NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals

Approval Date: June 5, 2002

ANDA 76-187

JUN 5 2002

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg.

Reference is also made to your amendments dated November 7, and November 12, 2001; and January 18, and April 19, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Levothyroxine Sodium Tablets UPS, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Unithroid® Tablets, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg, respectively, of Jerome Stevens Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The

Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVED

JUN - 5 2002

LVTX:R1

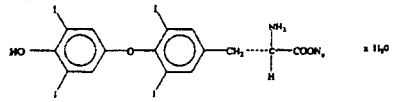
SPECIMEN

LEVOTHYROXINE SODIUM TABLETS, USP

25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

℞ only

DESCRIPTION: Levothyroxine Sodium Tablets, USP contain synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt (levothyroxine (T_4) sodium). Synthetic T_4 is identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has a molecular formula of $C_{15}H_{10}I_4N\,NaO_4 \times H_2O$, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown



Levothyroxine Sodium Tablets, USP, for oral administration, are available containing 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg or 300 mcg of levothyroxine sodium. In addition, each tablet contains the following inactive ingredients: butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, ethyl alcohol, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate and sucrose. The following are the coloring additives per tablet strength.

Strength (mcg)	Color additive(s)
25	FD&C Yellow No. 6 Lake
50	None
75	FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake
88	FD&C Yellow No. 6 Lake, FD&C Blue No. 1 Lake, D&C Yellow No. 10 Lake
100	FD&C Yellow No. 6 Lake, D&C Yellow No. 10 Lake
112	D&C Red No. 27 Lake, D&C Red No. 30 Lake
125	FD&C Yellow No. 6 Lake, FD&C Red No. 40 Lake, FD&C Blue No. 1 Lake
150	FD&C Blue No. 2 Lake
175	FD&C Blue No. 1 Lake, D&C Red No. 27 Lake, D&C Red No. 30 Lake
200	FD&C Red No. 40 Lake
300	FD&C Yellow No. 6 Lake, FD&C Blue No. 1 Lake, D&C Yellow No. 10 Lake

CLINICAL PHARMACOLOGY: Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), by the thyroid gland. Circulating serum T_3 and T_4 levels exert a feedback effect on both TRH and TSH secretion. When serum T_3 and T_4 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_3 and T_4 diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

The physiologic actions of thyroid hormones are produced predominately by T_3, the majority of which (approximately 80%) is derived from T_4 by deiodination in peripheral tissues.

Levothyroxine, at doses individualized according to patient response, is effective as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see INDICATIONS AND USAGE, PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Pharmacokinetics: ***Absorption:*** Absorption of orally administered T_4 from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine sodium tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption (see PRECAUTIONS, Drug Interactions and Drug-Food Interactions).

Distribution: Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins (see PRECAUTIONS: Drug Interactions and Drug-Laboratory Test Interactions). Thyroid hormones do not readily cross the placental barrier (see PRECAUTIONS: Pregnancy).

Metabolism: T_4 is slowly eliminated (see Table 1). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3; with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination: Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio Released from Thyroid Gland	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	20	1	6-7[1]	99.96
Liothyronine (T_3)	1	4	≤ 2	99.5

[1] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism
[2] Includes TBG, TBPA, and TBA

INDICATIONS AND USAGE: Levothyroxine sodium is used for the following indications:

Hypothyroidism: As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter.

Pituitary TSH Suppression: In the treatment or prevention of various types of euthyroid goiters (see PRECAUTIONS), including thyroid nodules (see PRECAUTIONS), subacute or chronic lymphocytic lyroiditis (Hashimoto's thyroiditis), multinodular goiter and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

CONTRAINDICATIONS: Levothyroxine is contraindicated in patients with untreated thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see PRECAUTIONS). Levothyroxine sodium is contraindicated in patients with hypersensitivity to any of the inactive ingredients in levothyroxine sodium tablets. (See DESCRIPTION section for complete list of inactive ingredients.)

WARNINGS:

WARNING: Thyroid hormones, including levothyroxine sodium, either alone or with other therapeutic agents, should not be used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

PRECAUTIONS: General: Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism.

Effects on Bone Mineral Density: In women, long-term levothyroxine sodium therapy has been associated with decreased bone mineral density, especially in postmenopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with Underlying Cardiovascular Disease: Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with Autonomous Thyroid Tissue: Exercise caution when administering levothyroxine to patients with autonomous thyroid tissue in order to prevent precipitation of thyrotoxicosis.

Associated Endocrine Disorders: ***Hypothalamic/Pituitary Hormone Deficiencies:*** In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see PRECAUTIONS: *Autoimmune Polyglandular Syndrome* for adrenal insufficiency).

Autoimmune Polyglandular Syndrome: Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see PRECAUTIONS, Drug Interactions).

Other Associated Medical Conditions: Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect) being the most common association.

Information for Patients: Patients should be informed of the following information to aid in the safe and effective use of levothyroxine sodium:

1. Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.
2. Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking levothyroxine sodium. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.
3. Use levothyroxine sodium only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.
4. The levothyroxine in levothyroxine sodium is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).
5. Take levothyroxine sodium tablets as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.
6. It may take several weeks before you notice an improvement in your symptoms.
7. Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
8. Notify your physician if you become pregnant while taking levothyroxine sodium. It is likely that your dose of levothyroxine sodium will need to be increased while you are pregnant.
9. Notify your physician or dentist that you are taking levothyroxine sodium prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of levothyroxine sodium therapy, but this is usually temporary.
11. Levothyroxine sodium should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep levothyroxine sodium tablets out of the reach of children. Store levothyroxine sodium away from heat, moisture, and light.

