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BRIEF REPORT

A new formulation of levothyroxine engineered to meet new specification standards

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ABSTRACT

Background: Small variations in the dose of levothyroxine have been associated with marked variations in thyroid function in people with hypothyroidism. Accordingly, regulators have identified levothyroxine as a "narrow therapeutic index" drug subject to more stringent regulations compared with other drugs, in terms of the accuracy and stability of the amount of active drug in each tablet (typically required to be 95–105% of the labelled amount over its full shelf life), and its bioavailability geometric mean ratios (90% confidence intervals between 90–111.1%, including 100%).

Review: This review describes a reformulation of a widely used levothyroxine product (Euthyrox.*). The new tablet fulfils all criteria according to the new specification regulations for dosage accuracy over a shelf life of 3 years in all climate zones, and for bioequivalence compared to the conventional formulation used for many years. In addition, a clinical trial demonstrated equivalent exposure between three different tablet strengths of the new formulation, amounting to the same total dose (dose form proportionality). As a consequence, switching from the conventional to the new formulation can be undertaken on a 1:1 dose-for-dose basis, without re-titration or additional thyroid function testing.

Conclusion: The new formulation, which is more stable, will assist in the accurate dosage and titration of levothyroxine in the management of hypothyroidism.

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Introduction

Thyroid disorders are common among patients managed in the primary care setting, and hormone replacement therapy with levothyroxine (T4) is the mainstay of management for people with an underactive thyroid (hypothyroidism)[1,2]. Indeed, levothyroxine has been the most-prescribed drug in the US in recent years[3]. Regulatory standards for the manufacturers regarding the specification of levothyroxine preparations have become more stringent in recent years[4–6] (described below), and some existing preparations needed a reformulation as a consequence. Here, we describe a new formulation of a widely used levothyroxine preparation, Euthyrox* New Formulation (NF), developed to meet these tightened requirements. A summary of the development and properties of the new formulation is followed by a summary of practical information relevant to its therapeutic use.

New regulatory standards for new formulations of levothyroxine

For any change of an approved formulation, a new bioequivalence study must be performed. However, standards for potency, bioequivalence between levothyroxine formulations, and stability (shelf life) have been progressively tightened in recent years. For example, in 2009, the US Food and Drug Agency (FDA) required tighter specification of the levothyroxine content of tablets over the product's expected shelf life, from 90–110% to 95–105% of the active ingredient[7]. Similar regulatory changes (95–105%) have been required in France by the Agence Nationale de Sécurité du Médicament et des Produits de la Santé (ANSM) in 2012[8], followed by other countries, whereas in the UK the margins for specification required by the Medicines and Healthcare Products Regulatory Agency (MRHA) are broader (90–105%)[9]. Further countries are likely to follow in requesting tightening of the specification for levothyroxine in the near future.

Approval of generic levothyroxine drugs or new formulations of marketed products must also meet the stricter criteria for bioequivalence with existing formulations, according to regulatory guidance[10], with the focus on the drug exposure over time (AUC) as well as plasma peak levels (C_{max})[11]. For most drugs, bioequivalence is concluded when the 90% confidence intervals (90% CI) of the geometric mean ratios of the AUC and C_{max} between test and reference fall within the acceptance range 80–125%. This does not apply to levothyroxine, however, because it is considered as a narrow therapeutic index (NTI) drug. Levothroxine is a prodrug for the biologically active hormone, triiodothyronine, and it is used in the management of hypothyroidism due to the observation that a log-linear relationship exists between its dosage and biological action (reducing thyroid stimulating

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Table 1. Details of the pharmacokinetic evaluation of Euthyrox NF in two randomized, single dose, parallel-group clinical trials in healthy volunteers.

