National Procedure

Preliminary Assessment Report

PHARMACOKINETIC ASSESSMENT OF A GENERIC APPLICATION

Levothyrox
(Levothyroxine sodium)

25, 50, 75, 100, 125, 150, 175, 200 mcg scored tablets

APN 2831

Applicant: Merck Santé S.A.S

NON-CLINICAL AND CLINICAL CRITICAL ASSESSMENT

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III. CLINICAL ASSESSMENT

III.1 Introduction

Levothyroxine sodium tablets by Merck KGaA have been authorized since 1972 (international birth date). The Periodic Safety Update Reports on Merck KGaA's levothyroxine sodium demonstrate the good efficacy and tolerability of the product.
Merck KGaA's levothyroxine sodium tablets are currently marketed worldwide with a shelf-life of 3 years and the storage instructions of "Do not store above 25°C". The product is manufactured with a 5%-overage to account for degradation of the drug substance during storage reflected in its end-of shelf-life specifications of 110.0-90.0% of the label claim (LC).

Since the beginning of 2011, Merck KGaA is performing a formulation optimization program for levothyroxine sodium tablets to enhance the product's stability. The new formulation has been developed to meet potency specifications of 95.0-105.0% at release and over the envisaged shelf life of at least 18 months at the storage condition of 25°C. This is to comply with the changing potency requirements for levothyroxine tablets, e.g. the revised United States Pharmacopoeia monograph for levothyroxine sodium tablets of 3 October 2009 and the request of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) dated 21 February 2012 to all companies marketing T4 products in France to adopt the 95.0-105.0% potency specifications for release.

The qualitative and quantitative composition of excipients have been changed in the new levothyroxine sodium tablets. The formulation, manufacturing process, in process controls, specifications and container closure system of the finished product are identical across all strengths, except for the levothyroxine sodium and the adapted filler amount. To support the proposed CMC changes Merck has developed an appropriate CMC data package including manufacturing information, specifications, test methods, supporting validation data, and a stability program to cover the entire product range.

This applications is made as a variation B.II.a.3. b/5 Type II. The clinical overview addendum was written in January 2015 by Dr Ulrike Hostalek, M.D. The report refers to eight bibliographical references, and two clinical studies.

Assessor's comment:
The clinical overview on the clinical pharmacology, efficacy and safety is in general considered sufficient.

III.2 GCP aspects

The bioequivalence studies provided in support of the application were performed in the clinical centre of PAREXEL International GmbH in Berlin, Germany. These studies were monitored to ensure Good Clinical Practice (GCP) compliance.

Assessor's comment:
The study clinical centre (for both studies) was in Germany and the analytical site (for the first study) was in South Africa. The applicant should tell if those German and South-African sites have been inspected by European health authorities, and provide the results of those inspections. Finally, the applicant should provide the information for the analytical site of the study.

III.3 Exemption / Biowaiver

If several strengths of a product are applied for, as it is the case for the new levothyroxine sodium tablets, the CHMP guideline allows under certain conditions establishing BE for only the most sensitive strength(s) to detect a potential difference between products. For active substances with linear pharmacokinetics (= proportional increase in AUC with increased dose), it is usually sufficient to investigate in vivo BE at the highest dosage strengths, as done in study EMR 200125-001, if the following conditions are met:

a) all strengths of the formulation are manufactured by the same manufacturing process,
b) all strengths have the same qualitative composition,
c) the composition of the strengths are quantitatively proportional,
d) appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo BE testing.

Conditions a) to c) are met as stated above. To fulfil condition d), in vitro dissolution tests in accordance with the CHMP guideline requirements were performed. The main results are provided in Module 3.2.P.2.2, section 3.1.
The third element of the biopharmaceutical program is study EMR 200125-002, which investigates the BE between the new lower 50mcg and middle 100mcg strengths and the BE between the new highest 200mcg strength and the new 100mcg and the new 50mcg strengths at a single dose of 600mcg levothyroxine in the fasted state. This trial was performed to establish dosage form proportionality across the whole range of new tablet strengths.

Assessor's comment:
For the Pharmacokinetic portion, the biowaiver is acceptable. For the other points, please refer to the quality report.

III.4 Clinical studies

GCPs compliance:
According to the applicant, the bioequivalence studies were monitored to ensure Good Clinical Practice (GCP) compliance.

Principal investigator:

Clinical study centre: PAREXEL International GmbH, Spandauer Damn 130, Haus 18, 14050 Berlin, Germany.

Analytical study centre:

- EMR 200125-001: Bioanalytical Services Division of PAREXEL, Early Phase Clinical Unit (EPCU), Bloemfontein, South Africa.
- EMR 200125-002 : Not Found

Sponsor: Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany

Dates of the clinical portion:

- EMR 200125-001: 18/11/2013 to 15/07/2014 (first dosing on 02/12/2014),
- EMR 200125-002: 19/11/2013 to 14/03/2014 (first dosing on 02/12/2013).

Dates of Bioanalytical phase:

- EMR 200125-001: 30/06/2014 to 19/08/2014.
- EMR 200125-001: Not Found

The studies were conducted under ICH-GCP guidelines.

For the reformulated product, a bioequivalence study comparing the new to the old (current) formulation investigating the highest dosage strength of 200mcg at a total dose of 600mcg (EMR 200125-001), and a study establishing dosage form proportionality across almost the complete range of tablet strengths (EMR 200125-002) were performed.

Assessor's comment:
The presented bioequivalence studies (conducted under fasting conditions) are considered appropriate and sufficient for demonstration of bioequivalence.
The dates and location of the bioanalytical phase of study EMR 200125-002 are unclear or not found. They should be provided by the applicant.

III.4.1 Pharmacokinetic study

III.4.1.1 Methods

Study Design (EMR200125-001)

An open-label, single-dose, randomized, two-period, two-sequence crossover, single-centre trial to assess bioequivalence of 600 mcg Levothyroxine new formulation versus old formulation (Merck KgAa, Germany) administered orally as 3 white tablets of 200 mcg in healthy volunteers has been conducted.

