

Draft Guidance on Levothyroxine Sodium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Levothyroxine sodium

Dosage Form; Route: Capsule; oral

Recommended Studies: One study

Type of study: Fasting

Design: Single-dose, four-way, fully replicated crossover in vivo

Strength: 0.2 mg at the dose of 0.6 mg (3 x 0.2 mg)

Subjects: Males and non-pregnant, non-lactating females, general population

Additional Comments:

1. Females should not be pregnant or lactating, and should practice abstinence or use appropriate forms of contraception during the study.
2. Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine may be truncated to 48 h post-dose.
3. Given the numerous drug-drug interactions for levothyroxine sodium, caution should be exercised in administering concomitant medications during the study.
4. Post-dose levothyroxine measurements by the baseline levothyroxine value should be corrected in each period for each subject.
5. The baseline value should be obtained from the average of three levothyroxine measurements taken before dosing (i.e., at 0.5 h, 0.25 h, and 0 h pre-dose).
6. Use the reference-scaled average bioequivalence approach for properly adjusting the bioequivalence acceptance criteria based on reference variability and comparing test and referenced product within-subject variability. For details about the Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, refer to the Guidance on Warfarin Sodium Tablets.

Analyte to measure (in appropriate biological fluid): Levothyroxine in serum

Bioequivalence based on (90% CI): Baseline-corrected levothyroxine

Waiver request of in-vivo testing: 0.013 mg, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, and 0.175 mg strengths based on (i) acceptable

bioequivalence study on the 0.2 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Explanation: FDA has concluded that levothyroxine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow;
- Some levothyroxine-associated toxicities are serious and/or irreversible;
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes;
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity;
- Therapeutic drug monitoring is routinely employed to facilitate levothyroxine dose titration; and
- Levothyroxine has small-to-medium within-subject variability.

The study design should be a fully replicated crossover approach to

- Scale bioequivalence limits to the variability of the referenced product; and
- Compare test and referenced product within-subject variability.