Laboratory Tests: ***General:*** The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity ≤ 0.1 mIU/L or third generation assay sensitivity ≤ 0.01 mIU/L) and measurement of free-T_4.

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of levothyroxine sodium may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T_4 potency of the drug product.

Adults: In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6 to 8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8 to 12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6 to 12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving levothyroxine sodium (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics: In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T_4. During the first three years of life, the serum total- or free-T_4 should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalize due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum T_4 to increase into the upper half of the normal range within 2 weeks of initiation of levothyroxine sodium therapy and/or of the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of levothyroxine sodium.

The recommended frequency of monitoring of TSH and total- or free-T_4 in children is as follows: at 2 and 4 weeks after the initiation of treatment, every 1 to 2 months during the first year of life; every 2 to 3 months between 1 and 3 years of age; and every 3 to 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if poor compliance is suspected or abnormal values are obtained. It is recommended that TSH and T_4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in levothyroxine sodium dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION).

Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism: Adequacy of therapy should be assessed by measuring serum free-T_4 levels, which should be maintained in the upper half of the normal range in these patients.

Drug Interactions. Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to levothyroxine sodium. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and action of other drugs. A listing of drug-thyroidal axis interactions is contained in Table 2.

The list of drug-thyroidal axis interactions in Table 2 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 2. Drug-Thyroidal Axis Interactions

Drug or Drug Class	Effect
Drugs that may reduce TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine/Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (≥ 1 μg/kg/min); Glucocorticoids (hydrocortisone ≥ 100 mg/day or equivalent), Octreotide (> 100 μg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T_4 absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Kayexalate Ferrous Sulfate Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.
Drugs that may alter T_4 and T_3 serum transport (changes in total-T_4), but free-T_4 concentrations remain normal, and, therefore, hyperthyroidism does not occur	
Drugs that may increase serum TBG concentration	**Drugs that may decrease serum TBG concentration**
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site displacement	
Furosemide (> 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone Salicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in free-T_4 (FT_4). Continued administration results in a decrease in serum T_4, and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4, is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T_4 levels may decrease by as much as 30%
Drugs that may alter T_4 and T_3 metabolism	
Drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoins Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T_4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.

200 mcg/day are seldom required. An inadequate response to daily doses ≥ 300 mcg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of 25 to 50 mcg/day of levothyroxine is recommended, with gradual increments in dose at 6 to 8 week intervals. The recommended starting dose of levothyroxine in elderly patients with cardiac disease is 12.5 to 25 mcg/day, with gradual dose increments at 4 to 6 week intervals. The levothyroxine dose is generally adjusted in 12.5 to 25 mcg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.

In patients with severe hypothyroidism, the recommended initial levothyroxine dose is 12.5 to 25 mcg/day with increases of 25 mcg/day every 2 to 4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine dose should be titrated until the patient is clinically euthyroid and the serum free-T_4 level is restored to the upper half of the normal range.

Pediatric Dosage - Congenital or Acquired Hypothyroidism (see PRECAUTIONS, Laboratory Tests): *General Principles*: In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development.

Undertreatment and overtreatment should be avoided (see PRECAUTIONS: Pediatric Use).

Levothyroxine sodium may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5 to 10 ml or 1 to 2 teaspoonful) of water. This suspension can be administered by spoon or dropper. **DO NOT STORE THE SUSPENSION.** Foods that decrease absorption of levothyroxine, such as soybean infant formula, should not be used for administering levothyroxine (see PRECAUTIONS: Drug-Food Interactions).

Newborns: The recommended starting dose of levothyroxine in newborn infants is 10 to 15 mcg/kg/day. A lower starting dose (e.g., 25 mcg/day) should be considered in infants at risk for cardiac failure, and the dose should be increased in 4 to 6 weeks as needed based on clinical and laboratory response to treatment. In infants with very low (< 5 mcg/dl) or undetectable serum T_4 concentrations, the recommended initial starting dose is 50 mcg/day of levothyroxine.

Infants and Children: Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see Table 3). However, in children with chronic or severe hypothyroidism, an initial dose of 25 mcg/day of levothyroxine is recommended with increments of 25 mcg every 2 to 4 weeks until the desired effect is achieved.

Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached.

Table 3: Levothyroxine Dosing Guidelines for Pediatric Hypothyroidism

AGE	Daily Dose Per Kg Body Weight*
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years	2-3 mcg/kg/day
Growth and puberty complete	1.7 mcg/kg/day

* The dose should be adjusted based on clinical response and laboratory parameters (see PRECAUTIONS: Laboratory tests and Pediatric Use).

Pregnancy: Pregnancy may increase levothyroxine requirements (see PRECAUTIONS: Pregnancy).

Subclinical Hypothyroidism: If this condition is treated, lower levothyroxine doses (e.g., 1 mcg/kg/day) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules: Levothyroxine is used as an adjunct to surgery and radioiodine therapy in the treatment of well-differentiated (papillary and follicular) thyroid cancer. Generally, TSH is suppressed to <0.1 mIU/L, and this usually requires a levothyroxine dose of greater than 2 mcg/kg/day.

