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ORIGINAL ARTICLE

New levothyroxine formulation meeting 95–105% specification over the whole shelf-life: results from two pharmacokinetic trials

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ABSTRACT

Objective: Small levothyroxine (L-T4) dose changes can lead to significant clinical effects. To ensure thyroid hormone levels are safely maintained, authorities are increasingly adopting stricter potency specifications for L-T4, the most stringent of these being 95–105% of the labeled dose over the whole shelf-life. Levothyroxine sodium (Euthyrox, Eutirox, Lévothyrox*) has been reformulated, and two studies performed, to ensure bioequivalence to the currently marketed formulation and dosage form proportionality of the new formulation.

Methods: The bioequivalence study was an open-label, randomized, single-dose, two-period, two-sequence crossover comparing the highest dosage strengths of the currently marketed and the new L-T4 formulation at a total dose of 600 µg. The dosage form proportionality study was an open-label, randomized, three-period, six-sequence crossover, comparing 50 µg, 100 µg, and 200 µg L-T4 tablets, at a total dose of 600 µg. Blood samples were taken at predefined time intervals. Primary outcomes were area under the curve (*AUC*) and maximum concentration (C_{max}) of thyroxine (T4) in plasma.

Results: In the bioequivalence study, comparing the T4 profiles for the new and current formulation of L-T4, the geometric least square mean ratio of the baseline-adjusted $AUC_{0-72,adj}$ was 99.3% (90% confidence interval [CI]: 95.6–103.2) and the $C_{max,adj}$ was 101.7% (90% CI: 98.8–104.6). Bioequivalence was established if the 90% CI lay within the predefined 0.9–1.11 limits. In the dosage form proportionality study, pairwise comparisons ranged from 99.3% to 104.8%, and all 95% CIs were within the predefined CI range (0.8–1.25): the three dose strengths were dosage form proportional.

Conclusions: The new formulation of L-T4 meets the most stringent potency specification guidelines, and has been demonstrated to be bioequivalent to the current formulation and to show dosage form proportionality. The new formulation will enable patients to receive a dose fine tuned to their medical needs, contributing to improved safety in the use of L-T4.

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Introduction

Thyroid hormones are a critical component in the regulation of metabolic rate. Insufficient production of thyroid hormones influences every tissue of the body, causing diverse and non-specific effects, with the symptoms of hypothyroidism, such as fatigue, depression, dry skin, muscle cramps, and constipation[1]. Prolonged, severe thyroid hormone deficiency can lead to myxedema coma, a rare manifestation with high mortality rate[2]. Patients who do not sufficiently produce the thyroid hormones triiodothyronine (T3) and thyroxine (T4) require appropriate, individually fine-tuned treatment to correct the imbalance of hormones and maintain a euthyroid state[1]. The treatment of choice is the synthetic thyroid hormone levothyroxine (L-T4), which substitutes for endogenously produced T4[3,4]. L-T4 is chemically identical to the naturally secreted T4: it increases metabolic rate; decreases thyroid-stimulating hormone (thyrotropin; TSH) production from the anterior lobe of the pituitary gland; and, in peripheral tissues, is converted to T3. Besides treating patients with insufficient production of T4 from the thyroid gland (hypothyroidism), L-T4 can be used to decrease TSH secretion in euthyroid goiter and suppress relapse of differentiated thyroid cancer[5]. Often considered a narrow therapeutic window drug, small changes in dose may have significant clinical effects in sensitive patients. Therefore, dosing of L-T4 must be carefully tailored to age, sex, clinical condition, and body weight, and requires regular fine-tuning, depending on the clinical course[3,4,6,7].

The synthetic L-T4 hormone, levothyroxine sodium, is the active ingredient of the products Euthyrox, Eutirox, and Lévothyrox, currently marketed by Merck KGaA, Darmstadt, Germany. In order to provide specific doses that perfectly meet a patient's individual T4 needs, they are provided in 11 different dosage strengths covering the range of 25 µg to 200 µg T4. Therefore, patients usually only need to take one tablet per day to control their hormone levels.

