Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Enolio 10 micrograms/ml Oral Solution
Liothyronine Sodium Alturix 10 micrograms/ml Oral Solution

liothyronine sodium

PL 44490/0009

ALTURiX Ltd

LAY SUMMARY
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This is a summary of the Public Assessment Report (PAR) for Enolio 10 micrograms/ml Oral Solution Liothyronine Sodium Alturix 10 micrograms/ml Oral Solution. 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 Enolio in this lay summary for ease of reading.

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

What is Enolio and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Tertroxin 20 micrograms Tablets.

Enolio is used in the treatment of some of the more severe conditions in which the thyroid does not produce enough thyroxine and to balance the effect of medicines used to treat an overactive thyroid.

How does Enolio work?
Enolio contains 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 is Enolio used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth). An oral syringe is provided to assist with dosing.

The recommended dose for adults will depend upon the condition being treated but will usually range from 1 ml (10 micrograms) to 6 ml (60 micrograms) daily in divided doses. In children and the elderly, the dose may be started at 0.5 ml (5 micrograms) a day.

Thyroid function may be monitored regularly to make sure that the right dose is provided and an ECG is often performed before or on starting treatment.

For further information on how Enolio is 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 Enolio have been shown in studies?

Because Enolio 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 Enolio?
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 their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Enolio is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Enolio approved?
It was concluded that, Enolio has 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 Enolio?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Enolio. The RMP details the important risks of Enolio, how these risks can be minimised, any uncertainties about Enolio (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Enolio.

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 Enolio are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Enolio
A Marketing Authorisation for Enolio was granted in the United Kingdom (UK) on 17 September 2024.

The full PAR for Enolio follows this summary.

This summary was last updated in October 2024.

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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 Enolio 10 micrograms/ml Oral Solution Liothyronine Sodium Alturix 10 micrograms/ml Oral Solution (PL 44490/0009) could be approved.

The product is 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.

- Liothyronine sodium can also be used 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.

Mechanism of Action

Liothyronine sodium is a naturally occurring thyroid hormone. Its biological action 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.

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, Tertroxin 20 micrograms Tablets (MAH: Mercury Pharma Group Ltd.) that has been licensed for a suitable time, in line with the legal requirements.

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 Marketing Authorisation for Enolio 10 micrograms/ml Oral Solution Liothyronine Sodium Alturix 10 micrograms/ml Oral Solution was granted in the United Kingdom (UK) on 17 September 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of an oral solution; each 1 ml contains 10 micrograms of liothyronine sodium.
In addition to Liothyronine Sodium, this product also contain the following excipients: glycerol, citric acid monohydrate, sodium citrate, sodium methyl parahydroxybenzoate (E 219), sodium hydroxide and purified water.

The finished product is packaged in type III amber glass bottles (50 ml or 100 ml) fitted with a polypropylene (PP) child-resistant and tamper evident cap fitted with a PP syringe adaptor, high-density polyethylene (HDPE) screw closure and low-density polyethylene (LDPE) plug. 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.

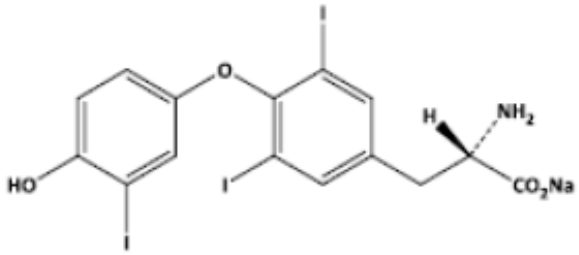
II.2 ACTIVE SUBSTANCE

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 g / mol

Appearance: White or slightly coloured, hygroscopic powder

Solubility: Practically insoluble in water, slightly soluble in ethanol (96%) and dissolves in dilute solutions of alkali hydroxides

The active substance 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 was provided.

Comparative *in vitro* impurity profiles were 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 were provided for all excipients.

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

This product does 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 30 months, with the storage conditions ‘Store in the original package in order to protect from light’, is acceptable.

Suitable in use studies have demonstrated that the product is stable after opening for the duration of potential use.

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 was 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
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an 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 was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of liothyronine sodium is 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. This study was an open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study comparing the test product (Enolio 10 micrograms / ml Oral Solution) with the reference product (Tetroxin 20 micrograms Tablets) in healthy volunteers under fasting conditions.

Subjects were administered a single oral dose of either the test or the reference product with 240 mL of drinking water after an overnight fast of 8 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results and 90% confidence intervals are presented in the tables below:

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	**Reference Product**
AUCt (ng/mL)*(hr)	83.153 (±17.345)	90.042 (±22.816)
AUCi (ng/mL)*(hr)	88.005 (±19.660)	94.702 (±24.920)
Cmax (ng/mL)	7.079 (±1.404)	7.990 (±2.144)
AUC_Extrap_obs (%)	5.199 (±3.935)	4.572 (±3.150)
Kel 1/(hr)	0.050 (±0.018)	0.053 (±0.019)
tHalf (hr)	15.672 (±6.076)	14.727 (±5.365)
Tmax[1] (hr)	2.250 (1.250, 4.000)	2.250 (1.500, 3.000)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals	CV%
AUC_t (ng/mL)*(hr)	93.78	(88.89%; 98.94%)	13.296
Cmax (ng/mL)	90.36	(85.57%; 95.41%)	13.510

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.

IV.3 Pharmacodynamics
No new pharmacodynamic data were 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 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 a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

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 Summary of Product Characteristics (SmPC), 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 UK version of the SmPC and

PIL for this product are available on the MHRA website.

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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**