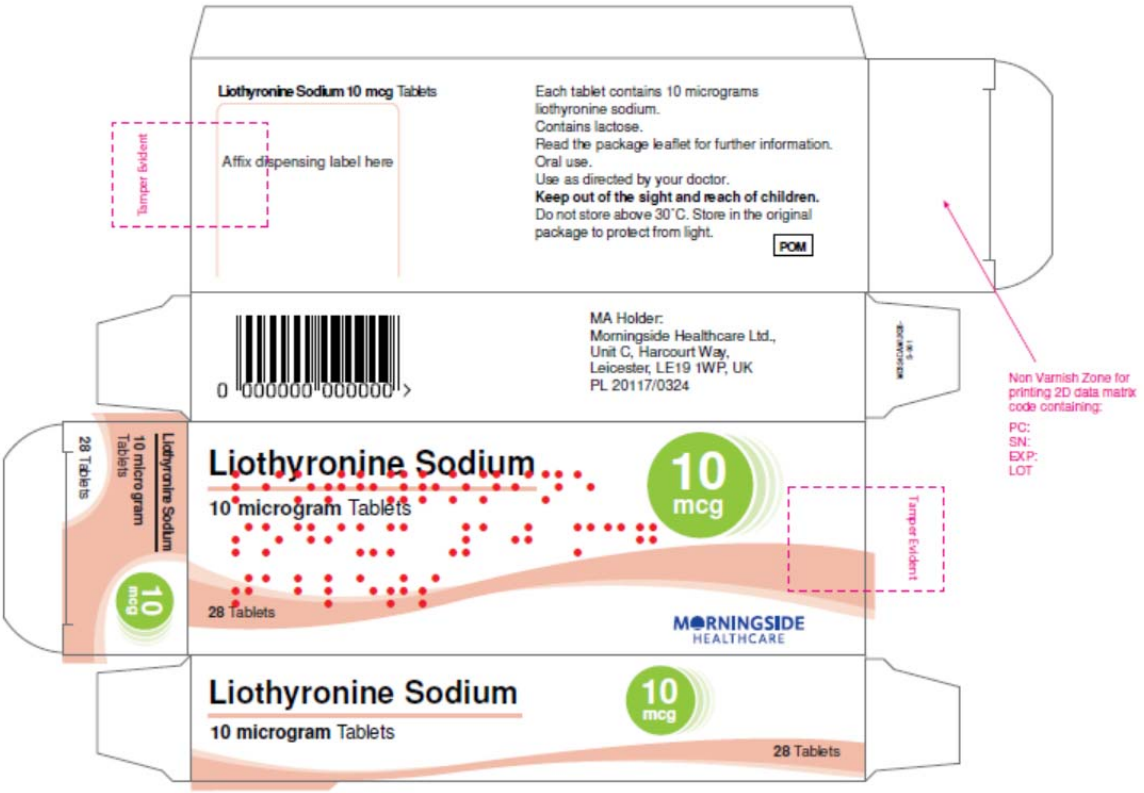
Extensive clinical experience with liothyronine sodium is considered to have demonstrated the therapeutic value of the products.

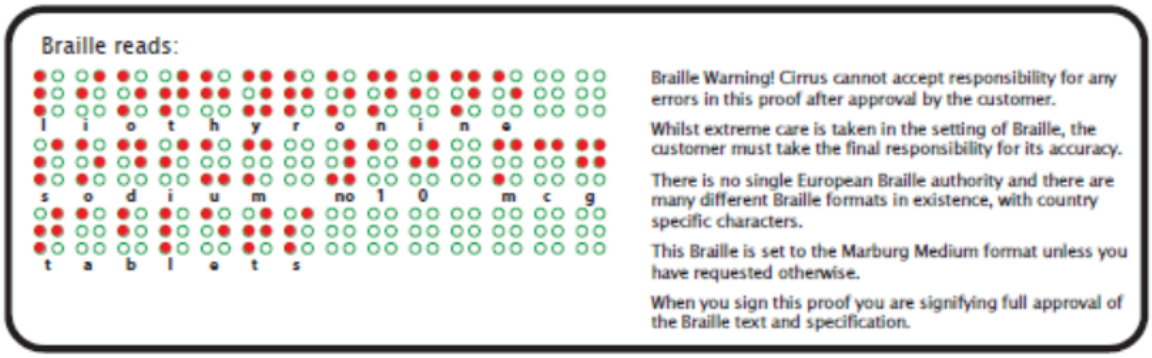
The benefit/risk is, therefore, considered to be positive.