The study was carried out between 18/11/2013 and 15/07/2014 (first dosing on 02/12/2013) and was designed according to an open-label, randomized, two-period, two-sequence crossover, single-centre trial. A single dose of 600 mcg Levothyroxine sodium was administered as 3 tablets of 200 mcg Levothyroxine sodium with 240 mL water in the morning of Day 1 (in either Period 1 or 2) after an overnight fast of at least 10 hours. Subjects remained fasted for 4 hours after dosing, with water only allowed after the first hour of IMP intake. The treatment phases were separated by a washout period of 35 to 38 days.

Blood samples were collected in blood collection tubes containing K^3EDTA in each study period, at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours following drug administration.

Blood samples were immediately stored on ice. Plasma was generated within 30 minutes by centrifugation under cooled conditions (~ 4°C), aliquoting into two tubes and immediately stored frozen at or below approximately –70°C until shipment to Bioanalytical Services Division of PAREXEL, Early Phase Clinical Unit (EPCU), Bloemfontein, South Africa.

Assessor's comment:
The washout period of 35 to 38 days is considered adequate to allow return of the T4 levels to normal in patients before subsequent dosing and to minimize the possibility of a carry-over effect. The sampling schedule is appropriate to determine C_{max} accurately.

Test and Reference products

Test product:
Euthyrox® (Levothyroxine) 200 mcg, scored tablets, new formulation,
Manufacturer: Merck KGaA, Darmstadt, Germany,
Biobatch No:
Batch size:
Manufacturing date: 21/06/2013,
Expiry date: 05/2014,
Purity: 103%.

Reference Product:
Euthyrox® (Levothyroxine) 200 mcg, scored tablets, old formulation,
Manufacturer: Merck KGaA, Darmstadt, Germany,
Biobatch No:
Batch size:
Manufacturing date: 05/03/2013,
Expiry date: **Not Found**,
Purity: 101%.

The reference product is marketed by Merck in France and different European countries.

Certificates of analysis of the test and reference products are presented.

Assessor's comment:
Adequate information is provided on the test and reference products. The reference product is acceptable. Purities of Test and Reference products have less than 5% difference. ***However, expiry date could not be found for the Reference product, the applicant should provide it.***

Population(s) studied

The sample size for this trial was based on intra-individual variability in T4 PK parameters from previous trials, shown below.

Table 1: Intra-individual variability of PK data

Trial	Ratio AUC	Ratio C_{max}	CV% AUC	CV% C_{max}
436-99-263	0.99	0.98	11.54	13.45
436-99-264	0.97	0.94	15.37	15.15
436-99-277	1.14	1.04	15.31	13.85

CV% = coefficient of variation percentage

These results were in agreement with data published in a summary by the FDA most recently, giving 15.5% as an upper bound for the coefficient of variation (CV) of AUC of Levothyroxine, and 18.6% as an upper bound for the CV of C_{max}. If the upper bounds of these CVs together with applicable BE criteria [0.90 to 1.11] for AUC and C_{max} are applied, (third set below), and if furthermore the true treatment ratio Test/Reference is allowed to vary within 0.95 and 1.05, 172 evaluable subjects would provide at least 83% overall power to show bioequivalence. For a compensation of possible drop-outs 44 subjects should have been included in addition, corresponding to a drop-out rate of around 20%. In total, 216 subjects should have been included in the trial (108 subjects per treatment sequence).

Subject disposition is presented in the table below.

Table 2: EMR 200125-001 Subject disposition

Subjects	Sequence 1 N = 108	Sequence 2 N = 108	Overall N = 216
	n (%)	n (%)	n (%)
Screened	-	-	762
Randomized	108 (100.0%)	108 (100.0%)	216 (100.0%)
Subjects Treated	108 (100.0%)	108 (100.0%)	216 (100.0%)
Completed	103 (95.4%)	101 (93.5%)	204 (94.4%)
Withdrawn	5 (4.6%)	7 (6.5%)	12 (5.6%)
Adverse event	2 (1.9%)	2 (1.9%)	4 (1.9%)
Protocol non-compliance	2 (1.9%)	3 (2.8%)	5 (2.3%)
Withdrawal by subject	1 (0.9%)	2 (1.9%)	3 (1.4%)
Safety population	108 (100.0%)	108 (100.0%)	216 (100.0%)
PK population	103 (95.4%)	101 (93.5%)	204 (94.4%)

N = number of subjects dosed with at least one treatment in that treatment sequence, or the number subjects in the safety population for the total summary; n = number of subjects in the specific category; PK = pharmacokinetics

Treatment Sequence 1: Test (new formulation)/Reference (old formulation)
Treatment Sequence 2: Reference (old formulation)/Test (new formulation)

Assessor's comment:
Adequate inclusion/exclusion criteria were followed. Drop-outs were all due to adverse events, protocol non-compliance (e.g. positive drug tests, unauthorised concomitant medications), or personal decision of the subject.

Analytical methods

The analytical part of the study was conducted at PAREXEL (South Africa) from the period of 30/06/2014 to 19/08/2014.
The main analyte quantitated in the study was T4, internal standard was T4-d4.

According to the applicant, the plasma samples were analysed in accordance with GLP regulations. Sample analysis was performed using a validated LC-MS/MS method. Stability of the analytes in K^3EDTA human plasma containing citric and ascorbic acid has recently been demonstrated for at least 69 days at -70°C as described in the Method Validation Report [Euthyrox - VAL251_01 (14-GR050-C0) - BMV in Human Plasma]. Further LTS investigations are scheduled to be performed at intervals of 3, 6, maximum clinical sample storage period (approximately 9 months), and 12 months.
Study samples were stored from sample collection to the end of sample analysis for a duration not exceeding 260 days (from 02/12/2013 to 19/08/2014).