	Bioequivalence study	Dose proportionality study
EudraCT no.	2013-000274-29	2013-000274-33
Subjects	Healthy volunteers (18–50 years, free T4, free T3 and TSH within normal ranges)	
n	216	42
Mean age (years)	34.5 ± 9.3	34.9 ± 10.1
Mean BMI (kg/m^2)	23.5 ± 2.2	23.0 ± 2.1
Randomized to	3 × 200 µg NF or OF	12 × 50 µg, 6 × 100 µg or 3 × 200 µg NF
Primary endpoints	$AUC_{(0-72,adj)}$[a] and $C_{max,adj}$[b]	$AUC_{(0-72,adj)}$[a]; $C_{(max,adj)}$[b]; $AUC_{(0-72)}$; C_{max}

Subjects received a single 600 µg dose of either the new formulation (NF) or the old formulation (OF) of levothyroxine in either study.
Abbreviations: BMI, body mass index; EudraCT, European Clinical Trials Database (https://eudract.ema.europa.eu); T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.
Endpoints: [a]baseline-adjusted area under the plasma concentration time curve, [b]maximal plasma concentration: each for total T4 from dosing to 72 h.
Means ± SD shown where applicable. Compiled from data presented in Zarbock et al.[16]

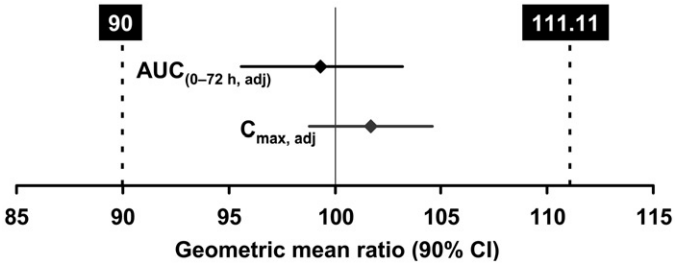

Figure 1. Bioequivalence of new vs old formulations. $AUC_{(0-72\,h,\ adj)}$: baseline-adjusted area under the plasma concentration time curve, $C_{max,\ adj}$: maximum plasma concentration: each for total T4 from dosing to 72 h. Drawn from data presented in Gottwald-Hostalek et al.[17]

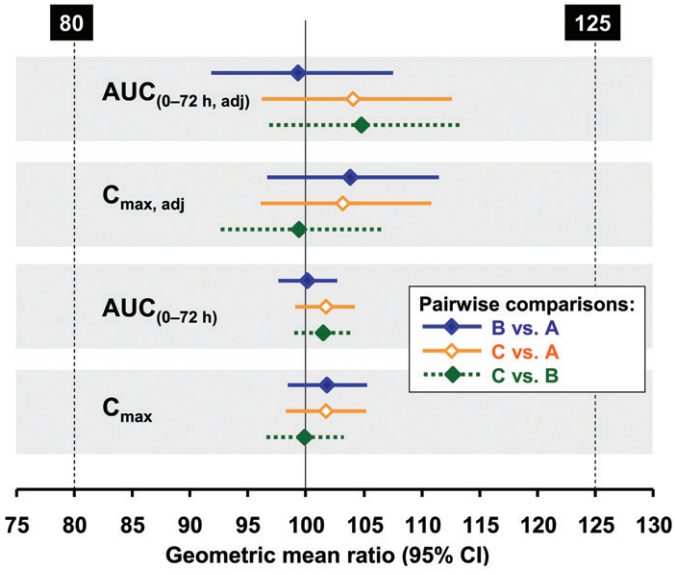

Figure 2. Comparable exposure to a 600 µg dose of levothyroxine new formulation from three regimens made up of different tablet strengths. New formulation study treatments: (a) 12 × 50 µg tablets; (b) 6 × 100 µg tablets; (c) 3 × 200 µg tablets. The use of 95% CI (as opposed to 90% CI for the formal evaluation of bioequivalence shown in Figure 1) is appropriate for this study as it evaluated parameters both with and without baseline adjustment; 95% CI within 80–125% confirms dose form proportionality. Drawn from data presented in Gottwald-Hostalek et al.[17]

hormone levels) in most individuals[12]. This amplification of its effects results in a relatively steep dose-response curve that explains the categorization as a "narrow therapeutic index drug".

In this case, according to the requirements of European health authorities, the 90% CI for geometric mean ratios of AUC and C_{max} has to lie between 90% and 111.1%, rather than the broader range described above. The healthcare professionals (treating physicians and pharmacists) are probably the most appropriate stakeholders to convey this information to patients. The same is true for other NTI drugs[13] such as cyclosporine A.