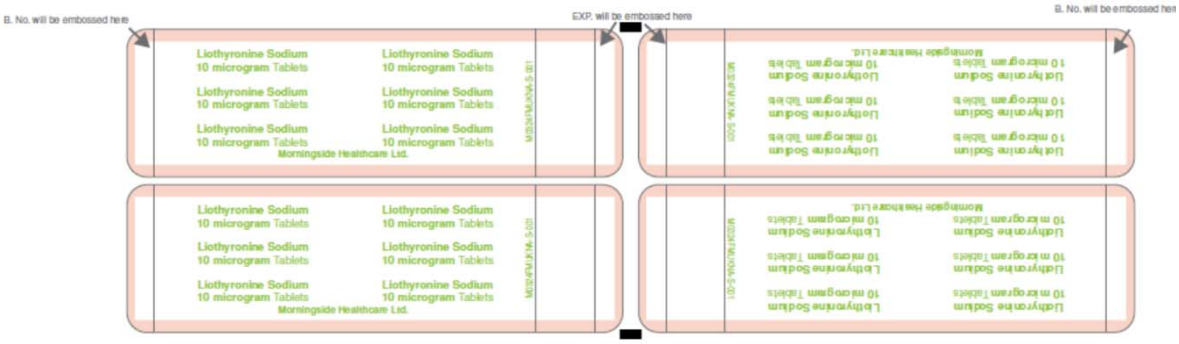
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

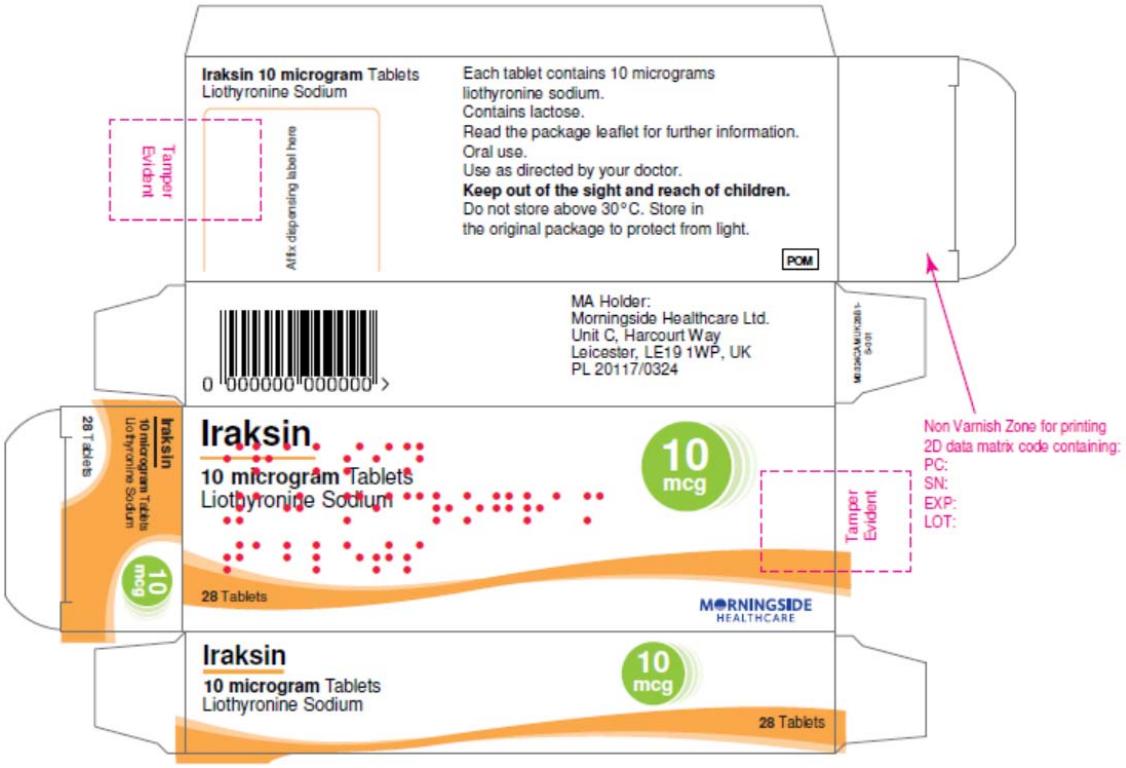
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