Due to the fact that T4 and T3 are endogenous compounds, K^3EDTA plasma needed to be stripped of the analytes for the preparation of calibration standards for the construction of a calibration curve. The stripping was performed by using activated charcoal. This stripping does however not completely devoid the plasma of T4 and T3 and therefore, following the original stripping process, an additional stripping with activated charcoal was performed at a pH of 3. Under these conditions, bound T4 and T3 were released from their endogenous binding protein (thyroid hormone binding globulin) resulting in stripped plasma completely devoid of the analytes. After stripping, the pH was adjusted to physiological pH (pH = 7.4). The stripping was done in batches. To ascertain complete stripping, each batch was screened using the approved assay procedure. Following the screening procedure, individual batches were pooled to produce pooled stripped K^3EDTA human plasma

Calibration standards and QC samples were used during the analysis as detailed in the table below.

Table 3: Calibration standards and quality control samples, study EMR200125-001

Analyte	Designation	Concentration level (ng/mL)
T3	Calibration standards	0.300 (STD B), 0.466 (STD C), 0.937 (STD D), 1.87 (STD E), 3.75 (STD F), 7.50 (STD G), 15.0 (STD H), 30.0 (STD I)
T4	Calibration standards	9.987 (STD B), 15.57 (STD C), 31.14 (STD D), 62.28 (STD E), 124.6 (STD F), 249.1 (STD G), 498.2 (STD H), 996.4 (STD I)
T3	Quality control samples (prepared 15-Apr-2014)	Stripped plasma: 0.749 (QC B), 4.99 (QC D), 24.0 (QC F) Normal plasma: 2.36 (QC G), 5.39 (QC H), 23.4 (QC I)
T3	Quality control samples (prepared 21-Jul-2014)	Stripped plasma: 0.749 (QC B), 4.99 (QC D), 24.0 (QC F) Normal plasma: 1.98 (QC G), 4.63 (QC H), 20.4 (QC I)
T3	Quality control samples (prepared 12-Aug-2014)	Stripped plasma: 0.749 (QC B), 4.99 (QC D), 24.0 (QC F) Normal plasma: 2.57 (QC G), 5.59 (QC H), 20.8 (QC I)
T4	Quality control samples(prepared 15-Apr-2014)	Stripped plasma: 24.87 (QC B), 165.8 (QC D), 797.7 (QC F) Normal plasma: 99.46 (QC G), 200.0 (QC H), 797.3 (QC I)
T4	Quality control samples(prepared 21-Jul-2014)	Stripped plasma: 24.87 (QC B), 165.8 (QC D), 797.7 (QC F) Normal plasma: 97.42 (QC G), 185.5 (QC H), 709.0 (QC I)
T4	Quality control samples(prepared 12-Aug-2014)	Stripped plasma: 24.87 (QC B), 165.8 (QC D), 797.7 (QC F) Normal plasma: 110.9 (QC G), 210.7 (QC H), 716.2 (QC I)

Results of calibration samples, regression parameters, and quality controls for T4 are detailed in the tables below.

Table 4 Calibration samples, study EMR200125-001

Nominal concentration (ng/mL)[a]	9.987	15.57	31.14	62.28	124.6	249.1	498.2	996.4
Mean (ng/mL)	10.05	15.49	30.92	61.88	124.9	249.0	501.8	999.7
Accuracy (%)	0.6	-0.6	-0.7	-0.7	0.2	0.0	0.7	0.3
CV (%)	5.0	4.8	5.2	5.4	4.3	5.1	4.8	5.1
N	146	144	140	144	143	145	143	146

Table 5: Regression parameters, study EMR200125-001

Nominal concentration (ng/mL)[a]	0.749	1.98	2.36	2.57	4.63	4.99	5.39	5.59	20.4	20.8	23.4	24.0
Mean (ng/mL):	0.726	2.05	2.44	2.64	4.68	4.77	5.50	5.60	19.6	22.1	22.2	24.2
Accuracy (%):	-3.1	3.5	3.4	2.7	1.1	-4.4	2.0	0.1	-3.9	6.3	-5.1	0.8
CV (%):	10.9	10.3	6.1	11.7	9.6	6.7	6.9	4.6	8.6	0.8	7.1	6.7
Number:	145	58	84	4	58	146	82	4	58	4	83	146

Table 6: Quality control, study EMR200125-001

Nominal concentration (ng/mL)[a]	24.87	97.42	99.46	110.9	165.8	185.6	200.0	210.7	709.0	716.2	797.3	797.7
Mean (ng/mL):	24.77	104.6	100.5	111.1	166.3	194.1	195.0	208.3	736.1	758.9	746.6	802.0
Accuracy (%):	-0.4	7.4	1.0	0.2	0.3	4.6	-2.5	-1.1	3.8	6.0	-6.4	0.5
CV (%):	8.0	8.5	7.7	4.6	5.7	8.3	7.4	6.1	9.4	5.7	7.0	6.0
Number:	145	54	84	8	146	54	82	9	54	8	83	146

A single analysis was performed for all study samples. Reanalyses were performed for the following reasons: 24 samples were lost in process
The affected samples were reanalysed in single fold and the repeated value is reported as the final value.

A total number of 7982 samples was analysed, 455 samples were used for ISR. Incurred sample reanalysis (ISR) showed reproducibility of the analytical assay. 80.2% of the reanalysed samples (365 of 455) of T4met the predefined acceptance criteria

A representative number of chromatograms was provided by the applicant.

Assessor's comment:
The method validation report was quoted but could not be found, the applicant should provide it.
The analytical technique used in the bioequivalence study is clearly described.
Latest results of the long term stability could not be found, they should be provided to show that long-term stability in biological samples was validated on at least 260 days.
A representative number of chromatograms was provided by the applicant. ISR were satisfactory.

Pharmacokinetic Variables

Relevant pharmacokinetic parameters of total T4 were estimated using a non compartmental analysis (NCA).
The primary variables were $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ of total T4 after dosing with the Test and Reference formulation of 600 mcg Levothyroxine given as 3 tablets of 200 mcg, adjusted for baseline (predose level).
The mean of the 3 predose samples was used to adjust for the baseline T4 level. If the baseline measurement (derived mean or single measurement) was higher than the first postdose T4 concentration, the baseline-adjusted PK parameters were not calculated for the specific treatment period. For the estimation of λz, and consequently $T_{1/2}$, baseline-adjusted concentrations were used. The mean of 3 predose measurements was subtracted from each concentration at each time point. Predose concentrations that were below the limit of quantitation (BLQ) were set to ½ lower limit of quantification (LLOQ) in the calculation of the mean baseline concentration. Below the limit of quantification values were set to ½ LLOQ in the estimation of $AUC_{0\text{-}t}$ and C_{max}.