Levothyroxine sodium tablets are manufactured with a shelf-life of up to 36 months and at the standard shelf-life specification of 90–110% of the label claim[8]. However, following adjustments to the potency specifications in the revised United States Pharmacopoeia (USP) monograph for

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levothyroxine sodium tablets[9], and the request by Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM)[10] for all companies to adopt this specification, increasingly authorities are adopting tighter potency specification requirements for T4[4]. To meet the more stringent potency criteria from various national regulatory bodies – the most stringent of which being 95.0–105.0% at release and over the envisaged shelf-life – the tablets have been redeveloped, with changes to the quantitative composition of excipients. Other agencies have been less stringent in their revisions, such as the Medicines and Healthcare products Regulatory Agency (MHRA), which recommends 90.0–105.0%[4]. In order to extrapolate the clinical data gained with the former formulation to the new one, a bioequivalence study with the objective of comparing the former and new formulation was carried out. A further trial was performed to establish dosage form proportionality across the new formulation tablet strengths.

Materials and methods

Overview

Two open-label, randomized, single-center studies were performed (in accordance with guidance from the European Medicines Agency [EMA], the Food and Drug Administration [FDA], and the US Pharmacopeial Convention [USP]) to test bioequivalence and dosage form proportionality[6,9,11]. The bioequivalence study compared the new formulation L-T4 (test) with the currently marketed L-T4 (reference). This study was single-dose, two-period, two-sequence crossover in design, comparing the highest dosage strength of 200 μg at a total dose of 600 μg of old and new formulation. The second study was three-period, six-sequence crossover in design, and assessed dosage form proportionality of the test formulation across three tablet strengths, 50 μg, 100 μg, and 200 μg, at a total dose of 600 μg each.

Study subjects

Subjects recruited in both studies (EUDRACT No. 2013-000274-29 and EUDRACT No. 2013-000274-33) were healthy volunteers, aged 18–50 years, with free T3, free T4, and baseline TSH within normal range. The main exclusion criterion was any medical condition or concomitant medication that may have significantly influenced the results. Subjects were randomly allocated equally to a test sequence.

Pharmacokinetic assessment

In both studies, following an overnight fast, 600 μg L-T4 was administered orally with water. In the bioequivalence study, 3 × 200 μg test or reference L-T4 were taken. In the dosage form proportionality study, L-T4 was administered as either 12 × 50 μg (A), 6 × 100 μg (B) or 3 × 200 μg (C). Subjects then remained fasted for a further 4 hours. Blood sampling was performed at predefined time intervals.

The primary endpoints for the bioequivalence study were the baseline-adjusted area under the curve from 0 to 72 hours ($AUC_{0-72,adj}$) and the baseline-adjusted maximum concentration ($C_{max,adj}$). Secondary endpoints were standard safety parameters, in addition to further pharmacokinetic (PK) parameters. Test/reference ratios of the geometric least square (LS) means of $AUC_{0-72,adj}$ and $C_{max,adj}$ and 90% confidence intervals (CIs) for the ratios were calculated. Bioequivalence was confirmed if the 90% CI for the ratios of geometric LS means for both $AUC_{0-72,adj}$ and $C_{max,adj}$ of total T4 in plasma were included in the most stringent ANSM bioequivalence acceptance interval of 90–111% for both $AUC_{0-72,adj}$ and $C_{max,adj}$.

In the dosage form proportionality study, proportionality was investigated for baseline adjusted and unadjusted parameters. Accordingly, the usual 90% confidence level was changed to 95%. Primary endpoints were $AUC_{0-72,adj}$, $C_{max,adj}$, AUC_{0-72}, and C_{max} of total T4 in plasma. The pairwise ratios of the geometric LS means were calculated (B/A, C/A, C/B). For each pairwise comparison, dosage form proportionality was confirmed if the 95% CIs for all primary parameter ratios were included in the acceptance interval 80–125%.