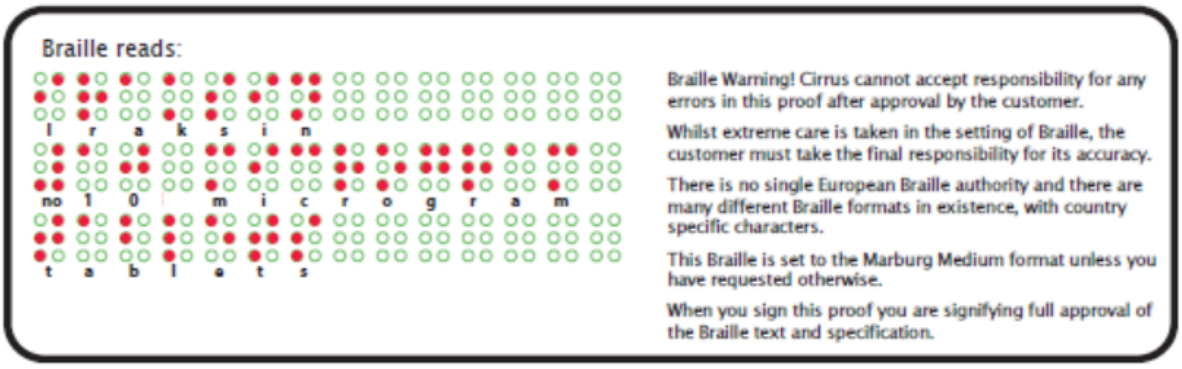
Representative copies of the labels at the time of UK licensing are provided below.

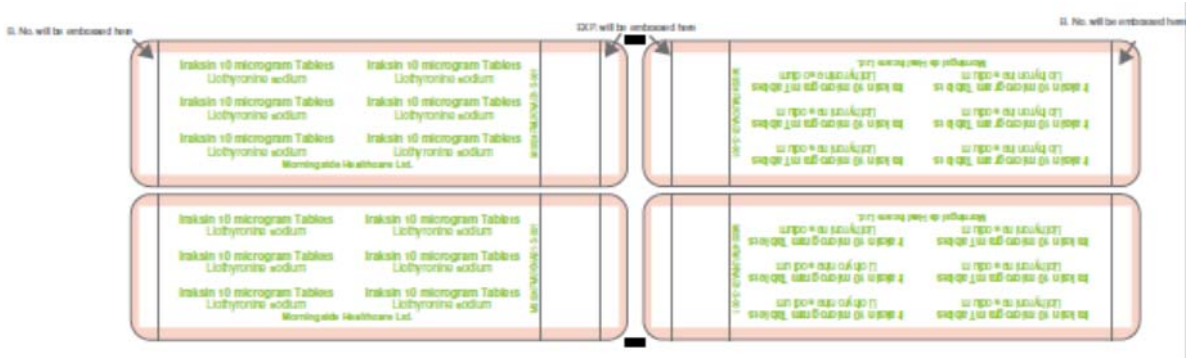







Iraksin 10 microgram Tablets
Liothyronine Sodium
Each tablet contains 10 micrograms liothyronine sodium.
Contains lactose.
Read the package leaflet for further information.
Oral use.
Use as directed by your doctor.
Keep out of the sight and reach of children.
Do not store above 30°C. Store in the original package to protect from light.
POM
Tamper Evident
Affix dispensing label here
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0324
Iraksin
10 microgram Tablets
Liothyronine Sodium
10 mcg
28 Tablets
MORNINGSIDE HEALTHCARE
Non Varnish Zone for printing 2D data matrix code containing:
PC:
SN:
EXP:
LOT:


Braille reads:
Braille Warning! Cirrus cannot accept responsibility for any errors in this proof after approval by the customer.
Whilst extreme care is taken in the setting of Braille, the customer must take the final responsibility for its accuracy.
There is no single European Braille authority and there are many different Braille formats in existence, with country specific characters.
This Braille is set to the Marburg Medium format unless you have requested otherwise.
When you sign this proof you are signifying full approval of the Braille text and specification.



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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