The pharmacokinetic parameters T_{max} and $T_{1/2}$ were also provided.

Assessor's comment:
The chosen pharmacokinetic parameters are adequate according to the current guidelines. Baseline adjustment was appropriate.

Statistical methods

ANOVA was performed on *ln*-transformed $AUC_{0-72,adj}$ and $C_{max,adj}$ and confidence intervals were calculated.
The ANOVA model included evaluation of sequence, subject nested into sequence, period and treatment effects.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means for the *ln*-transformed $AUC_{0-72,adj}$ and $C_{max,adj}$ were within the acceptable range 90% to 111%.

Assessor's comment:
The statistics have been adequately described and the standard acceptance criteria are acceptable. The restricted acceptable range is adequate for bioequivalence of Levothyroxine.

Study Design (EMR200125-002)

An open-label, single-dose, randomized, three-period, six sequence crossover, single-center trial to assess dosage form proportionality of 600 mcg Levothyroxine new formulation administered orally as either 12 white tablets of 50 mcg or 6 white tablets of 100 mcg or 3 white tablets of 200 mcg (Merck KgAa, Germany) in healthy volunteers has been conducted.

The study was carried out between 19/11/2013 and 14/03/2014 (first dosing on 02/12/2013) and was designed according to an open-label, randomized, three-period, six sequence crossover, single-center trial. A single dose of 600 mcg Levothyroxine sodium was administered as 3 tablets of 200 mcg Levothyroxine sodium with 240 mL water in the morning of Day 1 (in either Period 1 or 2) after an overnight fast of at least 10 hours. Subjects remained fasted for 4 hours after dosing, with water only allowed after the first hour of IMP intake. The treatment phases were separated by a washout period of 35 to 38 days.

Blood samples were collected in blood collection tubes containing K^3EDTA in each study period, at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours following drug administration.

Assessor's comment:
The washout period of 35 to 38 days is considered adequate to allow return of the T4 levels to normal in patients before subsequent dosing and to minimize the possibility of a carry-over effect. The sampling schedule is appropriate to determine C_{max} accurately.

Test products

Test product 1:
Euthyrox® (Levothyroxine) 50 mcg, scored tablets, new formulation,
Manufacturer: Merck KGaA, Darmstadt, Germany,
Biobatch No:
Batch size:
Manufacturing date: 19/06/2013,

Expiry date: 05/2014,
Purity: 102.1%.

Test product 2:
Euthyrox® (Levothyroxine) 100 mcg, scored tablets, new formulation,
Manufacturer: Merck KGaA, Darmstadt, Germany,
Biobatch No:
Batch size:
Manufacturing date: 20/06/2013,
Expiry date: 05/2014,
Purity: 102.9%.

Test product 3:
Euthyrox® (Levothyroxine) 200 mcg, scored tablets, new formulation,
Manufacturer: Merck KGaA, Darmstadt, Germany,
Biobatch No:
Batch size:
Manufacturing date: 21/06/2013,
Expiry date: 05/2014,
Purity: 103%.

The reference product is marketed by Merck in France and different European countries.

Certificates of analysis of the test and reference products are presented.

Assessor's comment:
Adequate information is provided on the test products. Purities of Test products have less than 5% difference.

Population(s) studied

The sample size for this trial was based on intra-individual variability in T4 PK parameters from previous trials, shown previously in Table 1.

These results were in agreement with data published in a summary by the FDA most recently, giving 15.5% as an upper bound for the coefficient of variation percentage (CV%) of AUC of Levothyroxine, and 18.6% as an upper bound for the CV% of C_{max}. If we apply the upper bounds of these CV% together with common BE criteria for AUC and C_{max} [0.80 – 1.25], and if we furthermore allow the true treatment ratio Test/Reference to vary within 0.95 and 1.05, 32 evaluable subjects would provide at least 80% overall power to show BE for all 3 pairwise comparisons. For a compensation of possible drop-outs 10 subjects should be included in addition, corresponding to a drop-out rate of around 20%. In total, 42 subjects should be included in the trial (7 subjects per treatment sequence). Since dosage form proportionality was tested for two sets of parameters, the usual one-sided alpha of 0.05 is adjusted to 0.025, corresponding to a confidence level of 95%.

Subject disposition is presented in the table below.

Table 7: **EMR 200125-002 Subject disposition**

Subjects	Sequence 1 N = 7	Sequence 2 N = 7	Sequence 3 N = 7	Sequence 4 N = 7	Sequence 5 N = 7	Sequence 6 N = 7	Overall N = 42
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screened	-	-	-	-	-	-	103
Randomized	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	42 (100.0%)
Subjects Treated	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	42 (100.0%)
Completed	7 (100.0%)	5 (71.4%)	7 (100.0%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	37 (88.1%)
Withdrawn	0	2 (28.6%)	0	1 (14.3%)	1 (14.3%)	1 (14.3%)	5 (11.9%)
Adverse event	0	1 (14.3%)	0	1 (14.3%)	0	0	2 (4.8%)
Protocol non-compliance	0	1 (14.3%)	0	1 (14.3%)	0	0	1 (2.4%)
Death	0	0	0	0	0	0	0
Subject withdrew at own request	0	0	0	0	1 (14.3%)	1 (14.3%)	2 (4.8%)
Safety population	7 (100.0%)	5 (71.4%)	7 (100.0%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	37 (88.1%)
PK population	0	2 (28.6%)	0	1 (14.3%)	1 (14.3%)	1 (14.3%)	5 (11.9%)

N = number of subjects for each treatment arm; n = number of subjects affected; PK = pharmacokinetics
Sequence 1: (A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg
Sequence 2: (B) 6 tablets of 100 µg/(C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg
Sequence 3: (C) 3 tablets of 200 µg/(A) 12 tablets of 50 µg/(B) 6 tablets of 100 µg
Sequence 4: (A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg
Sequence 5: (B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg/(C) 3 tablets of 200 µg
Sequence 6: (C) 3 tablets of 200 µg/(B) 6 tablets of 100 µg/(A) 12 tablets of 50 µg

Assessor's comment:
Adequate inclusion/exclusion criteria were followed. Drop-outs were all due to adverse events, protocol non-compliance (e.g. positive drug tests, unauthorised concomitant medications), or personal decision of the subject.