In the treatment of benign nodules and nontoxic multinodular goiter, TSH is generally suppressed to a higher target (0.1 to 0.3 mIU/L) than that used for the treatment of thyroid cancer. Exercise caution when administering levothyroxine to patients with autonomous thyroid tissue (see PRECAUTIONS).

Myxedema Coma: Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral levothyroxine is not recommended to treat this condition. Intravenous levothyroxine sodium should be administered.

HOW SUPPLIED: Levothyroxine Sodium Tablets, USP are available as caplet-shaped, biconvex tablets that are debossed with an M on one side of the tablet. The other side of each tablet is debossed with an L to the left of the score and an individual tablet identification number* to the right of the score. The scored side of the tablets is more fully described in the third column of the table, below.

Strength (mcg)	Color	Identification information debossed on scored side of tablet*	NDC # for bottles of 100
25	Orange	L 1 4	0378-1800-01
50	White	L 1 5	0378-1803-01
75	Violet	L 1 6	0378-1805-01
88	Olive	L 1 7	0378-1807-01
100	Yellow	L 1 8	0378-1809-01
112	Rose	L 1 9	0378-1811-01
125	Gray	L 1 10	0378-1813-01
150	Blue	L 1 11	0378-1815-01
175	Lilac	L 1 12	0378-1817-01
200	Pink	L 1 13	0378-1819-01
300	Green	L 1 14	0378-1821-01

*The identifying information debossed on the scored side of the tablet is listed in the above table by product strength.
Refer to the third column of the table, entitled 'Identification information debossed on scored side of tablet'.

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [See USP].

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2001
LVTX-R1

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Bioequivalence

A1.1 N Schwart.

OCT 10 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

In the assay methodology reports of all 3 studies:

1 [redacted]
2. [redacted]
3. [redacted]

4. [redacted]

In the study clinical reports, the following information was not provided for all 3 bio studies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

Please provide the above listed items.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 10 2001

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Sisto:

This facsimile is in reference to the bioequivalency data submitted on June 5, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, and 0.300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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BIOEQUIVALENCY AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 10 2001

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Kristu M. Scordino, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Sisto:

This facsimile is in reference to the bioequivalency data submitted on June 5, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, and 0.300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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LEVOTHYROXINE SODIUM TABLETS USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
ANDA 76-187
Reviewer: Hoainhon Nguyen
W #76187sdw.601

Mylan Pharmaceuticals
Morgantown, WV

Submission Date: 06/05/01

Review of Three Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

I. Introduction

Indication: For the treatment of hypothyroidism --As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Also, for the treatment or prevention of various types of euthyroid goiters including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Contents of Submission: Three single-dose fasting bioequivalence studies of the 0.300 mg, 0.125 mg and 0.075 mg strengths of the test and reference products, dissolution data for all strengths of the test and reference products, and waiver requests for the 0.200 mg, 0.175 mg, 0.150 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.050 mg and 0.025 mg strengths of the test product.

RLD: Unithroid tablets, 0.300 mg, manufactured by Jerome Stevens Pharmaceuticals; other available strengths are 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg.

NOTE: ***It should be noted that the reference products used in the in vivo bioequivalence studies and in vitro dissolution studies contained in this application are Thyrox Tablets and Levotab Tablets manufactured by Jerome Stevens. These products were used since the product sold under the brand name Unithroid was not available in the marketplace at the time the bioequivalence studies were conducted. The OGD informed Mylan that the formulations of Jerome Stevens' levothyroxine tablet products used in Mylan's bioequivalence studies are the same as the formulations approved in the NDA for Unithroid. (p. xxv, Vol. A 1.1, and the email from Don Hare to Gary Buehler, January 4, 2001, attached in the Vol. A1.1)***

Recommended Dose: The average full replacement dose of levothyroxine is approximately 1.7 mcg/kg/day (e.g., **100-125 mcg/day** for a 70 kg adult) for hypothroidism in adults and in children in whom growth and puberty are complete. For younger children with hypothyroidism, the recommended doses are as follows:

Levothyroxine Dosing Guidelines for Pediatric Hypothyroidism	
AGE	Daily Dose Per Kg Body Weight
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years	2-3 mcg/kg/day
Growth and puberty complete	1.7 mcg/kg/day

For TSH suppression in well-differentiated thyroid cancer and thyroid nodule, a levothyroxine dose of **greater than 2 mcg/kg/day** is usually required .

II. Background

Absorption --Absorption of orally administered levothyroxine (T_4) from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%.
T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption.

Distribution --Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to triiodothyroxine (T_3). Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins. Thyroid hormones do not readily cross the placental barrier.

Metabolism --T_4 is slowly eliminated . The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3; with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination --Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

The most frequent adverse events associated with levothyroxine are fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating. (Reference: Physicians' Desk Reference, pp.1374-1377, 1998)

Conditions for Bioequivalence Approval: The current bioequivalence conditions are as communicated in the [redacted] The DBE requests only a single-dose fasting *in vivo* bioequivalence study be conducted comparing the 300 mcg strength of the test product to the RLD product. Only levothyroxine (T4) is recommended for quantitation. Biowaiver requests for all of the lower strengths may be accepted based on (1) acceptable bioequivalence study of the 300 mcg strength, (2) acceptable *in vitro* dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths.

Financial Disclosure: p. 471, Vol. A1.1.

III. Protocol No. LEVO-0057: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (75 µg; Mylan) to Levothyroxine Sodium Tablets, USP (75 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	10/06/00 to 11/20/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	11/28/00 to 12/07/00 (T4 Analysis)
Maximum Storage Period:	62 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/15/00	N/A
Expiration Date:	N/A	04/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0747	004100
Potency:	99.5%	95.0%
Strength:	0.075 mg	0.075 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.600 mg (8x0.075 mg)	0.600 mg (8x0.075 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	42 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	34
Route of Administration:	oral	**No. of Subjects Completing:**	33
		No. of Subjects Serum Analyzed:	33
		No. of Dropouts:	1
		Sex(es) Included:	Male (16) Female (18)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 22 (18-29); Female: 27 (18-45)
		Mean Height (cm)(Range):	Male: 181 (165-190) Female: 166 (150-178)
		Mean Weight (kg) (Range):	Male: 80 (62-98) Female: 64 (54-75)

Dietary Restrictions:	No alcohol- or xanthine-containing beverages/foods for the 48 hours before dosing and throughout the period of sample collection.
Activity Restrictions:	Strenuous activity or complete rest was not permitted at any time during the housing period.
Drug Restrictions:	No medication (including over-the-counter products) for the 14 days preceding the study and throughout the entire study.
Confinement:	From the evening before dosing until after the 24-hour blood draw.
Inclusion/Exclusion Criteria:	pp. 542-544, Vol. A1.2.
Blood Sampling:	-0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Three and four mild drug-related adverse reactions were reported during the Test and Reference treatment, respectively. The reactions were abdominal pain and headache.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts: Subject #12 withdrew prior to dosing due to fainting during the pre-dose blood sampling of Period I. Subject #22 was dropped prior to dosing in Period I due to impetigo. Subject #27 withdrew after the 0.5 hour blood sampling of Period I for personal reasons.

3) Analytical (Not to be Released Under FOI) Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

Total T4 serum levels were determined by a radioimmunoassay (RIA).

Pre-Study Stability in Serum:
a) Short-term Storage:
b) Freeze-Thaw Cycles:
c) Long-term Storage:

Specificity: The specificity data for T4 anti-serum was provided by % Cross-reactivity for L-Thyroxine, D-Thyroxine, L-Triiodothyronine and D-Triodothyronine are 104, 92, 2.1 and 2.1, respectively. % Cross-reactivity for other substances was <0.1.

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0057

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear trapezoidal rule
Cmax	Observed Data
Tmax	Observed Data

Results:

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TABLE 1

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN THIRTY-THREE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 µg (8 x 75 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0057)

Parameter	Arithmetic Mean A = Mylan	Arithmetic Mean B = Levothyroxine Sodium Tablets, USP***	LSMEANS Ratio (A/B)	90% Confidence Interval**
AUC_{0-48} (ng x hr/mL)	5734 (12.77)	5824 (13.88)	0.99	96% - 101%
CPEAK (ng/mL)	155.4 (15.56)	160.8 (15.21)	0.97	94% - 100%
TPEAK (hr)	3.394 (48.27)	2.485 (52.40)	----	----

*Ratio (A/B) $= e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

***Manufactured by Jerome Stevens

TABLE 2

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0057 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY-THREE (33) SUBJECTS

	Treatment				
	A (Levothyroxine Na Mylan #R1H0747)		B (Levothyroxine Na, USP Jerome Stevens #004100)		A VS B
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Draw Time					
-0.50 hours	84.54	14.60	83.56	16.90	0.5776
-0.25 hours	82.85	17.95	83.94	14.45	0.5165
0.00 hours	85.09	15.57	82.42	14.06	0.0622
0.50 hours	91.62	17.68	93.99	18.11	0.4373
1.00 hours	115.83	17.21	133.25	20.75	0.0001
1.50 hours	129.89	18.95	147.82	20.09	0.0001
2.00 hours	139.88	16.58	149.48	16.14	0.0016
2.50 hours	142.52	18.13	149.31	12.79	0.0808
3.00 hours	143.64	14.57	148.24	13.25	0.1978
4.00 hours	142.89	16.04	144.25	13.35	0.7247
6.00 hours	135.45	14.47	137.58	12.62	0.3909
8.00 hours	128.28	12.92	128.77	14.02	0.8136
12.00 hours	124.42	14.11	127.76	14.05	0.2055
18.00 hours	115.00	13.31	116.96	15.94	0.3977
24.00 hours	117.86	14.51	119.86	16.36	0.3203
48.00 hours	112.15	13.61	111.56	14.46	0.7245

