Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Liothyronine Sodium 20 micrograms Tablets (liothyronine sodium)

PL 00142/1256

Accord-UK Limited (Trading style: Accord)

LAY SUMMARY

Liothyronine Sodium 20 microgram Tablets (liothyronine sodium)

This is a summary of the Public Assessment Report (PAR) for Liothyronine Sodium 20 micrograms Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product 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?
This application 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 Tertroxin Tablets 20 microgram/Liothyronine Sodium BP 20 microgram 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 this medicine is a tablet and the route of administration is oral (taken by mouth). They should be swallowed with a glass of water.

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.
- If the patient has been prescribed a dose lower than 20 micrograms, they should allow a tablet to dissolve/disperse in 20 ml of water for 10 minutes, in a small measuring cup.
- The patient should gently swirl the solution occasionally to aid the dissolution/dispersion.
- The patient should then swirl the solution for a few seconds prior to using a suitable oral syringe to withdraw the amount of liquid corresponding to the dose prescribed (5ml for a 5 micrograms dose; 10 ml for a 10 micrograms dose) and squirt the liquid directly into their mouth by gently pressing the plunger.
- Any remaining liquid should be discarded.

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

Use in children and adolescents:
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 the patient's doctor will monitor the thyroid function regularly to make sure that they are given the right dose for their condition.

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 Summary of Product Characteristics (SmPC) 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 Sodium Tablets have been shown in studies?
As Liothyronine Sodium Tablets are a generic medicine, studies in healthy volunteer consist of tests to determine that they are 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 this medicine, see Section 4 of the PIL or the SmPC 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 a generic medicine 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 medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of 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 SmPC 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 this application and are satisfactory.

Other information about Liothyronine Sodium Tablets
A Marketing Authorisation for Liothyronine Sodium Tablets was granted in the UK on 19 January 2022.

The full PAR for Liothyronine Sodium Tablets follows this summary.

This summary was last updated in March 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 application for Liothyronine Sodium 20 micrograms Tablets (PL 00142/1256) could be approved.

The product is approved for the following indications:

- Liothyronine sodium is indicated in adults and children for the treatment of coma of myxedema, the management of severe chronic thyroid deficiency and hypothyroid states occurring in the treatment of thyrotoxicosis.
- Liothyronine sodium can be used also as an adjunct to carbimazole to prevent subclinical 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, 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 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, Tertroxin Tablets 20 microgram/Liothyronine Sodium BP 20 microgram Tablets (Mercury Pharma Group Limited).

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product 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 this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

A national Marketing Authorisation was granted in the UK on 19 January 2022.

II QUALITY ASPECTS

II.1 Introduction

This product contains 20 micrograms of liothyronine sodium in each tablet.

In addition to liothyronine sodium, this product also contains the excipients pregelatinised maize starch, cellulose microcrystalline, light magnesium oxide, sodium starch glycolate and sodium stearyl fumarate.

The finished product is packaged in:
1. Polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium (PVC/PE/PVDC/Alu) blisters, in pack sizes of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90 and 112 tablets.
2. High-density polyethylene (HDPE) induction sealed bottles, each with a child-resistant tamper-evident screw cap containing 2 g desiccant and 28 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.

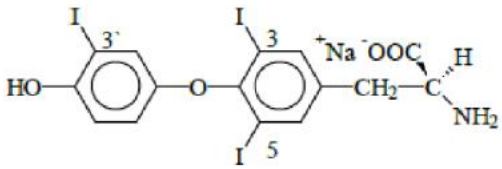
II.2 ACTIVE SUBSTANCE

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 white or slightly coloured, hygroscopic powder

Solubility: It is practically insoluble in water, slightly soluble in ethanol (96 per cent), and 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.

II.3 DRUG PRODUCT

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.

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

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

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications 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 24 months for the product in bottles and 16 months for the product in blisters, with the storage conditions 'Store below 25°C' and 'Store in the original package 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 a Marketing Authorisation 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 this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

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

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

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of 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 (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 BP 20 mcg (micrograms) versus the reference product Tertroxin Tablets 20 mcg (micrograms) in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (100 micrograms) of either the test (5 x 20 micrograms tablets) or reference product (5 x 20 micrograms tablets) with approximately 150 ml water. Blood samples were taken pre-dose and up to 72 hours post-dose, with a washout period of 24 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Bioequivalence analysis results (baseline corrected liothyronine)

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-72)}$	91.1	88.04 - 94.20	8.2
C_{max}	92.4	88.58 - 96.45	10.4

[1]Estimated from the Residual Mean Squares.

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 this application and none were required.

IV.4 Clinical efficacy

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

IV.5 Clinical safety

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

The safety data from the bioequivalence study showed that the test and reference 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 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 a Marketing Authorisation is recommended for this application.

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 with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to:

1. Liothyronine sodium 20 micrograms tablets (PL 20117/0270; Morningside Healthcare Limited), with respect to content and key messages.
2. Mycophenolic acid 180 mg and 360 mg gastro-resistant Tablets (ES/H.01/3/001-002/DC), with respect to design, layout and style.

The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The SmPC, PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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

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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**