

Howard M. Lando, MD

Docket Number 2005N-0137

TO: The Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

FROM: Howard M. Lando, MD

RE: Docket Number 2005N-0137

Meeting Name: Levothyroxine Sodium Therapeutic Equivalence; Public Meeting

Meeting Date: May 23, 2005

Pages: 1-4

#### T4 Statement

I am a practicing endocrinologist for the past 25 years with almost 40% of my practice dedicated to the treatment of patients with thyroid disorders of all types; including hypothyroidism, hyperthyroidism, thyroid nodules, goiters, and thyroid cancers. During that period of time, I have probably seen over 2-3000 patients with thyroid disease, many needing levothyroxine therapy. I have also been one of the AACE's practice guideline committee members for the treatment of thyroid cancer. Thus, I come before you today to discuss with you the reasons that I feel your recent decision regarding the bioequivalence of generic thyroxine therapy is incorrect.

Though most of you realize this, please let me remind you that it is critical in thyroid patients not to under or overtreat them. Overtreatment exposes my patients to the risk of accelerated bone loss perhaps worsening osteoporosis and the risk of fractures, cardiac arrhythmias such as atrial fibrillation which can lead to stroke or other evidence of cardiac dysfunction such as cardiac wall thickness, or other symptoms of hyperthyroidism such as nervousness, palpitations, tachycardia, increased sweating, weight loss, irritability, or loss of concentration. Undertreatment, on the other hand, can lead to fatigue, memory problems, lack of concentration, weight gain, bradycardia, hyperlipidemia – with resultant cardiovascular risk - , miscarriage or fetal developmental problems – especially mentation. Thus, it is absolutely essential that appropriate thyroxine therapy is available that keeps the patient within the narrow range of appropriate dosage that must be individually maintained.

It is a caveat of Endocrinology that the single best test of thyroid function, except for patients with hypothalamic or pituitary disease, is the TSH test. It is the “gold standard” that we use to appropriately judge if the dosage of thyroxine given to a patient is correct for them. If it is too high then undertreatment is occurring, if too low than overtreatment. The FDA itself recognizes the dangers inherent in thyroxine therapy by providing guidance for physicians in its use by stating in the drug labeling of these products that “For patients who have recently initiated levothyroxine therapy .... or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured every 8-12 weeks.” Most of our national societies or practicing endocrinologist actually recommend this testing even more frequently – every 4-6 weeks.

What does this mean to my patients if the bioequivalency decision is allowed to stand unchallenged? Simply put, insurance companies attempt to mandate that generic medications are to be used to save money, even though the price of “branded” thyroxine is not that much more than the generics – say \$55.00/100 tablets vs. \$20-25.00 at most pharmacies. Insurance companies do this by such incidious means as making co-pays for generics much less than “brand meds”, as much as by a factor of two to three times as much. They can do this as they can say the FDA has approved the generic as bioequivalent.

In the case of thyroxine however, I can tell you from experience that generics are not bioequivalent. In my practice, I tell my patients never to change brands as in case after case when it has happened because a prescription was written unknowingly by a physician allowing substitution, or the patient went along with a pharmacist or insurance company request to change, we have seen over or undertreatment when the next TSH is done – often many months or even years down the road.

Is this dangerous? If the patient should happen to have thyroid cancer, which is the second or third most frequent cancer by rate, we know that endogenous TSH is a co-carcinogen –ie it may stimulate thyroid cancer cells to proliferate and metastasize. We are required to keep the TSH level below normal, despite overtreatment risks as the risk of not doing so is too great. Just think what would happen if you were the patient who had to get a refill every 30 – 90 days of their medication (which is as long as the insurance company will allow) and each 30 – 90 days you would have to come in for repeat thyroid testing which is what we have to recommend now in order to adjust the dose to keep your TSH suppressed. The cost for a free T4 and TSH tests, which are the minimum necessary (and many MD’s do more) is about \$30-50.00. Thus the savings of \$25-30/100 tablets is quickly gone and often overshadowed by the cost of the testing necessary to be so exact, as generics are not equivalent to the brand products. In fact each of the brand products is not equivalent to each other.

But, it is not just with cancer patients that thyroxine is used. We use it to treat hypothyroidism – perhaps the most common thyroid disorder – and some like to use it in the treatment of goiter or nodules. Perhaps 20% of females and 5% of males have a thyroid disorder of one sort or another and many are on thyroxine therapy, thus the constant vigilance necessary with the constant switching of thyroxine preparations by using generics will have a devastating cost to society whether with lab bills, physician office visit costs, missed time from work, or medical problems associated with over or undertreatment.

This is in essence the problem. The FDA must change the way it defines bioequivalence for thyroxine products to make manufacturers show equivalence of TSH with their equivalent doseages – not using an assay of speed of dissolution of the tablets and the T4 level of high doseages of the tablets in vivo. If the TSH is the “gold standard” lets use it so generics are really bioequivalent and we can save patients time and money safely.

Thank you.

Howard M. Lando, MD, FACP,FACE  
Clinical Professor Endocrine and Medicine  
George Washinton University  
Washington, DC  
President Medical Staff  
INOVA Mt. Vernon Hospital  
Alexandria, VA

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