Pharmaceutical development of Euthyrox NF

New tablet formulation

The physico-chemical stability of the conventional formulation was increased by replacement of its lactose excipient with mannitol and by adding small amounts of citric acid; these changes prevent a reaction between lactose and levothyroxine resulting in levothyroxine-2-ketolactose, the main degradation product found in the old formulation (OF) tablet. The shelf life of all tablet strengths of this new formulation (NF) is 3 years in all climate zones (assessed using standard and approved methodology[14]), with the proportion of active ingredient remaining within the regulatory limits (see above) throughout this period. The NF may also be used in patient sub-groups with certain rare hereditary disorders of galactose metabolism[15,16]. The availability of all previous tablet strengths remained unchanged.

Bioequivalence of new vs old formulation

A clinical trial in healthy volunteers evaluated the bioequivalence of the NF vs the OF (Table 1)[16]. Mean values of the co-primary endpoints were similar for the NF and OF (mean baseline-adjusted $AUC_{(0-72\,h)}$ was 1852.1 and 1864.4 (h.ng/mL, respectively, and mean baseline-adjusted C_{max} was 53.5 and 52.7 ng/mL, respectively. The mean AUC and C_{max} ratios were 99.3% and 101.7%, respectively, with a 90% CI well within the 90–111.1 range (Figure 1). Therefore, the NF met the strict formal criteria for bioequivalence for a NTI drug compared with the reference.

Dose form proportionality

In addition to the bioequivalence study, a clinical dose-form proportionality study was performed with the NF[17]. This study compared three 600 µg doses of the new formulation, made up of lower (twelve 50 µg L-T_4 tablets), medium (six 100 µg L-T_4 tablets), and highest strength tablets (three 200

μg L-T_4 tablets) given to healthy volunteers (Table 1). Figure 2 shows that each of the three possible pairwise comparisons of study treatments met the formal criteria for dose form proportionality relevant to this study design.

Using the new formulation in practice

A number of factors can determine absorption of, and the therapeutic response to, levothyroxine in the individual patient, including gastrointestinal disorders, concomitant medications or vitamin supplements, diet, concurrent infections of comorbidities, weight gain, pregnancy, and others[18–20]. Levothyroxin NF, described above, has a more accurate and stable proportion of the active ingredient over time, in line with emerging regulatory requirements around the world. Thus, the new formulation will allow more precise and accurate dose titration of this NTI drug. This is relevant to all patients with hypothyroidism, but may be especially important for some patients with complex or unpredictable responses to LT4 therapy, as described above[18–24].

As the NF is fully bioequivalent to the OF, the risk/benefit balance of both formulations is similar. Moreover, the drug exposure did not vary significantly according to the tablet strengths taken, for a given total dose of levothyroxine. Therefore, patients can make up their prescribed dose of levothyroxine using any combination of the new formulation tablets. Switching from the OF to the NF can be performed dose-for-dose, without need for additional TSH testing or titration of therapy, followed by routine measurement of TSH levels in the usual way. Dose adjustments may be considered in the case of any adverse event.

One of the changes made to the new formulation was the removal of lactose. The amount present in each tablet was small, and unlikely to provoke symptoms in a patient with this condition, as observed previously[25]. Nevertheless, the presence of lactose could be a concern for some patients, who may attribute gastrointestinal symptoms to the presence of lactose, irrespective of their true causality[26]. It is important to bear in mind that theremoval of lactose from the tablet was primarily to improve its stability. In general, it is good practice to inform patients of the new formulation, at the time of switching, to explain the improvements in formulation and the reasons for developing it. The treating physicians and pharmacists, as well as other healthcare providers, are important stakeholders to help patients to receive and understand this information.

In conclusion, this new formulation provides more accurate and reproducible dosing of levothyroxine to support timely and precise dose titration with a stable amount of the active ingredient over the product's shelf life.

Transparency

Declaration of funding

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

Declaration of financial/other interests

H-PL has no relationships with or financial interests in any commercial companies related to this article. UH is an employee of Merck KGaA. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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