

Public Assessment Report

Scientific discussion

**Thyrofix 13, 62, 88, 112, 125, 137, 150, 175 and
200 micrograms tablets**

(levothyroxine sodium)

NL/H/3039/005-013/DC

Date: 26 August 2019

This module reflects the scientific discussion for the approval of Thyrofix 13, 62, 88, 112, 125, 137, 150, 175 and 200 micrograms tablets. The procedure was finalised at 7 April 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Thyrofix 13, 62, 88, 112, 125, 137, 150, 175 and 200 micrograms tablets, from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

The product is indicated for:

- Treatment of benign euthyroid goitre, especially in adults where iodine is not indicated
- Prophylaxis of relapse after surgery for euthyroid goitre, depending on the post-operative hormone status
- Substitution therapy in hypothyroidism
- Suppression therapy in thyroid cancer
- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.
- Diagnostic use for thyroid suppression testing (doses 100-150 and 200 micrograms)

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns an generic and hybrid application for extension of the already approved Thyrofix 25, 50, 75 and 100 micrograms tablets, which have been registered through a decentralised procedure (NL/H/3039/001-004/DC) by the same MAH since 29 October 2014.

Essential similarity is claimed with the innovator product Euthyrox tablets (NL License RVG 09009), which has been registered in the Netherlands by Merck B.V. since 15 December 1982 (100 micrograms strength). In addition, reference is made to Euthyrox authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Cyprus, Germany, Denmark, Spain, Finland, France, Poland and Portugal.

The marketing authorisation of the 88, 112, 125, 137, 150, 175 and 200 micrograms tablet strengths has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

The application for marketing authorisation of the 13 and 62 micrograms tablet is made under Article 10(3) of Directive 2001/83/EC as amended, i.e. this application concerns hybrid medicinal products, since the strengths of 13 and 62 micrograms tablets are not registered strengths of the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Thyrofix 13, 62, 88, 112, 125, 137, 150, 175 and 200 micrograms are white, round, biconvex tablets debossed with either “13”, “62”, “88”, “112”, “125”, “137”, “150”, “175” or “200” on one side. The tablets contain 13, 62, 88, 112, 125, 137, 150, 175 or 200 micrograms levothyroxine sodium.

The tablets are packed in PVC/TE/PVDC/Aluminum blisters.

The excipients are: powdered cellulose, sodium croscarmellose (E 468), colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate (E470b).

II.2 Drug Substance

The active substance is levothyroxine sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is an almost white to faintly brownish yellow powder, which is very slightly soluble in water. Levothyroxine sodium has one asymmetric carbon in its structure, the levorotary isomer is used in the drug product.

The CEP procedure is used for the active substance from three suppliers. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of each supplier.

Stability of drug substance

All three provided CEPs for the control of the quality of the active substance state a retest period. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies regarded the optimisation of the tablet composition and the performance of comparative dissolution studies with the reference product.

An additional bioequivalence study, to the previously conducted bioequivalence studies with the 25 and 100 microgram tablets, was performed with the 200 microgram strengths with their respective reference product strengths. The batch used in the studies was manufactured according to the finalised formulation and manufacturing process. The *Biowaiver of Strength* for the additional 13, 62, 88, 112, 125, 137, 150 and 175 micrograms tablet strengths was adequately supported by comparative dissolution profiles obtained in 0.1N HCl, pH 4.5 and pH 6.8 against the 200 microgram biobatch, Thyrofix 100 microgram tablets and Thyrofix 25 microgram. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are blending, lubrication, tableting and packing. The manufacturing process is considered a non-standard process due to the very low content of active substance. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches per strength.