Analytical methods

In the main assessment report, it was stated that analysis methods were defined in a bioanalytical protocol, and respective results were reported in a bioanalytical report (Appendix 16.1.12). This report could not be found.

Assessor's comment:
A validation report of the within study is provided with satisfactory results. The pre-study analytical report (method validation report) and the in-study analytical report could not be found. The applicant should provide them.

Pharmacokinetic Variables

Relevant pharmacokinetic parameters of total T4 were estimated using a non compartmental analysis (NCA).
The primary variables were $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ of total T4 after dosing adjusted for baseline (predose level).
The mean of the 3 predose samples was used to adjust for the baseline T4 level. If the baseline measurement (derived mean or single measurement) was higher than the first postdose T4 concentration, the baseline-adjusted PK parameters were not calculated for the specific treatment period. For the estimation of λz, and consequently $T_{1/2}$, baseline-adjusted concentrations were used. The mean of 3 predose measurements was subtracted from each concentration at each time point. Predose concentrations that were below the limit of quantitation (BLQ) were set to ½ lower limit of quantification (LLOQ) in the calculation of the mean baseline concentration. Below the limit of quantification values were set to ½ LLOQ in the estimation of $AUC_{0\text{-}t}$ and C_{max}.

The pharmacokinetic parameters T_{max} and $T_{1/2}$ were also provided.

Assessor's comment:
The chosen pharmacokinetic parameters are adequate according to the current guidelines. Baseline adjustment was appropriate.

Statistical methods

ANOVA was performed on *ln*-transformed $AUC_{0-72,adj}$ and $C_{max,adj}$ and confidence intervals were calculated.
The ANOVA model included evaluation of sequence, subject nested into sequence, period and treatment effects.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means for the *ln*-transformed $AUC_{0-72,adj}$ and $C_{max,adj}$.

Pairwise bioequivalence (BE) testing (3 BE tests for each set of primary endpoints) was also performed. Dose-form-proportionality was confirmed, if the 95% CI for the ratios of geometric means for both $AUC_{0-72,adj}$ and $C_{max,adj}$ of total T4 in plasma, were included in the interval 0.8 to 1.25 in all three pairwise comparisons.

Assessor's comment:
The statistics have been adequately described and the standard acceptance criteria are acceptable. Acceptance interval should have been restricted to 90%-111% as in previous studies, however this will not impact the final conclusions.

III.4.1.2 Results

Study Design (EMR200125-001)

Table 8: ANOVA results for study EMR200125-001

Parameter	Treatment	N	Geo-LSMean	Ratio (Test/Ref) (%)	90% CI of Ratio	Intra-CV (%)
$AUC_{0-72,adj}$ (hr*ng/mL)	Test	204	1852.079	99.3	95.6 - 103.2	23.7
	Reference	204	1864.359			
$C_{max,adj}$ (ng/mL)	Test	204	53.5473	101.7	98.8 - 104.6	17.7
	Reference	204	52.6736			

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; Geo-LSMean= Geometric Least Square Mean; N = Number of [illegible] included in the analysis.

were excluded from the PK Population.

Reference: levothyroxine old formulation.

Table 9: Summary of PK parameters for study EMR200125-001

	Statistic	$AUC_{0\text{-}72,adj}$ * (hr*ng/mL)	$C_{max,adj}$ (ng/mL)
Test	n (missing)	204 (0)	204 (0)
	Mean (SD)	1975.81 (626.137)	55.3788 (15.93241)
	Geo Mean (95% CI)	1851.94 (1751.43;1958.22)	53.5498 (51.7064;55.4589)
	Geo CV (CV%)	42.1 (31.7)	25.8 (28.8)
	SEM	43.838	1.11549
	Median	1944.15	53.6550
	Min; Max	140.4; 3749.7	27.520; 191.233
Reference	n (missing)	204 (0)	204 (0)
	Mean (SD)	1976.87 (619.892)	54.1358 (12.72064)
	Geo Mean (95% CI)	1865.11 (1772.77;1962.25)	52.6806 (50.9997;54.4170)
	Geo CV (CV%)	38.1 (31.4)	23.8 (23.5)
	SEM	43.401	0.89062
	Median	1915.95	52.4765
	Min; Max	253.5; 3466.1	28.300; 102.830

CI = Confidence Interval; CV% = Coefficient of Variation Percentage; GeoCV = Geometric Coefficient of Variation; GeoMean = Geometric Mean; Max = Maximum Value; Min = Minimum Value; n = The number of subjects with specific parameter calculable; SD = Standard Deviation; SEM = Standard Error of the Mean; T4 = thyroxine

* $AUC_{(0\text{-}last)}$ was used for Test subjects and Reference Subjects.

1. Normalization to exactly 72 hours was not possible because of invalid λz.

Test: levothyroxine new formulation.
Reference: levothyroxine old formulation.

Assessor's comment:
The 90% confidence intervals for Test/Reference ratios observed for $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ are within the pre-specified acceptance limits for bioequivalence, 90-111%.
Period or sequence effect discussion could not be found. The applicant should inform if period or sequence effects were observed, and if they were; justify those effects.

