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Dear Committee Members:

I am writing this brief letter to outline my concerns related to the substitution of levothyroxine (L-T4) preparations in the management of various disorders of the thyroid. The current method to determine bio-equivalence of various medications which are used to replace endogenous substances appears to be flawed. For example, the administration of a single supraphysiologed dose of 600 ug L-T4 to normal subjects might well affect the clearance of both the endogenous and administered hormone by increasing its deiodination. Furthermore, pituitary TSH secretion will almost certainly be decreased, resulting in a transient decrease in the thyroid secretion of endogenous T4. Finally, as shown by the results in study M02-417 (Abbott, unpublished data), failure to account for endogenous T4 resulted in an inability to distinguish between a 600 ug and 400 or 450 ug doses of administered L-T4. Correcting for endogenous T4 by any of three different methods outlined still resulted in an inability to distinguish between doses of 400 and 450 ug L-T4, a 12.5% error. Additionally, it is possible that the correction methods would not distinguish between doses of at least 12.5% and at most 24.9%.

It should be emphasized that therapy of hypothyroidism with L-T4 preparations requires extremely tight control as reflected by serum TSH concentrations. Under-treatment and over-treatment should be avoided since the consequences of both hypothyroidism (including subclinical) and hyperthyroidism (including subclinical) are well known and should be avoided. This is especially critical in the infant, in the elderly, and in the management of thyroid cancer. In view of the lack of proof of bio-equivalence using the current method of assessment, it would be extremely important for the clinician to maintain his/her patient on a single L-T4 preparation since switching from one preparation to another might well result in incorrect therapy. If such substitution is done, more frequent serum TSH values would be required, necessitating increased cost and the risk of even transient over- or under-treatment. It should be recognized that pharmacies, not infrequently, substitute one L-T4 preparation for another without the physician's approval or awareness. Finally, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) have published guidelines advising physicians to maintain patients on the same L-T4 preparation.

I appreciate the opportunity to render my opinion on this topic.

Most sincerely yours,

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