

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 Endocrinologists

On June 24, 2004, the U.S. Food and Drug Administration (FDA) rejected a citizen petition filed in August 2003 regarding bioequivalence of levothyroxine sodium products and approved first-time generic levothyroxine sodium for the treatment of hypothyroidism. The American Thyroid Association (ATA), The Endocrine Society (TES), and the American Association of Clinical Endocrinologists (AACE), representing more than 4,600 clinical endocrinologists, are concerned that the FDA has moved to approve generic levothyroxine preparations as equivalent to branded preparations without seeking the input of the expert clinicians treating thyroid disease.

The FDA had previously indicated that it would seek input from clinical endocrinologists and would carefully consider standards of thyroxine bioequivalence and testing before making such a decision. We believe that this recent FDA action may pose unnecessary risks for the 13 million Americans currently taking levothyroxine products and, therefore, want to alert physicians about this change so that they are prepared to advise their thyroid patients.

Levothyroxine is a drug recognized to have a narrow toxic to therapeutic ratio with significant clinical consequences of excessive or inadequate treatment. Some of the potential adverse events that could occur from excessive or inadequate treatment with levothyroxine include: recurrence of symptoms, osteoporosis, atrial fibrillation, worsening of ischemic heart disease, preterm delivery in pregnancy, and hypercholesterolemia. Those especially susceptible to incorrect titration of levothyroxine products include the elderly, pregnant women and their developing fetuses, and those with thyroid cancer.

The current recommendation by the FDA and our societies for patients switching between branded levothyroxine products is to have **repeat thyroid function testing** to allow for dose retitration if the therapeutic target is not being achieved with the new preparation. Under a policy of allowing generic levothyroxine substitution, more frequent thyroid function testing will be necessary. Furthermore, the patient and doctor may not be aware of a change in preparation before adverse events occur.

What should physicians caring for patients on levothyroxine therapy do to reduce the chances of adverse effects of generic levothyroxine?

1. Alert your patients that their levothyroxine preparation may be switched at the pharmacy.
2. Encourage your patients to ask to remain on their current levothyroxine

preparation.

3. Make sure your patients understand that if they receive a new levothyroxine preparation, they will need to be retested with a serum TSH to determine if they need dose retitration.

AACE, TES, and ATA Joint Position Statement on the Use and Interchangeability of Thyroxine Products

Recently, the FDA approved the use of additional thyroxine products. A press release and notice to the American Association of Clinical Endocrinologists (AACE), and The Endocrine Society (TES), and American Thyroid Association (ATA) members followed.

AACE, and TES, and ATA are issuing this joint statement to address the introduction of several generic levothyroxine products to the market that the FDA has deemed to be equivalent to some currently branded preparations.

- 1. We are concerned about the FDA's method for determining bioequivalence.**
The FDA had recently acknowledged concerns about its methods for determining bioequivalence. In fact it made a commitment to address the concerns of AACE, and TES, and ATA by agreeing to hold a workshop in order to do so.
- 2. The FDA has failed to satisfactorily address questions relating to the bioequivalence of thyroxine preparations.**
Despite a written commitment to address the concerns of AACE, and TES, and ATA as organizations that represent those most knowledgeable about caring for patients with thyroid disorders and thyroid hormone metabolism, the FDA proceeded to grant generic status to additional levothyroxine preparations.
- 3. Physicians and patients should be educated about our concerns.**
Practicing physicians and patients should be well informed of AACE's, and , TES's, and ATA's scientifically based concerns about the FDA's methodology for establishing generic status. These concerns are the basis for our recommendation not to substitute thyroxine preparations for one another-- FDA generic equivalence notwithstanding.
- 4. Physicians should become familiar with the historical background and glossary of terms related to the use of thyroxine preparations.**
This will enhance the ability of physicians to educate patients and other health care professionals about the use of thyroxine preparations.

Background¹:

Thyroid hormone was first used in 1891 by injecting sheep thyroid extract into a patient with myxedema. Kendall discovered thyroxine in 1914 and Harrington established its structure in 1926, and went on to synthesize it. Never the less,, desiccated thyroid, made from animal thyroid glands, remained the mainstay of therapy until the 1970's. A high yield synthetic technique was developed in 1949. However, it was not until 1962 that levothyroxine came to market after the realization that sodium L-thyroxine form was much better absorbed than the free acid thyroxine. In 1962 Tthe FDA did not require a New Drug Application (NDA) for levothyroxine, based on the belief that it was not a new drug.

Subsequently, Adverse Drug Experience Reports-some citing serious clinical consequences, brought to light problems with preparation potency (both under and oversuper), preparation stability, and consistency in lot-to-lot bioavailability. In some instances, reformulations with different excipients (including color agents and fillers that were generally thought to be inert) proved to be responsible for some within brand variations.

By 1997, the FDA concluded that no marketed levothyroxine preparation had been shown to have consistent potency and stability and therefore could not be recognized by the FDA as “safe and effective.” In light of this, the FDA ruled that an NDA would be required in order to market a levothyroxine product after August 14, 2000, and that pre-existing products that were “non-NDA approved” could only be distributed until August 14, 2001.

The FDA has been cognizant of the “narrow toxic to therapeutic ratio with significant clinical consequences of excessive or inadequate treatment” which may have an impact on the heart, bone, and pregnancy status. This is reflected in the shelf life potency requirements that prevent thyroxine preparations from losing more than 20% potency under standard storage conditions. It has continued to use pharmacokinetic methods to establish therapeutic equivalence that are potentially flawed for endogenously produced substances, and, by its own recent admission, should be subjected to formal review. These methods employ Area Under the Curve [AUC] and maximum concentration [Cmax] determinations in normal subjects with normal thyroid function. **These indices of bioavailability are used to establish bioequivalence and, in turn, conclude therapeutic equivalence.** Uncorrected, these methods fail to account for the subjects’ own endogenous contribution to thyroxine levels (baseline contribution). In addition, TSH levels, the widely accepted best single laboratory tool for establishing thyroid status, are not part of the FDA’s determinations of equivalence.

“Uncorrected,” the FDA’s methodology may lead to the conclusion that preparations that differ by as much as 33% are equivalent. “Correcting” for baseline values may reduce the difference detected to **less than 25% but greater than 12.5%**². Even though the FDA has asserted that its current methodology makes it unlikely that generics that differ by 9, 12, or 15% from a branded product will be approved, the sensitivity of their current methodology for detecting differences less than 25% has not been directly demonstrated. Moreover, the FDA recently approved Levothyroxine Sodium-Sandoz as a bioequivalent alternative to Synthroid, even though baseline corrected AUC data between 0 and 48 hours demonstrated that on average the Sandoz product had 12.5% greater bioavailability than Synthroid. It is widely appreciated that in many, if not most, clinical situations, a 33% or 25% difference in thyroxine dose may have a substantial clinical impact. What is perhaps less well appreciated is that **differences less than 25%** may not only have a significant impact on serum TSH levels, but in certain clinical settings, such as the elderly with cardiac disease or pregnancy, the impact may be clinically highly significant. In fact, this is the basis for manufacturing multiple thyroxine doses. For example, the difference between 137 mcg of thyroxine and 150 mcg is only 9%.

Not only did the FDA's new ruling have an impact on pharmaceutical companies making levothyroxine preparations, it also had an unintentional impact on patients taking thyroxine preparations as well as those physicians caring for them. A confusing array of new L-levothyroxine preparations came to market. To date, these have included: preparations made by companies that previously did not make thyroxine, reformulation of existing products, and replacement of one company's product with an FDA approved product made by another company. Most recently, the FDA has granted approval of three preparations as equivalent to longstanding branded products, despite the concerns referred to above. As a result, the following has frequently happened:

- Patients did not know that their thyroxine preparation was changed
- Physicians did not know that a different thyroxine preparation was dispensed to their patients
- Pharmacists did not know about formulation changes and, therefore, could not properly counsel patients about their thyroid medication
- Physicians were deluged with patients' concerns about the quality of their thyroxine preparations. This was particularly prevalent in 2001 when patients were led to believe that their thyroxine preparations (not yet FDA approved) may be unreliable and potentially hazardous to their health
- Physicians and other health care personnel have spent an extraordinary amount of time counseling patients about the use of thyroxine products, and money testing for therapeutic equivalence by employing TSH and other thyroid hormone levels, thereby adding a substantial burden to our health care system

Conclusion:

Best Physician Practices:

Patients should be maintained on the same brand name of levothyroxine product. If the brand of levothyroxine medication is changed, either from one brand to another brand, from a brand to a generic product, or from a generic product to another generic product, patients should be reevaluated, retested by measuring serum TSH in six (6) weeks, and the drug retitrated/reiterated as needed. Since small changes in levothyroxine administration can cause significant changes in TSH serum concentrations, precise and accurate TSH control is critical necessary to avoid potential adverse iatrogenic effects.

Best Patient Practices:

Use the same brand of thyroid medication throughout your treatment. Thyroid disease often requires lifelong therapy and is best managed with consistent and precise treatment with the same brand of thyroid hormone. Your doctor may change your dose of thyroid hormone, but the brand of your thyroid hormone medication should always stay the same.

When you go to the pharmacy, do not change the brand of your thyroid medication without checking with your doctor. You should not change your dose from one brand of thyroid medication to another, from your brand of thyroid medication to a generic

product, or from one generic product to another without first checking with your doctor. Repeat blood tests and visits to your doctor may be required, and your dose may need to be readjusted if your thyroid medication is changed, or if you switch to a generic product.

References

¹ Hennessey JV. Levothyroxine a New Drug? Since When? How Could That Be? *Thyroid*. 2003; 13:279-282.

² Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? *Thyroid*. 2004;14:191-200.

APPENDIX I

Glossary:

Generic Drugs: A generic drug is a copy that is the same as a brand-name drug in dosage, safety, strength, how it is taken, performance, and intended use (Source: FDA(cite the URL of the FDA website) web site). Note: a generic drug, bearing the chemical name of the drug, can only serve as a substitute for the brand(s) to which it was designated to be equivalent. In the case of thyroxine preparations it requires an AB rating (see below). Until recently (as of 2002), Mylan Pharmaceuticals made the only approved generic levothyroxine, which could only be used as a substitute for Unithroid, a brand of levothyroxine made by Stevens. Recently, the FDA approved a previously NDA approved levothyroxine preparation made by ALARA (Levo-T) and to be distributed by Sandoz that can be substituted for Synthroid made by Abbott Pharmaceuticals as well as Levoxyl made by Jones Pharmaceuticals. It also ruled that the levothyroxine preparation made by Mylan Pharmaceuticals could be substituted for Synthroid and Levoxyl and that Unithroid could be substituted for Levoxyl.

Therapeutic Equivalents (TE): Drugs that are pharmaceutical equivalents (identical amounts of the same active drug ingredient, same dosage, same route of administration) and bioequivalent (see below). Drugs can be considered therapeutic equivalents even if they have different release mechanisms. Therapeutic equivalents can be substituted for one another with the expectation that there will be similar clinical effects and that follow-up testing would not be required.

Bioavailability and Bioequivalence: Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available “at the site of drug action.” Two drugs are considered bioequivalent if they have an “equivalent rate and extent of absorption from these formulations,” or, in other words, appear to have comparable bioavailability. The FDA’s language (see web site) indicates that the formulations do not have to undergo comparison “at the site of

drug action,” which would be reflected in a pharmacodynamic parameter, such as serum TSH measurements in the case of levothyroxine. Bioequivalence, in turn, establishes therapeutic equivalence and, therefore, interchangeability. Hence, a generic drug that is demonstrated to be bioequivalent by pharmacokinetic methods along the lines outlined above to the pioneer (innovator) drug, may be marketed as a generic version of that product.

AB: This is one of a number of “Therapeutic Equivalent Evaluation Codes” used by the FDA to denote therapeutic equivalence to other pharmaceutically equivalent drug products, when “actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.”

Generic levothyroxine preparations have AB codes. Branded levothyroxine preparations that have generic equivalents have AB codes.

The terminology “AB to” or “AB rated to” thereby indicates that two products are considered interchangeable by FDA standards and will be substituted unless the physician designates that they are not (e.g., “NO SUBSTITUTION”) to be exchanged.

Note: Drug I may be AB to Drug II and Drug II AB to Drug III. However, this does not mean that Drug I and III are AB to each other. This is because Drug II and Drug III may not have been compared with one another rather, than proven not to be equivalent. This point is illustrated by the following example: Drug I on average is more bioavailable than II but close enough for FDA approval to be considered equivalent. Drug III is less bioavailable than II but close enough to be considered equivalent. However, when Drugs I and III are compared directly to one another they do not correspond sufficiently to be considered equivalent by the FDA.

AB-#: When more than one drug is listed under the same FDA “reference” (i.e. levothyroxine), and the drugs are not bioequivalent, the FDA employs three character designations: AB1, AB2, AB3, AB4... (See Appendix III from FDA Orange Book description of this designation and Appendix IV for Levothyroxine Sodium update) in order to classify products with identical active ingredients, dosage form, and route of administration. Since Levoxyl, for example, was not AB to Synthroid, we correctly anticipated that the FDA’s recent approval of additional generic products would lead to the implementation of three character designations for levothyroxine products.

We believe that multiple character designations makes matters even more complex for pharmacists, physicians, and patients. As a result, not only will it continue to be virtually impossible to remain on the same generic product (which is one of our fundamental concerns about generic products), but it will also become increasingly difficult for patients to remain on the same branded product.

BX: This is one of a number of Therapeutic Equivalent Evaluation Codes used by the FDA to denote that a pharmaceutically equivalent drug product is not therapeutically equivalent because actual or potential bioequivalence problems have not been resolved

by adequate evidence of bioequivalence. The BX code is the designation used by the FDA when the data reviewed by the FDA are “insufficient to determine therapeutic equivalence.” Currently, branded levothyroxine preparations that do not have generic equivalents, and therefore cannot be interchanged with a pharmaceutically equivalent drug product, *common pharmacy practices to the contrary notwithstanding*, have a BX code.

APPENDIX II

Current List and Status of Thyroxine Preparations:

Before June 23, 2004 only Unithroid (Stevens) and Levothyroxine (Mylan) were AB rated.

Synthroid (Abbott), Levo-T (Alara), Novothyrox (Genpharm), Levoxyl (Jones [related to Monarch and King]), Thyro-Tabs (which has become the new Levothroid preparation made by Lloyd but owned by Forest), and Levolet (Vintage) were all BX rated

Since June 23, 2004, the FDA deemed Levo-T (ALARA), to be distributed as levothyroxine (Sandoz), to be equivalent to Synthroid and Levoxyl. The makers of Levoxyl are currently contesting this. In addition, levothyroxine (Mylan) was deemed equivalent to Synthroid and Levoxyl, while Unithroid was designated bioequivalent to Levoxyl. The FDA Orange Book should reflect this by changing Levo-T, Synthroid, and Levoxyl from BX to AB and adding the levothyroxine preparation (Sandoz) to its AB listings. Levothyroxine (Mylan) previously was AB to Unithroid, as noted above.

Of especial interest is the fact that the bioequivalence of the designated generic preparations levothyroxine (Mylan) and levothyroxine (Sandoz) have not been compared to one another, and would therefore be considered BX to one another even though each one is designated AB3 to Levoxyl and AB2 to Synthroid! (move paragraph up)

APPENDIX III (From the FDA Web site [www.fda.gov/cder/ob/docs])

AB, AB1, AB2, AB3... Products meeting necessary bioequivalence requirements

Multisource drug products listed under the same heading (i.e., identical active ingredients(s), dosage form, and route(s) of administration) and having the same strength (see [Therapeutic Equivalence-Related Terms, Pharmaceutical Equivalents](#)) generally will be coded AB if a study is submitted demonstrating bioequivalence.

In certain instances, a number is added to the end of the AB code to make a three-

character code (i.e., AB1, AB2, AB3, etc.). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. If a study is submitted that demonstrates bioequivalence to a specific listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against. For example, Adalat® CC (Miles) and Procardia XL® (Pfizer), extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Generic drug products deemed by FDA to be bioequivalent to Adalat® CC and Procardia XL® have been approved. Adalat® CC and Procardia XL® have been assigned ratings of AB1 and AB2, respectively. The generic drug products bioequivalent to Adalat® CC would be assigned a rating of AB1 and those bioequivalent to Procardia XL® would be assigned a rating of AB2. (The assignment of an AB1 or AB2 rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product, if the application holder's drug product is rated either with an AB or three-character code or is single source in the List. Drugs coded as AB under a heading are considered therapeutically equivalent only to other drugs coded as AB under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

APPENDIX IV

APPROVED DRUG PRODUCTS with THERAPEUTIC EQUIVALENCE EVALUATIONS 24th EDITION Cumulative Supplement 6

Prepared By Office of Pharmaceutical Science Office of Generic Drugs Center for Drug
Evaluation and Research, FDA June 2004

1.4 LEVOTHYROXINE SODIUM

Because there are multiple reference listed drugs of levothyroxine sodium tablets and some reference listed drugs' sponsors have conducted studies to establish their drugs' therapeutic equivalence to other reference listed drugs, FDA has determined that its usual practice of assigning two or three character TE codes may be potentially confusing and inadequate for these drug products. Accordingly, FDA provides the following explanation and chart of therapeutic equivalence evaluations for levothyroxine sodium drug products.

Levothyroxine Sodium (Mylan ANDA 76187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Unithroid (Jerome Stevens NDA 021210) tablets.

Levo-T (Alara NDA 021342) and Levothyroxine Sodium (Mylan ANDA 76187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Synthroid (Abbott NDA 021402) tablets.

Levo-T (Alara NDA 021342), Unithroid (Jerome Stevens NDA 021210) and Levothyroxine Sodium (Mylan ANDA 076187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levoxyl (King/Jones Pharma NDA 021301) tablets.

Novothyrox (Genpharm NDA 021292) requires further investigation and review to establish therapeutic equivalence to corresponding strengths of any other levothyroxine sodium drug products and is rated BX.

