

## BIOEQUIVALENCE OF SODIUM LEVOTHYROXINE

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### Introduction

The Endocrine Society is concerned that patients are frequently being placed at risk by the undisclosed substitution of sodium levothyroxine (L-T4), a prescription medication used for the treatment of thyroid disease. While substitutions of most prescription medications usually have no effect on an individual, a change from a patient's established source of L-T4 can result in deleterious health effects. Several manufacturers produce L-T4, a synthetic version of a hormone made naturally in the body (thyroxine or T4). The body is very sensitive to small alterations in thyroid hormone levels, which physicians control in patients with thyroid disease by administering precise doses of L-T4. L-T4 doses from different manufacturers that the U.S. Food and Drug Administration (FDA) considers the same (ie bioequivalent) can, in fact, deliver significantly different amounts of drug to the patient, resulting in different biological responses and potential clinical problems. Under the FDA's current ruling, patients can be switched between certain sources of L-T4 without the express written consent of the prescribing physician. Furthermore, not all manufacturers include instructions to patients to consult their physicians for further testing if they are switched from one L-T4 product to another. These practices put patients at risk for adverse biological effects and burden the healthcare system when physicians have to determine the source of the patient's problem and re-determine the dose of L-T4 the patient should receive.

### Background

Thyroid hormones regulate important biological functions, including metabolism, the nervous system, and the cardiovascular system. The thyroid system is also important for proper growth and development in children, including a critical role for normal brain development in infants and toddlers.

When assessing thyroid function, measurement of serum concentrations of the pituitary hormone thyroid stimulating hormone (TSH) is a more sensitive indicator of the body's exposure to thyroid hormone than the direct measurement of thyroid hormone levels in the blood. TSH is controlled by thyroid hormones; high

levels of T4 suppress TSH, and low levels result in increases in serum TSH levels (classic negative feedback). Small changes in TSH levels, even in the absence of measurable changes in blood levels of thyroid hormone, have been associated with significant adverse clinical consequences. For example, a subnormal TSH can be associated with an increased risk of abnormal heart rhythms that have been associated with stroke, while a high TSH in a patient with thyroid cancer can cause growth of the cancer. It is therefore critical that the regulation of TSH by thyroxine be precise.

A pharmacovigilance study conducted by The Endocrine Society, the American Association of Clinical Endocrinologists, and the American Thyroid Association in 2007 resulted in reporting of 160 adverse events related to switching sources of L-T4, 85% of which were done by the pharmacy, as mandated perhaps by state pharmacy laws, without the knowledge of the prescribing physician.<sup>1</sup> That's nearly three times the number of events that caused the FDA in 1997 to begin requiring that L-T4 products be approved under a New Drug Application or Abbreviated New Drug Application, an action the Agency took after receiving 58 adverse event reports related to the use of L-T4. The FDA's recent focus on tablet dissolution time and tightening the requirements for accuracy of tablet content of L-T4 is appropriate, but is not a surrogate for providing accurate bioequivalence data, which would require adopting a method to measure TSH in preferably thyroidectomized individuals who receive graded doses of L-T4. Nonetheless, the Agency continues to claim bioequivalence of L-T4 products based on flawed methodology and does not require product labeling to alert patients or physicians to the potential adverse effects of switching between L-T4 brands.<sup>2</sup>

<sup>1</sup> Preliminary analysis of Pharmacovigilance Survey data; presented to FDA on 10-06-06 and available at <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4228-OPH1-03%20Hennessey.pdf>

<sup>2</sup> Joint Statement on the U.S. Food and Drug Administration's Decision Regarding Bioequivalence of Levothyroxine Sodium; American Thyroid Association, The Endocrine Society, and American Association of Clinical

For most drugs that it monitors, the FDA uses a standard system to determine if two versions of that drug are the same (or bioequivalent). For L-T4, large amounts of the two versions to be compared are given to a number of healthy volunteers, and the amount of the drug in the blood after a specified period of time is measured. Drugs are determined to be bioequivalent if these measurements are similar (plus or minus an allowable and unavoidable margin of error). This “one size fits all” approach does not work for L-T4 for several reasons: T4 is made naturally in the body (administered L-T4 is not the only source of the measured hormone); the thyroid system is in delicate balance; and small changes in thyroid hormones can greatly disrupt this balance and this may not be appreciated by measurement of thyroid hormone levels alone. Furthermore, the standard of care for physicians is to monitor the more sensitive serum TSH levels, which may change in the absence of measurable changes in T4 levels, when assessing the thyroid status of patients. The inherent margins of error in the FDA’s method are large enough that two versions of L-T4 that are determined to be bioequivalent could have vastly different clinical effects. In summary, bioequivalence as determined by the FDA is not therapeutic equivalence – a much more clinically important measure.

