CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levothyroxine natrium Uni-Pharma 25, 50, 75 and 100 micrograms, tablets Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A, Greece

levothyroxine (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2567/001-004/DC
Registration number in the Netherlands: RVG 111899-111902

6 March 2014

Pharmacotherapeutic group:	thyroid hormones
ATC code:	H03AA01
Route of administration:	oral
Therapeutic indication:	benign euthyroid goitre; prophylaxis of relapse after surgery for euthyroid goitre; substitution therapy in hypothyroidism; suppression therapy in thyroid cancer; concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism
Prescription status:	prescription only
Date of authorisation in NL:	2 October 2013
Concerned Member States:	Decentralised procedure with IT, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Levothyroxine natrium Uni-Pharma 25, 50, 75 and 100 micrograms, tablets from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A. The date of authorisation was on 2 October 2013 in the Netherlands.

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.

The synthetic levothyroxine contained in Levothyroxine natrium Uni-Pharma tablets is identical in effect to the naturally occurring major hormone secreted by the thyroid. It is converted to T3 in peripheral organs and, like the endogenous hormone, develops its specific effects at the T3 receptors.

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 marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the 25 and 100 microgram products is compared with the pharmacokinetic profile of the reference products Euthyrox 25 and 100 microgram tablets, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active 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. 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
A CEP has 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 CEP without any additional requirements. 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 full-scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Levothyroxine natrium Uni-Pharma 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/PE/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 qualitatively the same and only the amount of cellulose microcrystalline is changed to account for the change in the amount of active substance.

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 has 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 assay and 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. At all three storage conditions a decrease in dissolution was seen. 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.2 Non-clinical aspects

This product is a generic formulation of Euthyrox, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of levothyroxine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 in which the pharmacokinetic profile of the test product Levothyroxine natrium Uni-Pharma 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
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch 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.

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 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 Levothyroxine natrium Uni-Pharma 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 Note for Guidance on the investigation of bioavailability and bioequivalence.

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. 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.

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).

Risk management plan
Levothyroxine was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levothyroxine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. Submission of a Risk Management Plan was not required at the time of this application.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Euthyrox.

Readability test
The package leaflet 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, followed by two

rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levothyroxine natrium Uni-Pharma 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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 Levothyroxine natrium Uni-Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 September 2013. Levothyroxine natrium Uni-Pharma 25, 50, 75 and 100 micrograms, tablets were authorised in the Netherlands on 2 October 2013.

The date for the first renewal will be: 4 September 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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