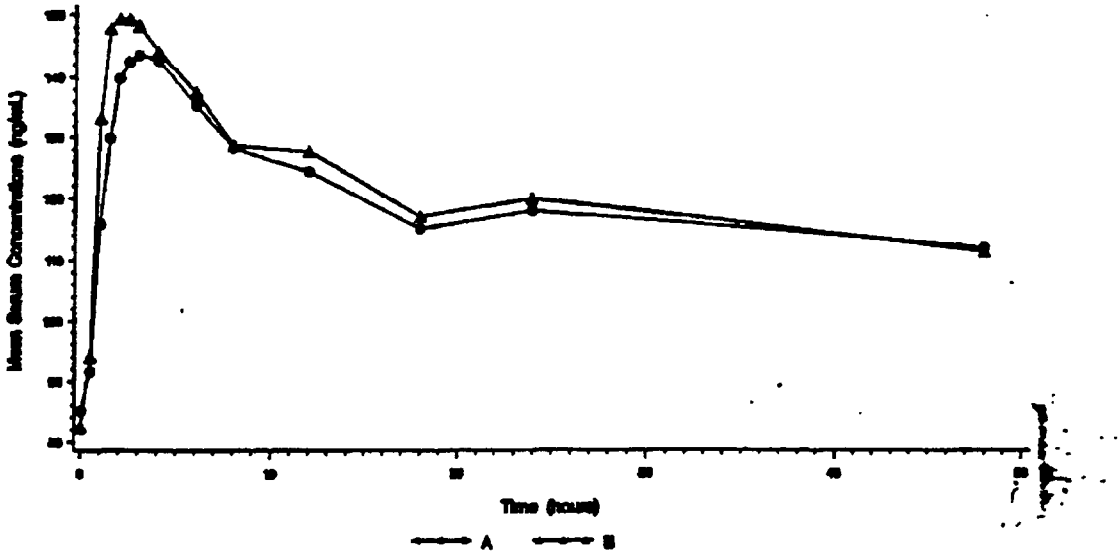
FIGURE 1

LEVOTHYROXINE Na (LEVO-0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na--Mylan #R9[illegible])
Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

5) **Statistical Analysis:** Thirty-three of 34 enrolled subjects completed the study (See Dropouts, p. 5 above). Thirty-three data sets were used in the statistical analysis for the study.

There was no statistically significant difference (alpha=0.05) between treatments for LAUC(0-T) or LCMAX.

Comments: The study is incomplete, see Deficiency Comments, page 30.

IV. Protocol No. LEVO-0054: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (125 µg; Mylan) and Levothyroxine Sodium Tablets, USP (125 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	09/23/00 to 11/07/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	11/16/00 to 11/28/00
Storage Period:	66 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/16/00	N/A
Expiration Date:	N/A	05/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0750	003799
Potency:	97.2%	94.6%
Strength:	0.125 mg	0.125 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.500 mg (4x0.125 mg)	0.500 mg (4x0.125 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	42 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	30
Route of Administration:	oral	**No. of Subjects Completing:**	27
		No. of Subjects Analyzed:	30*
		No. of Dropouts:	3
		Sex(es) Included:	Male (15) Female (15)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 26 (18-44); Female: 33 (20-48)
		Mean Height (cm)(Range):	Male: 181 (168-193) Female: 167 (152-188)
		Mean Weight (kg) (Range):	Male: 78 (67-100) Female: 68 (58-95)

***NOTE:** Although Subjects #2, 3 and 6 were dropped from the study (See page 17 of this review), these subjects completed Period I and their Period I samples were analyzed and included in the study results.

Dietary/Drug/Activity Restrictions: See the Fasting Study of the 75 μg strength above.

Blood Sampling: -0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Two and one mild drug-related adverse reactions were reported during the Test and Reference treatments, respectively. The reactions were dyspepsia and headache.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts:

Subjects #2 and 6 failed to report for Period II check-in. Subject #3 was dropped prior to dosing in Period II due to a scheduled eye surgery.

3) **Analytical (Not to be Released Under FOI)** Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

T4 serum levels were determined by a radioimmunoassay (RIA).

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0054

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided, see Deficiency Comments, page 30.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear Trapezoidal Rule
Cmax	Observed Data
tmax	Observed Data

Results:

TABLE 3

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 500 µg (4 x 125 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0054)

Parameter	Arithmetic Mean A = Mylan N=28	Arithmetic Mean B = Jerome Stevens N=29	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUC_{0-48hr} (ng x hr/mL)	5539 (12.47)	5537 (11.66)	0.99	97% - 101%
CPEAK (ng/mL)	142.5 (13.18)	147.1 (12.98)	0.96	93% - 99%
TPEAK (hr)	3.089 (42.03)	2.724 (57.33)	—	—

*Ratio (A/B) = $e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

TABLE 4
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0054 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY (30) SUBJECTS

	Treatment				
	A (Levothyroxine Na-Mylan #R1H0750)		B (Levothyroxine Na--Jerome Stevens #003799)		A VS B
Draw Time	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
-0.50 hours	84.43	15.35	82.18	13.64	0.3726
-0.25 hours	83.77	13.17	82.71	13.23	0.8036
0.00 hours	83.57	13.90	82.52	13.52	0.7733
0.50 hours	92.79	17.02	92.00	16.66	0.9615
1.00 hours	113.44	17.43	124.30	16.89	0.0015
1.50 hours	126.67	17.95	138.86	16.29	0.0007
2.00 hours	132.57	16.85	141.95	13.40	0.0085
2.50 hours	133.22	13.32	139.08	10.26	0.0144
3.00 hours	132.98	12.91	137.78	12.29	0.0243
4.00 hours	133.12	13.57	135.47	12.08	0.1410
6.00 hours	130.20	13.55	129.89	11.39	0.7767
8.00 hours	123.43	12.75	122.40	12.18	0.9999
12.00 hours	122.07	14.62	119.63	11.82	0.5194
18.00 hours	110.42	16.97	112.63	10.51	0.2434
24.00 hours	113.57	12.49	114.47	13.33	0.2981
48.00 hours	109.38	12.81	106.13	12.42	0.1192

