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.

Keywords: Bioequivalence, dosage form proportionality, levothyroxine, pharmacokinetic trials, specification