Study Design (EMR200125-002)

Table 10: ANOVA results for study EMR200125-002

Parameter	Treatment	N	Geo-LSMean	Ratio (Treatments) (%)	95% CI of Ratio	Intra-CV (%)
$AUC_{0\text{-}72}$ (hr*ng/mL)	B	37	6780.981	100.1	97.6 - 102.7	5.4
	A	37	6772.424			
	C	37	6884.607	101.7	99.1 - 104.2	5.4
	A	37	6772.424			
	C	37	6884.607	101.5	99.0 - 104.1	5.4
	B	37	6780.981			
C_{max} (ng/mL)	B	37	125.1199	101.8	98.4 - 105.3	7.3
	A	37	122.9188			
	C	37	125.0102	101.7	98.3 - 105.2	7.3
	A	37	122.9188			
	C	37	125.0102	99.9	96.6 - 103.3	7.3
	B	37	125.1199			
$AUC_{0\text{-}72,adj}$ (hr*ng/mL)	B	37	2222.979	99.3	91.8 - 107.5	17.1
	A	37	2237.745			
	C	37	2329.393	104.1	96.2 - 112.6	17.1
	A	37	2237.745			
	C	37	2329.393	104.8	96.8 - 113.4	17.1
	B	37	2222.979			
$C_{max,adj}$ (ng/mL)	B	37	62.1190	103.8	96.7 - 111.5	15.5
	A	37	59.8409			
	C	37	61.7588	103.2	96.1 - 110.8	15.5
	A	37	59.8409			
	C	37	61.7588	99.4	92.6 - 106.8	15.5
	B	37	62.1190			

CI: Confidence Interval; CV%: Coefficient of Variation Percentage; Geo-LSMean: Geometric Least Square Mean;
N: Number of subjects included in the analysis. T4: Tetraiodothyronine;
Subjects) were excluded from the PK Population.
Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;

Table 11: Summary of PK parameters for study EMR200125-002

	Statistic	$AUC_{0\text{-}72adj}$ * (hr*ng/mL)	$C_{max,adj}$ (ng/mL)	$AUC_{0\text{-}72}$ * (hr*ng/mL)	C_{max} (ng/mL)
Treatment A	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2312.18 (525.549)	61.5394 (13.24115)	6828.58 (674.946)	124.267 (15.2342)
	Geo Mean (95% CI)	2249.63 (2073.95;2440.19)	60.0991 (55.7575;64.7787)	6796.27 (6576.12;7023.78)	123.343 (118.321;128.577)
	Geo CV (CV%)	24.8 (22.7)	22.8 (21.5)	9.9 (9.9)	12.5 (12.3)
	SEM	86.400	2.17683	110.960	2.5045
	Median	2363.56	62.3370	6863.29	124.900
	Min; Max	1265.0; 3531.2	32.547; 90.860	5718.7; 8157.7	94.58; 150.40
Treatment B	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2333.14 (649.583)	63.6903 (14.41836)	6846.87 (838.557)	126.381 (17.7666)
	Geo Mean (95% CI)	2237.16 (2021.46;2475.88)	62.1576 (57.7031;66.9560)	6797.17 (6525.39;7080.26)	125.208 (119.599;131.081)
	Geo CV (CV%)	31.1 (27.8)	22.6 (22.6)	12.3 (12.2)	13.8 (14.1)
	SEM	106.791	2.37036	137.858	2.9208
	Median	2324.91	60.1670	6602.39	125.700
	Min; Max	1056.8; 3796.0	44.287; 99.350	5601.4; 8455.1	101.20; 161.50
Treatment C	n (missing)	37 (0)	37 (0)	37 (0)	37 (0)
	Mean (SD)	2386.83 (518.752)	62.8319 (12.25621)	6937.85 (704.070)	126.041 (15.1427)
	Geo Mean (95% CI)	2334.75 (2175.34;2505.85)	61.7272 (57.9543;65.7457)	6903.36 (6674.44;7140.13)	125.159 (120.246;130.273)
	Geo CV (CV%)	21.5 (21.7)	19.1 (19.5)	10.1 (10.1)	12.1 (12.0)
	SEM	85.282	2.01491	115.748	2.4895
	Median	2335.06	60.9600	6941.44	126.200
	Min; Max	1528.9; 3954.6	45.293; 87.290	5657.4; 8289.1	102.60; 152.50

CI: Confidence Interval; CV%: Coefficient of Variation Percentage; GeoCV: Geometric Coefficient of Variation; GeoMean: Geometric Mean; Max: Maximum Value; Min: Minimum Value; n: The number of subjects with specific parameter calculable; SD: Standard Deviation; SEM: Standard Error of the Mean; T4: Tetraiodothyronine
*: $AUC_{(0\text{-}flast)}$ was used in many instances (See Table 15.4.1.1.2). Normalization to exactly 72 hours was not possible because of invalid Lambda_z.
Treatment A: 12 tablets of 50 µg of levothyroxine;
Treatment B: 6 tablets of 100 µg of levothyroxine;
Treatment C: 3 tablets of 200 µg of levothyroxine;

Assessor's comment:
The 90% confidence intervals for Test/Reference ratios observed for $AUC_{0\text{-}72}$ and C_{max} are within the pre-specified acceptance limits for bioequivalence, 90-111%.
The 90% confidence intervals for Test/Reference ratios observed for $AUC_{0\text{-}72,adj}$ and $C_{max,adj}$ are mostly within the pre-specified acceptance limits for bioequivalence, 90-111%, as the highest upper limit is at 113.4%.
Period or sequence effect discussion could not be found. The applicant should inform if period or sequence effects were observed, and if they were; justify those effects.

III.4.1.3 Pharmacokinetic conclusion

Based on the two bioequivalence studies EMR200125-001 and EMR200125-002, as well as the biowaiver, the 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® new formulation scored tablets can be considered bioequivalent with the 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® old formulation scored tablets (comparing old and new formulations of similar strength), with respect to rate and extent of absorption of Levothyroxine.

Nevertheless, there are some issues that should be clarified (see LoQ).

Conclusion pharmacocinétique

Sur la base des deux études de bioéquivalence EMR200125-001 et EMR200125-002, ainsi que sur le biowaiver, les comprimés de la nouvelle formulation 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® peuvent être considérés comme bioéquivalents avec les comprimés de l'ancienne formulation 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® pour la vitesse et la quantité d'absorption de la lévothyroxine.
Néanmoins, il reste quelques points de clarification à résoudre.