Results

Bioequivalence of new vs. reference formulation

From the 216 subjects randomized (108 per sequence), 204 subjects completed the trial: 103 in sequence 1, 101 in sequence 2. The baseline characteristics of the population are presented in Table 1. Overall, the population had a mean age of 34.5 ± 9.3 years, 59.3% were male, and mean BMI was 23.5 ± 2.2 kg/m^2, with similar distribution observed between the treatment sequences.

Pharmacokinetics results

The arithmetic mean total plasma T4 concentration vs. time profiles are shown in Figure 1. The profiles of the new and current L-T4 formulation are very similar to each other. The results for the primary target parameters are summarized in Table 2. The geometric LS mean ratio of the test and reference formulations for $AUC_{0-72,adj}$ was 99.3% (90% CI: 95.6–103.2%). For $C_{max,adj}$, the geometric LS mean ratio was 101.7% (90% CI: 98.8–104.6%). The CI for both of these measures lies within the acceptance interval of 90–111%, this

Table 1. Subject baseline characteristics in the bioequivalence study (safety population).

Baseline parameter	Sequence 1 $N = 108$	Sequence 2 $N = 108$	Overall $N = 216$
Age, years, mean (SD)	35.0 (9.6)	34.1 (9.1)	34.5 (9.3)
Gender			
Male, *n* (%)	64 (59.3)	64 (59.3)	128 (59.3)
Female, *n* (%)	44 (40.7)	44 (40.7)	88 (40.7)
Ethnicity			
White/Caucasian, *n* (%)	108 (100.0)	106 (98.1)	214 (99.1)
Black/African American, *n* (%)	0	2 (1.9)	2 (0.9)
BMI, kg/m^2, mean (SD)	23.4 (2.0)	23.5 (2.3)	23.5 (2.2)

BMI: body mass index; SD: standard deviation.
Sequence 1: new formulation levothyroxine (test), followed by currently marketed formulation levothyroxine (reference); sequence 2: currently marketed formulation levothyroxine (reference), followed by new formulation levothyroxine (test).

being the most stringent of the conditions stipulated for bioequivalence to be determined. Therefore, the new formulation can be considered bioequivalent to the currently marketed formulation.

Safety results

Overall, both formulations were well tolerated, with 204 subjects completing the study as planned per protocol. Treatment-emergent adverse events (TEAEs) were similar for both formulations, with headache being the most frequently reported drug-related TEAE (test: 7.7% subjects with 22 events vs. reference: 7.6% subjects with 26 events). Four subjects were withdrawn from the trial due to adverse events (AEs) and two due to severe adverse events (SAEs). These were all considered unrelated to the study drug.

Dosage form proportionality of new formulation levothyroxine

From the 42 subjects randomized to 6 sequences (7 per sequence), 37 subjects completed the trial. The baseline characteristics of the population are presented in Table 3. Overall, the population had a mean age of 34.9 ± 10.1 years, 45.2% were male, and the mean BMI was 22.95 ± 2.12 kg/m^2.

Pharmacokinetics results

Figure 2 shows the arithmetic mean concentration–time profiles for total plasma T4 measured in the dosage form proportionality study. The three dose variants, 12 × 50 μg (A), 6 × 100 μg (B), and 3 × 200 μg (C), were observed to have similar concentration vs. time profiles. To test for dosage form proportionality, all pairwise comparisons between the different dosage forms for baseline adjusted and non-adjusted primary target parameters (AUC_{0-72} and C_{max}) of total plasma T4 are shown in Table 4. The treatment ratios ranged from 99.3% ($C_{max,adj}$ for C/B) to 104.8% ($AUC_{0-72,adj}$ for C/B). All the 95% CI of the geometric LS mean ratios were within the predefined bioequivalence limits of 80–125%. Accordingly, the three dosage forms (50 μg, 100 μg, and 200 μg tablets) of the new L-T4 formulation administered as 600 μg single doses were determined to be dosage form proportional.