Control of excipients

The excipients comply with their Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, shape identification, assay, related substances, average weight, uniformity of dosage units, disintegration, dissolution, water content, resistance to crushing, friability and microbiological quality. Except for water content, the release and shelf-life requirements are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full-scale batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. At the storage conditions an increase of the individual and total impurities was seen, as well as a decrease in assay. Also an increase of water content was seen at all storage conditions, which was most pronounced at accelerated conditions. All results were within the specified limits and no changes or trends were observed for the

other tested parameters. A photostability study in accordance with the ICH Guideline demonstrated that the product is photostable. Based on the data submitted, the proposed shelf-life of 36 months and storage conditions 'Store in the original package in order to protect from moisture' and 'This medicinal product does not require any special temperature storage conditions' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Thyrofix has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments was made:

- If the Committee for Medicinal Products for Human Use classifies Levothyroxine as a Narrow Therapeutic Index drug and if it is concluded that *in vitro* dissolution studies are not predictive for waiving additional strengths, the MAH is committed to submit a new bioequivalence study (with narrowed acceptance ranges as defined by CHMP) between the 200 microgram tablet strength and Euthyrox 200 microgram tablet, through a type II variation, before Thyrofix is marketed in Spain.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Thyrofix is intended for generic/hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic/hybrid formulation of Euthyrox which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levothyroxine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic/hybrid application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Thyrofix 25, 100 and 200 micrograms (Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., Greece) is compared with the pharmacokinetic profile of the reference products Euthyrox 25, 100 and 200 microgram tablets (Merck B.V., the Netherlands).

The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Food effect

As recommended in the SmPC, levothyroxine should be taken on an empty stomach. Therefore the bioequivalence studies under fasting conditions are considered appropriate, in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr Note for Guidance on the investigation of bioequivalence.

Biowaiver

The additional 13, 62, 88, 112, 125, 137, 150 and 175 micrograms tablet strengths have the same qualitative and quantitative composition, except for the amount of levothyroxine and of cellulose microcrystalline, which is used in the formulation as filler. The amount of levothyroxine is less than 5% of the total tablet core weight. The tablets are manufactured by the same process.

Dissolution profiles at three different pHs (pH 6.8, pH 4.5 and pH 1.2) were determined for test and reference batches used in the bioequivalence study. Dissolution data showed

comparable dissolution between the strengths. Since all the requirements have been met, a biowaiver was granted .

Bioequivalence studies

Bioequivalence study I – 25 micrograms

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (13 females and 23 males), aged 18 – 45 years. Each subject received a single dose of 24 tablets (600 micrograms) of one of the 2 levothyroxine formulations. The tablets were orally administered with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 45 days.

Blood samples were collected at -0.5 and -0.25 hours prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 32, 48 and 72 hours after administration of the products.

The study design of this single dose, crossover study under fasting conditions to assess bioequivalence for levothyroxine is considered adequate. Subjects were included with low total serum levothyroxine levels, which were still in the lower normal range to minimise endogenous interference, which is acceptable for levothyroxine. Plasma levels of levothyroxine were corrected for the baseline concentration.

The 600 µg dose was used to ensure that adequate levothyroxine plasma levels can be measured with regard also to the endogenous levels. This is acceptable.

Results

No subjects were withdrawn. Thirty-six subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levothyroxine under fasted conditions.

Treatment N=36	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)	t _{1/2} (h)
Test	1939 ± 526	--	56 ± 17	3.0 (1.0 – 6.0)	74 ± 29
Reference	1948 ± 498	--	55 ± 12	2.0 (1.0 – 5.0)	72 ± 38
*Ratio (90% CI)	0.99 (0.94 – 1.04)	--	1.00 (0.95 – 1.06)	--	--
CV (%)	11.6	--	13.5	--	--

AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
t_{1/2}	half-life
CV	coefficient of variation

**In-transformed values*

Bioequivalence study II – 100 micrograms

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (19 females and 17 males), aged 18 – 44 years. Each subject received a single dose of 6 tablets (600 micrograms) of one of the 2 levothyroxine formulations. The tablets were orally administered with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 45 days.

Blood samples were collected at -0.5 and -0.25 hours prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 32, 48 and 72 hours after administration of the products.

The study design of this single dose, crossover study under fasting conditions to assess bioequivalence for levothyroxine is considered adequate. Administration of 6 tablets is acceptable to ensure that adequate levothyroxine plasma levels can be measured with regard also to the endogenous levels. Subjects were included with low total serum levothyroxine levels, which were still in the normal range, to minimise endogenous interference, which is acceptable for levothyroxine. Plasma levels of levothyroxine were corrected for the baseline concentration.