IV. LIST OF QUESTIONS AS PROPOSED BY THE RMS

Clinical aspects

Major objections

Pharmacokinetics
None

Points for clarification

Pharmacokinetics

1. (Both studies) The applicant should tell if the German clinical site of PAREXEL has been inspected by competent European health authorities, and provide the results of those inspections.
2. (EMR 200125-001) The applicant should tell if the South-African analytical site of PAREXEL has been inspected by competent European health authorities, and provide the results of those inspections.
3. (EMR 200125-002) It was not clear where the analytical site for this study was located. The applicant should provide the name and address if that site, if it has been inspected by European health authorities, provide the results of those inspections, and finally provide the dates of the analytical phase.
4. (EMR 200125-001) Expiry date could not be found for the Reference product, the applicant should provide it.
5. (EMR 200125-001) The method validation report was quoted but could not be found, the applicant should provide it.
6. (EMR 200125-001) Latest results of the long term stability could not be found, they should be provided to show that long-term stability in biological samples was validated on at least 260 days.
7. (EMR 200125-002) The pre-study analytical report (method validation report) and the in-study analytical report could not be found. The applicant should provide them
8. (Both studies) Period or sequence effect discussion could not be found. The applicant should inform if period or sequence effects were observed, and if they were; justify those effects.

1. (Les deux études) Le laboratoire devrait dire si le site Clinique Allemand de PAREXEL a été inspecté par des autorités de santé européennes compétentes, et transmettre les résultats de ces inspections.
2. (EMR 200125-001) Le laboratoire devrait dire si le site analytique Sud-Africain de PAREXEL a été inspecté par des autorités de santé européennes compétentes, et transmettre les résultats de ces inspections.
3. (EMR 200125-002) Le site analytique de cette étude n'était pas clair. Le laboratoire devrait le préciser, dire s'il a été inspecté par des autorités de santé européennes compétentes, et transmettre les résultats de ces inspections, et enfin transmettre les dates de début et de fin de la période analytique.
4. (EMR 200125-001) La date d'expiration pour le produit de référence n'a pas pu être trouvée, le laboratoire devrait la communiquer.
5. (EMR 200125-001) La validation de la méthode analytique était citée mais n'a pas pu être trouvée, le laboratoire devrait la communiquer.
6. (EMR 200125-001) Les derniers résultats de stabilité long-terme dans les échantillons biologiques n'ont pas pu être trouvés. Le laboratoire devrait les communiquer pour prouver que cette stabilité a été validée sur au moins 260 jours.
7. (EMR 200125-002) Le rapport de validation de la méthode analytique (pré-étude) et le rapport analytique de l'étude n'ont pas été trouvés, le laboratoire devrait les communiquer.
8. (Les deux études) Une discussion des éventuels effets séquence ou période n'a pas pu être trouvée. Le laboratoire devrait dire si des effets séquence ou période significatifs ont été trouvés et, si oui, les discuter.

Levothyrox (Levothyroxine sodium) 25, 50, 75, 100, 125, 150, 175, 200 mcg scored tablets, Merck
APN 2831
Assessment of the applicant's responses to the questions raised by FR

Pharmacokinetics:

Point for clarification PoC 1:
(Both studies) The applicant should tell if the German clinical site of PAREXEL has been inspected by competent European health authorities, and provide the results of those inspections.

Applicant's response:
The PAREXEL site in Berlin, Germany, where the in-life part of studies EMR 200125-001 and 002 were conducted, has not been inspected by a European health authority.

Assessor's comment:
The German site has not been inspected by any of the European agencies, however it has been inspected by one of the German regional (Länder) agencies in 2007. The inspection revealed a critical finding for monitoring, but this critical finding should have no impact on the present study.
Issue resolved.

Point for clarification PoC 2:
(EMR 200125-001) The applicant should tell if the South-African analytical site of PAREXEL has been inspected by competent European health authorities, and provide the results of those inspections.

Applicant's response:
The PAREXEL site at Brandhof, South Africa, including the Bioanalytical Services Division, where the bioanalyses of studies EMR 200125-001 and -002 were performed, has been inspected by the MHRA in August 2014. The GCP inspection statement issued on November 17, 2014 is attached.

Assessor's comment:
Inspection of the South-African site of Parexel has been performed by a competent European authority.
Issue resolved.

Point for clarification PoC 3:
(EMR 200125-002) It was not clear where the analytical site for this study was located. The applicant should provide the name and address if that site, if it has been inspected by European health authorities, provide the results of those inspections, and finally provide the dates of the analytical phase.

Applicant's response:
The PAREXEL site in South Africa has performed the bioanalyses for both studies -001 and 002 (see also bioanalytical report 14-GR086-C0, page 1 in section 16.1.13 of the clinical study report EMR 200125-002).
For the inspection status of the site, see our answer to question no. 2.
The start and end dates of the sample analyses are provided in the report 14-GR086-C0 on page 3. They were Start Date: 03-09-2014 and End Date: 19-09-2014.

Assessor's comment:
All the missing information have been given or clarified.
Issue resolved.

Point for clarification PoC 4:
(EMR 200125-001) Expiry date could not be found for the Reference product, the applicant should provide it.

Applicant's response:
The reference product used in study EMR 200125-001 was Euthyrox® 200 µg tablets, batch no. 015608, which is currently marketed by Merck KGaA worldwide and is the same product as **Levothyrox 200 microgrammes, comprimé sécable** marketed in France by Merck Santé. The reference product has a shelf-life of 3 years. Based on the date of manufacturing of 05-03-2013 (see Certificate of Analysis in CSR-001, Section 16.1.6), the expiry date of the reference product is 05-03-2016

Assessor's comment:
Expiry date was March 2016.
Issue resolved.

Point for clarification PoC 5:
(EMR 200125-001) The method validation report was quoted but could not be found, the applicant should provide it.

Applicant's response:
The validation report of the analytical method had been submitted in the initial application and is included again for convenience.

The quantitative determination of T_3 (triiodothyronine) and T_4 (thyroxine) in acidified K_3EDTA human plasma in all samples of studies -002 and -001 was performed using a validated LCMS/MS method which is detailed in the Method Validation Report (refer to Euthyrox® – VAL 251/01 (14-GR050-C0) - BMV in Human Plasma including Amendment 1 providing additional long-term stability data).