Safety results

Thirty-seven subjects completed the study, and all three dosage strengths were well tolerated, with a similar incidence of TEAEs reported at each dose (TEAEs reported: 27 by 11 subjects, 27 by 16 subjects, and 31 by 13 subjects, for the dosage forms 50 μg, 100 μg, and 200 μg, respectively). The most frequently reported AE was headache (22 of 85 TEAEs). Two subjects were withdrawn due to an AE: one subject due to

Table 2. Summary of ANOVA of primary pharmacokinetic parameters for baseline-adjusted total T_4 (pharmacokinetic population).

Parameter	Geo-LSMean		Ratio (Test/Reference) % (95% CI)	Intra-CV%
	Test ($n = 204$)	Reference ($n = 204$)		
$AUC_{0-72,adj}$ (hr*ng/ml)	1852.1	1864.4	99.3 (95.6–103.2)	23.7
$C_{max,adj}$ (ng/ml)	53.5	52.7	101.7 (98.8–104.6)	17.7

CI: confidence interval; CV%: coefficient of variation percentage; Geo-LSMean: geometric least square mean; test, new formulation levothyroxine; reference, currently marketed levothyroxine.

Table 3. Subject baseline characteristics in the dosage form proportionality study (safety population).

Baseline parameter	$N = 42$
Age, years, mean (SD)	34.9 (10.13)
Gender	
Male, *n* (%)	19 (45.2)
Female, *n* (%)	23 (54.8)
Ethnicity	
White/Caucasian, *n* (%)	42 (100.0)
BMI, kg/m^2, mean (SD)	23.0 (2.1)

BMI: body mass index; SD: standard deviation.

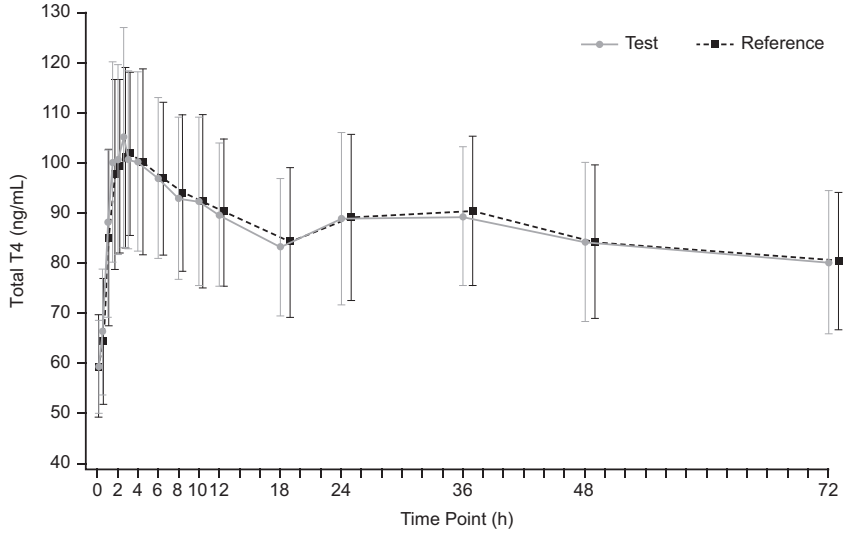

Figure 1. Concentration–time profiles for plasma T4 in bioequivalence study (PK population). Arithmetic mean (± standard deviation) of plasma total T4 vs. time following 600 μg test (grey circles) or reference (black squares) levothyroxine.