### Considerations

Though bioequivalence is determined by the FDA, generic substitution laws and practices are determined on the state level. As of 2005, most states required and/or permitted substitution of an FDA-approved bioequivalent generic drug for the brand-name drug.<sup>3</sup> Given this, the FDA must take great care in determining bioequivalence as it is the first line of defense for patients. In order to ensure patients’ safety and good health, the FDA must reverse its current ruling of bioequivalence among L-T4 products and use a more sensitive and clinically relevant method to determine bioequivalence of these drugs, which must take into account that the entire thyroid system must be stabilized in patients with thyroid dysfunction over a long period of time.

The most sensitive and clinically relevant measure of thyroid function is serum TSH concentration and not the level of thyroid hormone in the blood. With significant time and effort, doctors can stabilize TSH when treating patients with L-T4.<sup>4</sup> They do this by testing different doses of one brand of medication and measuring the patient’s TSH levels over time. When the physician finds the dose and preparation that maintains TSH at ideal levels, it is critical that the patient not stray from this dose or preparation. Unfortunately, under the FDA’s current determination of L-T4 bioequivalence, there is no guarantee that a patient’s effectively absorbed dose will remain constant enough to stabilize TSH levels if the patient is switched from product to product.

Even a slight change in L-T4 dose—such as one that might be encountered when a patient is switched from one source of L-T4 to another—can alter TSH levels and adversely affect cardiac and brain function, among other things. These effects are even more pronounced in children, who can also suffer long-term developmental delay.

In order to ensure the safety of patients, the FDA should determine bioequivalence of L-T4 products based on equivalent stabilization of TSH over time in appropriate subjects and not on a snapshot of the level of L-T4 in the blood of normal volunteers after administration of large doses of the drug.

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Endocrinologists; [http://www.endo-society.org/publicpolicy/policy/upload/Joint\\_Statement\\_Levothyroxine-Thyroxine.pdf](http://www.endo-society.org/publicpolicy/policy/upload/Joint_Statement_Levothyroxine-Thyroxine.pdf).

<sup>3</sup> Avalere Health news release; <http://www.avalerehealth.net/wm/show.php?c=1&id=636>.

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<sup>4</sup> [http://www.endo-society.org/publicpolicy/legislative/testimony/upload/Becker\\_Bioequivalence\\_Testimony.pdf](http://www.endo-society.org/publicpolicy/legislative/testimony/upload/Becker_Bioequivalence_Testimony.pdf)

## Positions

The Endocrine Society is concerned that patients are being placed at risk when their L-T4 prescriptions are switched between brands, from a brand to a generic, or from one generic to another. This switching can occur without the knowledge of the prescribing physician. Though not recognized by FDA's current methods for determining bioequivalence, changes in L-T4 source may result in a large enough difference in dose to cause deleterious effects in a patient's health due to therapeutic non-equivalence. Therefore, the Society supports the following actions:

- Congress should encourage the FDA to design and implement a method to determine therapeutic bioequivalence of L-T4 that will consider TSH levels over time, the most sensitive and clinically relevant measure of L-T4 efficacy.

Until such time as new methods are in place, the Society requests the following actions be taken to protect patients and decrease the burden on the healthcare system in the short term:

- The FDA should rescind its current determinations of bioequivalence among L-T4 products and instead announce that the products have not been shown to be bioequivalent. This will ensure that patients' prescriptions are not switched without the order of the prescribing physician thus eliminating the automatic (state required/permitted) substitution of L-T4 products
- The FDA should require patient warning information in L-T4 products emphasizing the importance of consulting the prescribing physician if the source of L-T4 is switched.
- Physicians who are not thyroid specialists must be fully informed of the potential consequences of even slightly altered doses of L-T4. Therefore, physician-targeted information in L-T4 products must clearly communicate the potential problems with even slight alterations in dose and the need to re-evaluate the patient upon substitution.