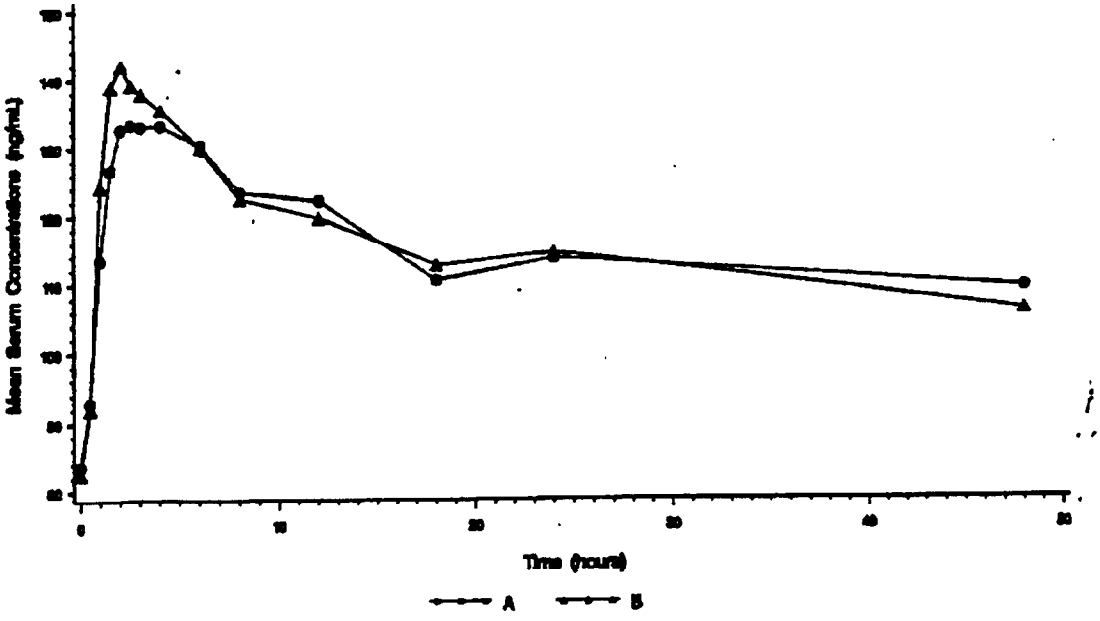
FIGURE 2

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=30



Treatment A is A (Levothyroxine Na--Mylan #R1H0780)
Treatment B is B (Levothyroxine Na--Jerome Stevens #003739)

5) Statistical Analysis: Twenty-seven of 30 enrolled subjects completed the study (See Dropouts, p. 11 above). Subjects #2, 3, and 6 completed only Period I. However, the Period I data from these subjects were also included in the statistical analysis for the study and the analysis was based on 30 subjects.

There was statistically significant difference (alpha=0.05) between treatments for LCMAX (p=0.0304).

Comments: The study is incomplete, see Deficiency Comments, page 30.

V. Protocol No. LEVO-0062: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (300 µg; Mylan) and Levothyroxine Sodium Tablets, USP (300 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	12/08/00 to 01/15/01
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	01/23/01 to 02/08/01
Storage Period:	62 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/17/00	N/A
Expiration Date:	N/A	06/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0708	008500
Potency:	102.2%	97.1%
Strength:	0.300 mg	0.300 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.600 mg (2x0.300 mg)	0.600 mg (2x0.300 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	35 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	36
Route of Administration:	oral	**No. of Subjects Completing:**	34
		No. of Subjects Analyzed:	36*
		No. of Dropouts:	2
		Sex(es) Included:	Male (25) Female (11)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 25 (18-50); Female: 29 (18-46)
		Mean Height (cm)(Range):	Male: 182 (173-196) Female: 168 (152-180)
		Mean Weight (kg) (Range):	Male: 78 (60-93) Female: 67 (58-90)

***NOTE:** Although Subjects #13 and 31 withdrew from the study, they completed Period I. Their Period I samples were analyzed and included in the study results.

Dietary/Drug/Activity Restrictions: See the Fasting Study of the 75 μg strength above.

Blood Sampling: -0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Two and three mild drug-related adverse reactions were reported during the Test and Reference treatments, respectively. The reactions were headache, body aching and rhinitis.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts:

Subjects #13 and 31 elected to withdraw prior to Period II dosing.

3) Analytical (Not to be Released Under FOI) Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

T4 serum levels were determined by a radioimmunoassay (RIA).

