CBG MEB

Public Assessment Report

Scientific discussion

Thyrofix 25, 50, 75 and 100 micrograms tablets

(levothyroxine sodium)

NL/H/3039/001-004/DC

Date: 19 February 2015

This module reflects the scientific discussion for the approval of Thyrofix 25, 50, 75 and 100 micrograms tablets. The procedure was finalised on 29 October 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Thyrofix 25, 50, 75 and 100 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.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Euthyrox 100 microgram tablets (NL License RVG 09009), which has been registered in the Netherlands by Merck B.V. since 15 December 1982 (original product). Subsequently marketing authorisations were obtained for Euthyrox 50 micrograms (1985), 25 micrograms (1986) and 75 micrograms (1997). 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 Denmark, France, Germany, Portugal and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Thyrofix 25, 50, 75 and 100 micrograms are white, round, biconvex tablets debossed with either “25”, “50”, “75” or “100” on one side.

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).

The composition of the different tablet strengths is qualitatively the same and only the amount of cellulose microcrystalline is changed to account for the change in the amount of active substance.

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 both 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 CEPs. 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 both suppliers.

Stability of drug substance
The active substance from both suppliers is stable for 36 months when stored under the stated conditions. 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 optimization of the tablet composition and the performance of comparative dissolution studies with the reference product. Bioequivalence studies were performed with the 25 and 100 microgram strengths with their respective reference product strengths. The batches used in the bioequivalence studies were manufactured according to the finalized formulation and manufacturing process. A biowaiver of the 50 and 75 microgram strengths is supported by comparative dissolution data. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are blending, lubrication, tabletting 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 four 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, identification, assay, related substances, uniformity of mass, 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 six full-scale batches of the 25 and 100 microgram strengths and on four full-scale batches of the 50 and 75 microgram strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on four full-scale batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) and on two full-scale batches of only the 25 and 100 microgram strengths stored at 25°C/60% RH (36 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 all three 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 three 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 24 months and storage conditions 'Do not store above 25°C' and 'Store in the original package in order to protect from moisture' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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. Magnesium stearate is sourced from vegetables.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Thyrofix tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Thyrofix is intended for generic 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 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 application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

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

Biowaiver
The 50 and 75 µg tablets have the same qualitative and quantitative composition as the 25 and 100 µg tablets, 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 25 and 100 µg tablets strengths and the 50 and 75 µg tablet strengths. The MAH did not sufficiently substantiate whether levothyroxine has linear pharmacokinetics or more than dose proportional pharmacokinetics. It was considered sufficient to carry out studies with the lowest and highest strength to support the extrapolation. Since all the requirements have been met, a biowaiver was granted for the 50 and 75 µg tablets. The results of the studies with the 25 and 100 µg strengths can be extrapolated.

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. Subjects were included with total serum levothyroxine (T4) level of less than 110 nmol/l. 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 dropped out. 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	**$AUC_{0-72\ h}$** ng.h/ml	**$AUC_{0-\infty}$** 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	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72}	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

**ln-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. Subjects were included with total serum levothyroxine (T4) level of less than 130 nmol/l. 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	**$AUC_{0-\infty}$** 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	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72}	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

**ln-transformed values*

Conclusion on bioequivalence studies I and II

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 25 & 100 microgram and Euthyrox 25 & 100 microgram tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.

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.

Summary of Safety concerns	
Important identified risks	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.
	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	*N/A*
Missing information	*N/A*

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

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 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 25, 50, 75 and 100 micrograms, tablets have a proven chemical-pharmaceutical quality and are generic forms of Euthyrox 25, 50, 75 and 100 micrograms 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 29 October 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached