

May 16, 2005

Dear Gentlemen & Gentlewomen:

I am writing this letter to the FDA to plead for a more stringent evaluation for FDA approval of various brand and generic levothyroxine preparations. As a past Secretary and President and recipient of many awards from the American Thyroid Association, a previous member and chair of NIH study sections, a past member of the Endocrine Society Council, a recent member of an NAS Committee to recommend guidelines for iodine supplementation in the event of a nuclear reactor accident, a co-editor (with Dr. Robert Utiger) of the major thyroid text since 1985 (2005 latest edition), a past Editor-in-Chief of the Journal of Clinical Endocrinology and Metabolism and the current Editor of Current Opinion in Endocrinology & Diabetes, author of more than 500 publications in refereed journals and invited reviews and chapters, educator, and, above all, actively engaged in caring for patients with disorders of the thyroid for 45 years, I feel that I can comment on the bioequivalence of levothyroxine sodium (L-T4) products.

Since L-T4 is a narrow therapeutic range drug, it is imperative that L-T4 preparations have consistent and accurate action when ingested orally. Rather than the current 0.8 to 1.25 recommended bioequivalence range, a far more stringent narrow range of 0.9 to 1.10 should be instituted. This is especially important in view of the recent approval of many generic L-T4 preparations, resulting in a flood of frequent substitutions of the various brand and generic L-T4 preparations currently available at the pharmacy. Although the FDA has recommended, but not mandated, that pharmacists inform patients that they must be retested with a serum TSH in approximately three months when L-T4 preparations are switched from brand to generic and generic to generic, it is my experience that this recommendation to patients is never stated by the pharmacist. The FDA should *mandate* that this information be given to patients when a new L-T4 preparation is given. The inconvenience and cost both in time and money to the patient is unfair and certainly inconvenient.

The use of accurate and consistent L-T4 dosing is especially important in patients with thyroid cancer, pregnant women and the elderly since under- and over-treatment can be and is clinically harmful. In the past year, since the flood of various generic L-T4 preparations have reached pharmacies nationwide, I have had at least 20 patients who were switched from brand to generic L-T4 preparations who required readjustment of their serum TSH concentrations to the desired level. This is absolutely not appropriate for L-T4 substitution therapy in this current milieu in a nation which prides itself in the excellence of its medical care.

Of greater importance is the current method the FDA is using to determine bioequivalence of L-T4 preparations. No current method can accurately assess therapeutic equivalence of L-T4 preparations (a narrow therapeutic equivalence medication) since the only measure required is an assessment of serum L-T4 concentrations following the oral administration of L-T4 and not, as in anticoagulation therapy (INR or prothrombin time), a

biological or *therapeutic* end point. In the case of disorders of the thyroid, the serum TSH is the current and best indicator of the therapeutic equivalence of L-T4 preparations. Yet, serum TSH data is not currently required to evaluate the efficacy and consistency of various L-T4 preparations. Until such studies in athyreotic patients are carried out, interchange from brand to generic L-T4 preparations should not be permitted. I realize that such studies would be expensive and difficult to carry out and, until such time as they are conducted, the least that the FDA can do is to narrow the approval variability of L-T4 preparation from 0.8 to 1.25 to 0.9 to 1.1 and to *mandate* that substitution from brand to generic, generic to generic, or brand to brand require a serum TSH retest at approximately three months after the switch.

Thank you for considering this statement.

Sincerely yours,

Lewis E. Braverman, M.D.
*Chief, Section of Endocrinology, Diabetes
and Nutrition*
Boston Medical Center
Professor of Medicine
Boston University School of Medicine