



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center For Drug Evaluation and Research

DATE: July 23, 2002

FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-402  
Synthroid (levothyroxine sodium tablets, USP)  
Abbott Laboratories

SUBJECT: NDA review issues and action

**Background**

This application was submitted July 31, 2001.

In the Federal Register of August 14, 1997, FDA announced that oral drug products containing levothyroxine sodium (T4) are considered new drugs and subject to the new drug requirements of the FFD&C Act. This declaration was based upon longstanding and repeated documentation of problems in product quality relating to lack of stability and variability in batch-to-batch potency. Such problems have occurred with many levothyroxine products across different manufacturers, including Synthroid. These deficiencies in drug quality have the potential to cause serious health consequences to patients requiring chronic levothyroxine therapy. In normals, thyroid hormone levels are extremely tightly regulated, and patients may suffer significant short and long-term problems if plasma thyroid hormone concentrations are either too high or too low.

As per the Federal Register of August 14, 1997, with revisions issued in the Federal Register of April 26, 2000, sponsors wishing to continue to market oral T4 products after August 14, 2001 were required to submit NDAs, including 505(b)(2) applications, containing literature references supporting the safety and effectiveness of LT4 for the proposed indications and acceptable data relating to chemistry, manufacturing, and controls. In addition, bioavailability and *in vitro* dissolution studies are required in order to establish that the product proposed for marketing is readily and consistently absorbed across the full dosage range proposed. In short, the approach to development of levothyroxine-containing new drug products relies on the fact that levothyroxine itself is the appropriate treatment for supplementation or replacement in patients with insufficient endogenous thyroid hormone and for suppression of TSH in patients with thyroid nodules or cancer. However, the approvability of an oral T4 drug product based on a judgment that the specific product is safe and effective depends upon demonstration by the sponsor of acceptable quality, quantity, and *in vitro* and *in vivo* performance. This is accomplished through submission and review of manufacturing information, data from stability studies, and the results of bioequivalence/bioavailability and dissolution studies.

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Of note, and relevant to the currently marketed Synthroid product, those sponsors of applications pending before the Agency as of August 14, 2001, have two years to obtain final approval, during which time they must reduce distribution of product according to a prescribed "ramp-down" process such that by August 14, 2003, absent approval, distribution of unapproved LT4 products will cease. To date, Abbott has complied with the ramp down requirement.

NDA 21-402 was submitted with the clinical section in accordance with the August 1997 FR notice, with the required sections addressing chemistry, manufacturing, and stability, and with additional content in accordance with Division guidance on the bioavailability/bioequivalence and dissolution studies required for approval of levothyroxine-containing products.

Abbott's application contains satisfactory information in support of approval of Synthroid.

#### **Clinical rationale**

This is a 505(b)(2) application and contains no clinical data. The sponsor has provided extensive literature references supporting the safety and effectiveness of LT4 for its proposed uses. Dr. Temeck has reviewed these references and has completed her independent review of the clinical literature addressing thyroid physiology, thyroid hormone action and metabolism, clinical states of thyroid hormone excess and deficiency, and on the clinical efficacy and safety of levothyroxine. In addition, she has summarized the available information on thyroxine dosage and administration in adults and children and on drug-drug and drug-disease interactions for thyroid hormone. Much of the aforementioned has been adequately incorporated or reflected in draft labeling for LT4 drug products that is appended to Dr. Temeck's review.

Levothyroxine is an iodinated derivative of tyrosine and is the major product of the mammalian (including man) thyroid gland. While T4 is the most abundant circulating thyroid hormone, activation of thyroid hormone receptors intracellularly requires enzymatic deiodination to T3 in the periphery. Thus, T3 is the major active thyroid hormone in the circulation. Thyroid hormones are essential for survival. Administration of T4 simply supplements or replaces endogenously synthesized T4. Levothyroxine is used to supplement patients with absent or diminished thyroid function due to a variety of causes. In addition, replacement doses of T4 will suppress the hypothalamic-pituitary-thyroid axis, resulting specifically in reduced circulating TSH, and is thus used in the therapy of goiter, thyroid nodules, and thyroid cancer, all potentially TSH dependent.