Results

One subject dropped out during the washout phase due to an adverse event. Thirty-five subjects completed the study and were included in the analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levothyroxine under fasted conditions.

Treatment N=35	AUC _{0-72 h} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	1979 ± 557	--	58 ± 16	2.0 (1.0 – 8.0)	62 ± 24
Reference	2140 ± 497	--	64 ± 14	2.0 (1.0 – 6.0)	71 ± 97
*Ratio (90% CI)	0.91 (0.87 – 0.96)	--	0.89 (0.85 – 0.95)	--	--

CV (%)	12.8	--	13.9	--	--
AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity				
AUC₀₋₇₂	area under the plasma concentration-time curve from time zero to 72 hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
t_{1/2}	half-life				

**In-transformed values*

Bioequivalence study III – 200 micrograms

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy subjects (19 females and 17 males), aged 18 – 43 years. Each subject received a single dose of 3 tablets (600 micrograms) of one of the 2 levothyroxine formulations. The tablets were orally administered with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 42 days.

Blood samples were collected at -0.5, -0.25 hours and -0.083h prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 32, 48 and 72 hours after administration of the products.

The study design of this single dose, crossover study under fasting conditions to assess bioequivalence for levothyroxine is considered adequate. Administration of 3 tablets is acceptable to ensure that adequate levothyroxine plasma levels can be measured with regard also to the endogenous levels. Subjects were included with low total serum levothyroxine levels, which were still in the normal range, to minimise endogenous interference, which is acceptable for levothyroxine. Plasma levels of levothyroxine were corrected for the baseline concentration.

Results

One subject did not return to the study. 27 subjects completed the study and were included in the analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levothyroxine under fasted conditions.

Treatment	AUC _{0-72 h}	AUC _{0-∞}	C _{max}	t _{max}	t _{1/2}
N=27	ng.h/ml	ng.h/ml	ng/ml	h	h

Test	1657 ± 472	--	51 ± 9	3.0 (1.5 – 4.0)	71 ± 58
Reference	1712 ± 455	--	52 ± 11	2.5 (1.0 – 32.0)	72 ± 38
*Ratio (90% CI)	0.95 (0.86 – 1.04)	--	0.98 (0.93 – 1.05)	--	--
CV (%)	17.8	--	12.5	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of levothyroxine under fasted conditions, it can be concluded that Thyrofix and Euthyrox tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Thyrofix.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Use in patient who are hypersensitive to the active substance or the product's excipients. - Use in patients with untreated adrenal insufficiency, untreated pituitary insufficiency and untreated thyrotoxicosis. - Use in patient with acute myocardial infarction, acute myocarditis and acute pancarditis.
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	<ul style="list-style-type: none"> - Hyperthyroidism or hypothyroidism from treatment imbalance - Interaction with antithyroid agents during pregnancy - Interactions with anti-diabetic agents - Interaction with Coumarin derivates - Use in patients with known history of epilepsy. - Use in patients with cardiac arrhythmias (including Tachycardia and palpitations) - Substitution of a drug with greater or lesser potency (switching) - Off Label use for weight reduction
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. In addition however, a specific *direct healthcare professional communication* for only Finland is proposed. According to the MAH the healthcare professionals in Finland (physicians and pharmacies) should be aware of the potential risk regarding differences in the quantity of levothyroxine in the Medithyrox medicinal products and in the medicinal products already marketed in Finland. The proposal is acceptable.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic/hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. As a result of the pilot testing no changes to either the leaflet or the questionnaire were deemed necessary. This is also the case after the first round of testing. After two rounds of user testing, 100% of the subjects were able to locate the requested information and gave the correct answer. As a result, no changes were deemed necessary to the patient information leaflet of levothyroxine sodium.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Thyrofix 13, 62, 88, 112, 125, 137, 150, 175 and 200 micrograms, tablets have a proven chemical-pharmaceutical quality and are generic/hybrid forms of Euthyrox tablets. Euthyrox is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Thyrofix with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 April 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse