

May 11, 2005

Docket #2005N-0137  
Divisions of Dockets Management (HSA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

To Whom It May Concern:

We, the undersigned, are writing this letter in support of the position of the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society regarding bioequivalence of thyroxine preparations. We are submitting it in anticipation of the meeting on this topic on May 23, 2005.

We represent the Thyroid Core Group of the Division of Endocrinology at Mayo Clinic, Rochester, Minnesota. The Thyroid Core Group consists of seven clinicians and two clinical laboratory directors, who spend the majority of our time seeing and caring for patients with thyroid disorders. Cumulatively, we represent more than 200 clinician-years of this practice and represent one of the largest groups of thyroid specialists in the World. No member of our group has any conflict of interest with any of the manufacturers of levothyroxine, either branded or generic.

Levothyroxine is the most commonly prescribed medication for patients with thyroid disease. Consequently, we have a particular interest in the recent issue of bioequivalence. We have been troubled by the decisions of the FDA regarding this issue, and after careful consideration, we believe that the FDA should reconsider its position. We are aware of the pre-existing data and the background behind the decisions of the FDA regarding generic equivalence of thyroxine preparations. We agree completely with the joint position statement of the AACE, TES, and ATA regarding use and interchangeability of thyroxine products. In particular, we agree with the need for measuring TSH in the assessment of bioequivalence of thyroxine preparations.

Although we have not scientifically studied this issue in our own laboratory, we each have numerous examples in our patients who have been switched knowingly or unknowingly by their pharmacist to generic levothyroxine only to have significant changes in their TSH levels that require re-titration of the dose. While this may be of minimal significance for some patients, there are many others for whom even small changes can be clinically relevant. This is particularly the case for patients with thyroid cancer, who require thyroid hormone suppression, and elderly patients, who may be more susceptible to cardiac consequences of hyperthyroidism. Furthermore, there is widespread acceptance that, amongst pregnant women, especially those who have had prior surgery or radioiodine ablation, the maintenance of uniform thyroxine and TSH concentration is critical to ensure normal fetal development and health.

Collectively, we have spent numerous hours fielding phone calls or in face to face interviews with our patients explaining the reasons behind the changes in the formulation of their levothyroxine and why it may be causing these difficulties. We now must routinely counsel our patients not to accept generic substitution and inform the pharmacist through our prescriptions similarly to disallow this substitution.

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It has increased the level of concern and anxiety on the part of our patients substantially, increased our workload, and has had a significant negative impact on the management of patients with thyroid disease.

We urge the FDA to reconsider its decision regarding bioequivalence of levo-thyroxine preparations. In particular, it is essential that there be sufficient recognition that the TSH measurement be accepted as the only appropriate end-point in the objective assessment of thyroid hormone bioequivalence. The current table of bioequivalence allows free substitution from any brand of thyroxine to almost any other brand of thyroxine or generic in step wise fashion. This is both illogical and scientifically unfounded, and further increases the confusion of the situation, both on the part of the pharmacist, patient, and physician.

In conclusion, we support the discussion and reassessment of levothyroxine bioequivalence and strongly urge that the FDA re-evaluate its position by, at least, inclusion of TSH measurement in this process. This will allow both physicians and patients a better opportunity to maintain constant and therapeutically effective levothyroxine levels in the management of their thyroid disorders.

Sincerely yours,

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Chair, Thyroid Core Group

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Chair, Division of Endocrinology  
Member, Thyroid Core Group

VF/JCM:rlh