For the uses described above, T4 is safe and effective. Of critical clinical importance, though, is that dose must be titrated to optimum TSH and T4 blood levels in order to ensure effectiveness and to avoid consequences of over- or under-treatment. These include, among others, effects on growth and development, cardiovascular function, bone, reproductive function, cognitive and emotional state, and on glucose and lipid metabolism. Safe and effective titration requires availability of multiple dosage strengths that permit the full range of total daily dosages (e.g., 25-300 mcg) in increments of 12 or 12.5 mcg. This may be accomplished clinically by combined dosing using more than one dosage strength to render the total daily dose needed and may also involve splitting tablets (e.g., for 12.5 mcg increments, taking half a 25 mcg tablet one day and the other half the next).

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As above, no new clinical data have been submitted, pursuant to guidance from the Division.

**Labeling**

The product label proposed conforms to the template label developed by the division for LT4 products. Final labeling has been submitted and is acceptable. ODS has recommended changes to the blister labels for the hospital packs of Synthroid as well as to the professional samples. These recommendations are included in the action letter as suggested changes at a subsequent printing.

**Biopharmaceutics**

Dr. Johnson reviewed the reports of studies M01-324 and M01-323, relative bioavailability and dosage strength proportionality studies, respectively. The relative bioavailability of two Synthroid 300 mcg tablets was approximately 93% of a single 600 mg oral dose of levothyroxine. In study 323, the proportionality between 50, 100, and 300 mcg tablets was established based on Cmax and AUC. OCPB therefore finds the bioavailability and "dosage-form equivalence" data acceptable. Dissolution method and tolerance specifications have been set, are included in the review, and will be conveyed in the action letter.

**Pharmacology/Toxicology**

There are no preclinical toxicology issues with this product or with levothyroxine sodium generally.

**Chemistry/ Microbiology**

Dr. Lewis has reviewed the chemistry, manufacturing, and controls information in the application. The currently marketed product is manufactured using a \_\_\_\_\_, and targets greater than 100% of labeled claim at release. The registry lots for this NDA and the proposed product are manufactured using \_\_\_\_\_ ranging from \_\_\_\_\_ depending on the dosage strength, targeting 100% of labeled claim at release. This specification (100% of labeled claim at release) has been met by the current manufacturing method. Otherwise, the formulation for Synthroid has not changed from currently marketed product to NDA product. Stability information has been provided sufficient to support a 10-month expiry for all strengths packaged in 1000-count bottles and a 9-month expiry for all strengths packaged in 100-count bottles). The ONDC team recommends approval with 10- and 9-month expiration dating as in the preceding.

The establishment evaluations were all acceptable.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

**DSI/Data Integrity**

The analytical portions of the bioavailability studies were audited by DSI. Minor deficiencies were noted and a Form 483 was issued. The sponsor addressed the 483 item to the satisfaction of DSI. DSI recommends that the data are acceptable for review.

**Financial disclosure**

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The financial disclosure information is in order.

**OPDRA/nomenclature**

The proprietary name, Synthroid, has been found acceptable by ODS and is likewise acceptable to the Division.

**Pediatric Rule**

The sponsor has requested a waiver of requirements for pediatric studies based on the fact that adequate information exists in the published medical and scientific literature to support the safety and efficacy of LT4 (and thus Synthroid) in children.

A waiver has been granted.

**Phase 4 commitments**

The sponsor has made a commitment to develop an analytical method for the determination of impurities and degradation products in the drug substance and the drug product. The sponsor is reminded of this commitment in the letter.

**Conclusions**

The current application contains adequate information to support the clinical use of Synthroid for the proposed indications.

**Recommendation**

NDA 21-402 may be approved.

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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David Orloff  
7/23/02 05:41:03 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**