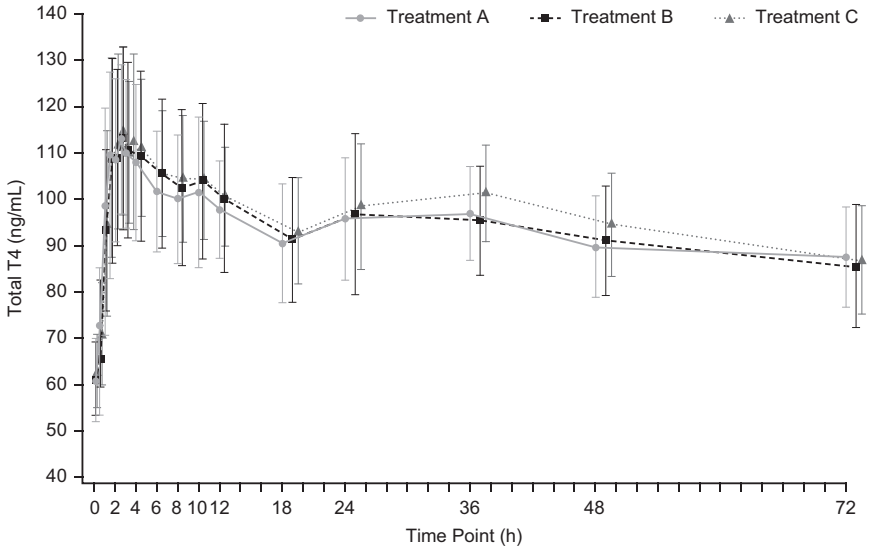

Figure 2. Concentration–time profiles for plasma T4 in dosage form proportionality study (PK population). Arithmetic mean (± standard deviation) of plasma total T4 vs. time following 600 µg test levothyroxine formulation as 12 tablets of 50 µg (treatment A; light grey circles); 6 tablets of 100 µg (treatment B; black squares) or 3 tablets of 200 µg (treatment C; dark grey triangles).

Table 4. Summary of ANOVA of the primary pharmacokinetics parameters for baseline-adjusted and non-adjusted total plasma T4 in the dosage form proportionality study.

Parameter	Geo-LSMean ($n = 37$)			Ratio of Test Treatments, % (95% CI)			Intra-CV, %
	A	B	C	B to A	C to A	C to B	
$AUC_{0-72,adj}$ (hr*ng/ml)	2237.7	2223.0	2329.4	99.3 (91.8–107.5)	104.1 (96.2–112.6)	104.8 (96.8–113.4)	17.1
$C_{max,adj}$ (ng/ml)	59.8	62.1	61.8	103.8 (96.7–111.5)	103.2 (96.1–110.8)	99.4 (92.6–106.8)	15.5
AUC_{0-72} (hr*ng/ml)	6772.4	6781.0	6884.6	100.1 (97.6–102.7)	101.7 (99.1–104.2)	101.5 (99.0–104.1)	5.4
C_{max} (ng/ml)	122.9	125.1	125.0	101.8 (98.4–105.3)	101.7 (98.3–105.2)	99.9 (96.6–103.3)	7.3

CI: confidence interval; CV%: coefficient of variation percentage; Geo-LSMean: geometric least square mean; T4: thyroxine.
Treatment A: 12 × 50 µg of new formulation levothyroxine; treatment B: 6 × 100 µg of new formulation levothyroxine; treatment C: 3 × 200 µg of new formulation levothyroxine.

an SAE unrelated to the study medication, and one subject due to an AE of mild vomiting.

Discussion

Both American and European medical authorities are adopting tighter potency specifications for L-T4. Currently, the most stringent of these revised specifications is 95–105% of the label claim, set out by the ANSM and the US Pharmacopeia. L-T4 tablets have therefore been redeveloped to meet these potency specifications over a reasonable shelf-life of at least 24 months. In order to extrapolate clinical data from the currently marketed formulation, demonstration of the bioequivalence of the new and current formulation is required[12–14]. The results of the present study support the conclusion that the newly developed levothyroxine sodium tablets are bioequivalent to the previously marketed tablets. Furthermore, the results of the second trial demonstrate dosage form proportionality for the 50 µg, 100 µg, and 200 µg tablets.