The report was already included in the initial submission and amended by a follow-up submission to include additional stability data of the analytes in human plasma. For ease of review we have included the report also in this response.
The bioanalytical assay was fully validated over the concentration range 0.300 ng/mL (LLOQ) to 30.0 ng/mL (up to 239 ng/mL when using a dilution factor of 10) for T_3, and 9.987 ng/mL (LLOQ) to 996.4 ng/mL (up to 7972 ng/mL when using a dilution factor of 10) for T_4. Incurred sample reanalysis in clinical studies showed reproducibility of bioanalytical results meeting the predefined acceptance criteria.

Assessor's comment:
The method validation report was provided. As a note, this report, being linked with a clinical study, was expected in module 5, not module 4.
It was performed between 24th March 2014 and 10th February 2015. The analytes were total T3 and total T4 in human plasma containing K_3EDTA as anticoagulant agent. We will focus on total T4.
Concentration range for method validation was 9.987 ng/mL (LLOQ) to 996.4 ng/mL (up to 7972 ng/mL when using a dilution factor of 10) for T4. Matrix effect, including haemolysed and lipemic matrices was satisfactory. Internal standard was Tyroxine-D4. Long-term stability at -70°C is detailed in PoC6.
Blank plasma was stripped on activated charcoal at normal pH (7.4) and then at pH3, then pH was readjusted to 7.4.
Calibration was performed at 9.987, 15.57, 31.14, 62.28, 124.6, 249.1, 498.2, 996.4 ng/mL.
Two-fold, 5-fold and 10-fold dilution were tested and successfully validated.
Between-run and within run accuracy and precision were all within acceptance criteria.
Overall, this analytical method validation is acceptable.
Issue resolved.

Point for clarification PoC 6:
(EMR 200125-001) Latest results of the long term stability could not be found, they should be provided to show that long-term stability in biological samples was validated on at least 260 days.

Applicant's response:
The last long-term stability results have been submitted separately on 09 June 2015 with Amendment 1 of the Validation Report [4.2.2.1].The stability of T_3 and T_4 in acidified K_3EDTA normal human plasma was investigated after storage during sample preparation for at least 16 hours at ambient temperature, after 3 freeze/thaw cycles and after long-term storage at ~ -70°C for up to 297 days (this covers the maximum storage period of the study samples). T3 and T4 were stable under all conditions tested.

Assessor's comment:
Latest long-term stability results were provided, and it was investigated for long term storage up to 297 days at around -70°C, longer than the 260 days expected.
Issue resolved.

Point for clarification PoC 7:
(EMR 200125-002) The pre-study analytical report (method validation report) and the in-study analytical report could not be found. The applicant should provide them.

Applicant's response:
The validation report Euthyrox® – VAL 251/01 (14-GR050-C0) - BMV in Human Plasma including Amendment 1 [4.2.2.1] with long-term stability results refers to both studies -001 and 002.

Assessor's comment:
Pre-study method validation is discussed in PoC 5, and acceptable.
The applicant also submitted the analytical report for Study EMR 200125-002.

Samples were measured between 03rd and 19th September 2014 (first sample taken on 02/12/2013). Long term stability in plasma at -70°C was studied long enough, see question 6.
Blank plasma for controls are prepared with anticoagulant K_3EDTA.
QCs and calibration samples resulted in accuracy and precision within acceptable ranges.
Samples reanalysed (out of ISR) were justified by loss in process, which is acceptable.
2214 sample were analysed. Incurred sample reanalysis (ISR) showed reproducibility of the analytical assay. 74.4% of the re-analysed samples of T3 (125 of 168) and 85.3% of the re-analysed samples (145 of 170) of T4 met the predefined acceptance criteria.
Issue resolved.

Point for clarification PoC 8:
(Both studies) Period or sequence effect discussion could not be found. The applicant should inform if period or sequence effects were observed, and if they were; justify those effects.

Applicant's response:
Potential sequence and period effects were evaluated for both studies EMR 200125-001 and 002:

No sequence effects were found in both trials: see section *16.1.9.2 Statistical Model Output, Tests of Hypotheses Using the Type III MS for SUBJID(TRTSEQAN) as an Error Term* in both study reports.

There is one p-value <0.05 for period in trial -001 (AUC72_A, p=0.0380), and two p-values < 0.05 for period in trial -002 (CMAX, p=0.0086, CMAX_A, p=0.0392).
Considering the large number of calculated exploratory p-values there is good reason to find p values <0.05 just by chance. Furthermore, the low p-values are not supported by low p-values for period of the corresponding parameters, CMAX_A, CMAX and T3 parameters in 001, and AUC72_A, AUC72 and T3 parameters in 002, which would have been expected in the event of a real period effect. Therefore, equal conditions were concluded for the periods in both trials.

Assessor's comment:
Sequence and period effects were detailed, and the period effect in study 001 with a p value below 0.05 was properly justified.
Issue resolved.

Overall summary and conclusion:
The RMS is of the opinion that all PK questions have been answered sufficiently.
Based on the bioequivalence studies as well as the biowaiver, the 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® new formulation scored tablets can be considered bioequivalent with the 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® old formulation scored tablets (comparing old and new formulations of similar strength), with respect to rate and extent of absorption of Levothyroxine.
A marketing authorisation can be recommended from a pharmacokinetic point of view.

Résumé et conclusion générale
Toutes les questions touchant à la pharmacocinétique ont été résolues.
Sur la base des études de bioéquivalence ainsi que sur la base du biowaiver, les comprimés de la nouvelle formulation 25, 50, 75, 100, 125, 150, 175 and 200 mcg Levothyrox® peuvent être considérés comme bioéquivalents avec les comprimés de l'ancienne formulation 25, 50, 75,

100, 125, 150, 175 and 200 mcg Levothyrox® pour la vitesse et la quantité d'absorption de la lévothyroxine.
D'un point de vue pharmacocinétique, une autorisation de mise sur le marché peut être accordée.