Thyro-Tabs (Lloyd NDA 021116) requires further investigation and review to establish therapeutic equivalence to corresponding strengths of any other levothyroxine sodium drug products and is rated BX.

Levolet (Vintage NDA 021137) requires further investigation and review to establish therapeutic equivalence to corresponding strengths of any other levothyroxine sodium drug products and is rated BX.

The chart outlines TE codes for all 0.025mg products with other products being similar. **Therapeutic equivalence has been established between products that have the same AB+ number TE code. More than one TE code may apply to some products. One common TE code indicates therapeutic equivalence between products.**

Trade Name	Applicant	Potency	TE Code	Appl No	Product No
UNITHROID	STEVENS J	0.025MG	GAB1	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	GAB1	7618	001
LEVOXYL	JONES PHARMA	0.025MG	GAB1	21301	001
SYNTHROID	ABBOTT	0.025MG	GAB2	21402	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	GAB2	76187	001
LEVO-T	ALARA PHARM	0.025MG	GAB2	21342	001
LEVOXYL	JONES PHARMA	0.025MG	GAB3	21301	001
LEVO-T	ALARA PHARM	0.025MG	GAB3	21342	001
UNITHROID	STEVENS J	0.025MG	GAB3	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	GAB3	76187	001
NOVOTHYROX	GENPHARM	0.025MG	GBX	21292	001
THYRO-TABS	LLOYD	0.025MG	GBX	21116	001

BASEURL = <http://www.fda.gov/cder/orange/supplement/cspreface.htm>

URL= <http://fda.gov/cder/orange/supplement/cspreface.htm>

Modified=DOAC29F6DC74C401B0

APPENDIX VIII

THYROXINE PRODUCT STATUS: JUNE 23, 2004

	Synth-roid	Lev-oxyl	Levo-throid	Uni-throid	LT4-Sandoz	LT4-Mylan	Novo-thyrox	Lev-olet
Synthroid (Abbott)	-	BX BX	BX	AB2	AB2	BX	BX	
Levoxyl (Jones)	BX	- BX	AB3	AB3	AB3	BX	BX	
Levothroid (Forest: Formerly Lloyd Thyro-tabs)	BX	BX -	BX	BX	BX	BX	BX	
Unithroid¹ (Stevens)	BX	AB1 BX	-	BX	AB1	BX	BX	
LT4-Sandoz	AB2	AB3 BX	BX	-	BX	BX	BX	
LT4-Mylan	AB2	AB3 BX	AB1	BX	-	BX	-	
Novothyrox (Gen-pharm)	BX	BX BX	BX	BX	BX	-	BX	
Levolet (Vintage)	BX	BX BX	BX	BX	BX	BX	-	

AB1: Product rating using Unithroid as “reference drug,”² considered interchangeable with Unithroid. Generic product LT4-Mylan listed may be exchanged with Unithroid.

AB2: Product rating using Synthroid as “reference drug,” considered interchangeable with Synthroid. Generic products LT4-Mylan and LT4-Sandoz may be exchanged with Synthroid³.

AB3: Product rating using Levoxyl as “reference drug,” considered interchangeable with Levoxyl. Generic products LT4-Mylan and LT4-Sandoz may be exchanged with Levoxyl³.

Drugs within a TE rating will likely be interchanged within the same three character products unless prescriber specifies “No Substitution,” “Brand Name Necessary,” “Dispense as Written,” etc.

BX: Not Interchangeable

NOTE¹: Lannett is distributing Unithroid (made by Stevens) as a generic product “LT4-Lannett,” which the FDA has designated as TE to Levoxyl. We decided to omit this from our This has been omitted from the table, because FDA postings did not cite its three-character designation(s) by the time this document was completed.

NOTE²: a) When applicable, row titles list “reference drugs” with table columns designating the drug that is being compared to the “reference drug.” Examples:

Row 2: Unithroid is “AB3 to Levoxyl”

Row 4: Levoxyl is “AB1 to Unithroid”

b) For completeness we created rows for the “Generic products” (LT4-Sandoz, LT4-Mylan). These are not “reference drugs.” Therefore, the respective three character designations listed in their rows are “referenced” to the products appearing in the columns. Examples:

Row 5: LT4-Sandoz is “AB2 to Synthroid”

Row 6: LT4-Mylan is “AB3 to Levoxyl”

NOTE³: LT4-Sandoz and LT4-Mylan are both AB2 to Synthroid and AB3 to Levoxyl. However, LT4-Mylan and LT4-Sandoz are not interchangeable (BX) because they have not been evaluated in regard to one another. See page 4 section “AB:” for explanation.