The revised specifications have the ultimate purpose of ensuring that patients receive the appropriate level of medication required to treat their thyroid disorder. Accurate dosing in L-T4 is of particular importance: the sensitivity of patients to the active ingredient varies considerably; it is thus considered a critical dose drug[4,6,15]. Consequently, relatively small differences in dose may result in significant clinical consequences[4,6,15]. Close titration and regular monitoring is required to ensure thyroid hormone levels are safely maintained. Pregnant women, the developing fetus, and patients with thyroid cancer are particularly susceptible to incorrect dosing[4,15]. Decreased absorption due to concomitant medications or a high-fiber diet may require the dose to be adjusted, and drugs that accelerate metabolism also affect the dose needed[3,5,16–19].

The control of TSH levels by TSH-releasing hormone (TRH) is highly sensitive to thyroid hormone levels via negative feedback mechanisms. A study of chronic treatment with small doses of T3 and L-T4 (15 and 60 µg, respectively, per day) in clinically normal subjects caused a 76% reduction in the TSH response to 400 µg TRH, while serum thyroid hormone concentrations remained within the normal range. In patients with partially treated primary hypothyroidism, a small increase in dose inhibited the serum TSH response to TRH from above normal or upper normal to below normal[20]. Due to the high sensitivity of the negative feedback control of thyroid hormone concentrations, variability in the dose of L-T4 may lead to a loss of control in some patients[4]. The resultant under- or over-treatment of hypothyroidism can have a considerable negative impact on patients and resources[21]. A study investigating the effects of a small increase or decrease in L-T4 dose in patients with normal TSH found

that altering the dose by 25 μg/day caused TSH levels to diverge outside of the normal range in most subjects[22]. The pathological effects of mildly abnormal TSH levels are changes in lipid levels, cardiac function, and other parameters of thyroid action[5,23]. There is also evidence that high TSH levels within the normal range increase the likelihood of metabolic syndrome[24].

Generally, TSH-suppressive doses of L-T4 are associated with arrhythmias, decreased left ventricle function, bone loss, and fractures[21,25]. The risks associated with over-treatment have been found to depend on the level of TSH: between 0.1 and 0.5 mU/L TSH, the risk of atrial fibrillation increases somewhat; however, suppression of TSH to <0.1 mU/L greatly increases this risk[25]. In fact, in patients with coronary heart disease, a small increase in L-T4 dose can have SAEs[6]. Over extended time periods, over-treatment leading to TSH suppression is associated with osteoporosis, especially in postmenopausal women[26–28]. Under-treatment of patients, especially a serum TSH level above 10 mU/L is associated with the clinical aspects of hypothyroidism, weight gain, and cardiovascular problems, i.e. atherosclerosis and hypertension[5,23,29].

Since the tightening of the potency specifications for L-T4 by the medical authorities is intended to improve the quality and consistency of the product to ensure that patients receive the precise level of medication required, the risks associated with over- and under-treatment of L-T4 necessitate consistent potency and bioavailability to minimize risks for patients[4,30]. While substitution of the drug with a product with a lesser potency or bioavailability may generate a suboptimal response and fail to adequately treat the hypothyroidism, substitution with a drug of greater potency or bioavailability could result in a potentially hazardous hyperthyroid state[6].

In conclusion, in the present paper, we have demonstrated the bioequivalence and dosage form proportionality of the new formulation of L-T4 that meets the tighter potency specifications, and satisfies the most stringent guidelines published. Once available, this new formulation will provide a product that enables physicians to make a more precise prescription, and allows patients to receive a dose fine-tuned to their medical needs. With more precise control of thyroid hormone levels, the new formulation will contribute to improved safety in the use of L-T4.

Transparency

Declaration of funding

This study was funded by Merck KGaA, Darmstadt, Germany.

Author contributions: All authors were involved in the concept and design of the study, analysis and interpretation of data, and critical revision of the manuscript. All authors also provided approval for submission of the manuscript and are fully accountable for all aspects of the work.

Declaration of financial/other relationships

U.G.-H. and P.W. have disclosed that they are employees of Merck KGaA. W.U. has disclosed that he is a former employee of Merck KGaA. G.J.K. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article.

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