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0062

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear Trapezoidal Rule
Cmax	Observed Data
tmax	Observed Data

Results:

TABLE 5

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 µg (2 x 300 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0062)

Parameter	Arithmetic Mean A = Mylan N=35	Arithmetic Mean B = Jerome Stevens N=35	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUC_{0-48hr} (ng x hr/mL)	5952 (9.920)	6050 (10.31)	0.99	97% - 100%
CPEAK (ng/mL)	159.4 (10.55)	165.1 (10.26)	0.96	94% - 98%
TPEAK (hr)	3.129 (73.48)	2.400 (40.99)	----	----

*Ratio (A/B) $= e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

TABLE 6

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0062 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY-SIX (36) SUBJECTS

	Treatment				
	A (Levothyroxine Na-- Mylan #R1H0708)		B (Levothyroxine Na, USP- Jerome Stevens #008500)		A VS B
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Draw Time					
-0.50 hours	82.99	16.13	83.62	14.71	0.8958
-0.25 hours	82.18	14.41	84.05	14.66	0.2531
0.00 hours	84.35	14.73	84.85	13.50	0.9192
0.50 hours	92.98	15.73	92.76	16.17	0.7408
1.00 hours	123.33	19.22	132.94	18.37	0.0199
1.50 hours	144.16	17.89	151.36	16.06	0.0813
2.00 hours	148.87	14.50	154.89	12.85	0.0963
2.50 hours	147.07	10.55	156.42	10.85	0.0060
3.00 hours	150.42	11.65	151.01	10.42	0.8120
4.00 hours	145.44	10.65	149.53	11.54	0.0562
6.00 hours	141.71	10.37	147.39	11.95	0.0065
8.00 hours	137.73	10.92	140.01	10.00	0.1951
12.00 hours	132.89	10.41	131.26	11.13	0.4719
18.00 hours	119.09	11.82	120.15	11.54	0.6739
24.00 hours	121.53	11.32	124.31	11.68	0.1863
48.00 hours	114.45	11.97	115.91	11.39	0.7205

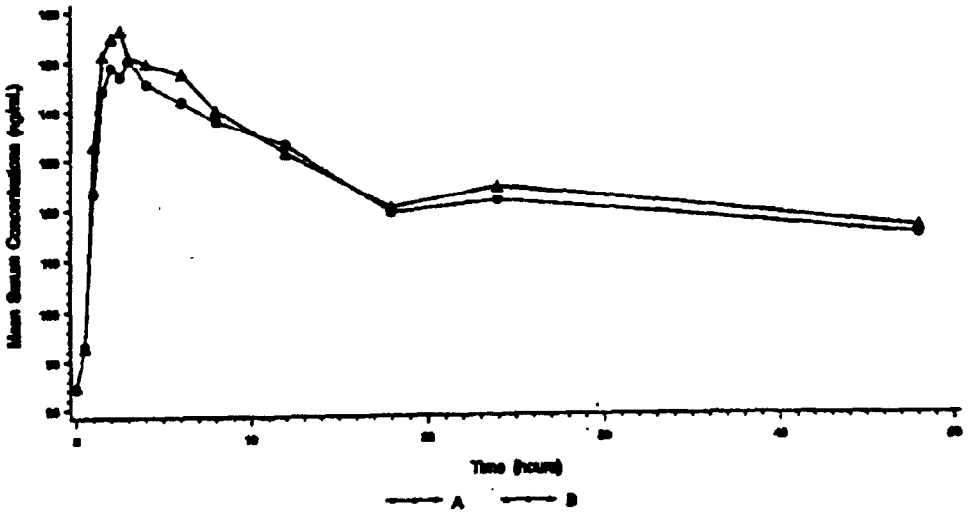
FIGURE 3

LEVOTHYROXINE Na (LEVO-0062)

Total Dose: 600 ug (2x300ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=36



Treatment A is A (Levothyroxine Na--Mylan #R[illegible])
Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #[illegible])

5) **Statistical Analysis:** Thirty-four of 36 enrolled subjects completed the study (See Dropouts, p. 17 above). Subjects #13 and 31 completed only Period I. However, the Period I data from these subjects were also included in the statistical analysis for the study and the analysis was based on 36 subjects.

There was no statistically-significant difference (alpha=0.05) between treatments for LCMAX or LAUC (0-48).

Comments: The study is incomplete, see Deficiency Comments, page 30.

VI. Waiver Request: The waiver requests for the 0.025 mg, 0.050 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.150 mg and 0.200 mg strengths of the test product are granted based on the acceptable bio studies of the 0.075 mg, 0.125 mg and 0.300 mg strengths above, the dissolution testing of all strengths (See below) and proportionality between the formulations of all strengths (See below).

1) Formulations:

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COMPARATIVE QUANTITATIVE COMPOSITIONS

LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

	25MCG		50MCG		75MCG		88MCG		100MCG		112MCG	
	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
ACTIVE COMPONENT												
Levothyroxine Sodium, USP	0.025	0.02	0.050	0.04	0.075	0.06	0.088	0.07	0.100	0.08	0.112	0.09
INACTIVE COMPONENTS												
Mannitol USP,												
Sucrose, NF												
Butylated Hydroxyanisole, NF												
Povidone, NF												
Purified Water, USP[1]												
Alcohol USP												
Microcrystalline Cellulose, NF												
Crospovidone, NF												
Magnesium Stearate/Sodium Lauryl Sulfate												
Colloidal Silicon Dioxide, NF												
FD&C Yellow #6 Lake HT												
FD&C Blue #2 Lake HT												
FD&C Red #40 Lake HT												
FD&C Blue #1 Lake HT												
D&C Yellow #10 Lake HT												
D&C Red #27 Lake HT												
D&C Red #30 Lake HT												
FD&C Red #40 Lake HT												
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

(1) Purified Water USP and Alcohol USP, [illegible] do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

COMPARATIVE QUANTITATIVE COMPOSITIONS (continued)

LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

	125MCG	150MCG	175MCG	200MCG	300MCG
	MG PER TABLET	MG PER TABLET	MG PER TABLET	MG PER TABLET	MG PER TABLET
ACTIVE COMPONENT					
Levothyroxine Sodium, USP	0.125	0.150	0.175	0.200	0.300
INACTIVE COMPONENTS					
Mannitol USP,					
Sucrose, NF					
Butylated Hydroxyanisole, NF					
Povidone, NF					
Purified Water, USP[1]					
Alcohol, USP					
Microcrystalline Cellulose, NF					
Crospovidone, NF					
Magnesium Stearate/Sodium Lauryl Sulfate					
Colloidal Silicon Dioxide, NF					
FD&C Yellow #6 Lake HT					
FD&C Blue #2 Lake HT					
FD&C Red #40 Lake HT					
FD&C Blue #1 Lake HT					
D&C Yellow #10 Lake HT					
D&C Red #27 Lake HT					
D&C Red #30 Lake HT					
FD&C Red #40 Lake HT					
TOTAL THEORETICAL WEIGHT	130.0	130.0	130.0	130.0	130.0

(1) Purified Water USP and Alcohol USP, do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

Formulation Comments: All inactive ingredients in the formulations of all strengths were reviewed and found to be present at or below levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products. The formulations are proportionally similar by Definition 2 of the current general BA/BE guidance.

2) **Dissolution** (Not to be released under FOI)

NOTE: All dissolution testing in support of this application was conducted in the Chemistry Research and Development Laboratories of Mylan Pharmaceuticals Inc. located at 3711 Collins Ferry Road, Morgantown, WV, 26505. The name of the person responsible for oversight of the dissolution testing is Dan Snider, Ph.D., Director, Chemistry Research and Development. The **Date of Assay** indicated on each Dissolution Profile is the date that the dissolution testing was performed.

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LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS

DISSOLUTION PROFILE SUMMARY

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0856 (25mcg) Mean	57%	77%	83%	87%
Range				
RSD	15.5%	4.8%	[illegible]	6.3%
Thyrox® Lot 001600 (25mcg) Mean	60%	85%	91%	94%
Range				
RSD	14.5%	6.3%	4.7%	4.6%
Mylan Lot R1H0[illegible] (50mcg) Mean	62%	76%	79%	[illegible]
Range				
RSD	8.7%	6.2%	5.4%	[illegible]
Thyrox® Lot 003800 (50mcg) Mean	53%	84%	91%	94%
Range				
RSD	7.9%	6.2%	4.2%	3.7%
Mylan Lot R1H0[illegible] (75mcg) Mean	70%	78%	82%	85%
Range				
RSD	6.7%	5.8%	5.2%	4.9%
Thyrox® Lot 004100 (75mcg) Mean	55%	89%	96%	99%
Range				
RSD	15.7%	5.7%	2.9%	2.7%
Mylan Lot R1H0748 (88mcg) Mean	72%	80%	83%	86%
Range				
RSD	10.4%	7.2%	6.1%	5.7%
Unithroid® Lot 013800 (88mcg) Mean	55%	84%	93%	94%
Range				
RSD	18.5%	8.1%	3.2%	2.8%

CONDITIONS (USP METHOD):

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate, 37°C ± 0.5°C, 500 mL

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

DISSOLUTION PROFILE SUMMARY (continued)

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0707 (100mcg) Mean Range RSD	73% 3.8%	79% 4.1%	82% 4.3%	85% 4.3%
Thyrox® Lot 001200 (100mcg) Mean Range RSD	56% 15.5%	83% 9.2%	92% 4.2%	93% 3.1%
Mylan Lot R1H0749 (112mcg) Mean Range RSD	51% 18.6%	75% 5.8%	[illegible] 5.0%	[illegible]
Unithroid® Lot 014000 (112mcg) Mean Range RSD	59% 17.8%	84% 7.6%	87% 4.3%	88% 3.7%
Mylan Lot R1H0750 (125mcg) Mean Range RSD	63% 13.0%	76% 5.1%	BDL 4.4%	83% 3.9%
Levotab® Lot 003799 (125mcg) Mean Range RSD	57% 13.9%	84% 6.7%	91% 4.5%	94% 3.9%
Mylan Lot R1H0752 (150mcg) Mean Range RSD	61% 8.9%	79% 3.5%	84% 3.8%	86% 5.9%
Thyrox® Lot 010399 (150mcg) Mean Range RSD	59% 18.2%	85% 7.6%	90% 5.6%	93% 3.8%

CONDITIONS (USP METHOD):

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate, 37°C ± 0.5°C, 500 mL

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

DISSOLUTION PROFILE SUMMARY (continued)

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0752 (175mcg) Mean Range RSD	66% 10.9%	77% 7.0%	81% 6.5%	85% 5.9%
Unithroid® Lot 014200 (175mcg) Mean Range RSD	55% 13.5%	84% 6.1%	88% 5.3%	88% 4.6%
Mylan Lot R1H0751 (200mcg) Mean Range RSD	60% 15.9%	78% 5.5%	82% 4.6%	87% 5.0%
Levotab® Lot 012798 (200mcg) Mean Range RSD	49% 13.0%	78% 9.3%	84% 7.0%	86% 4.6%
Mylan Lot R1H0708 (300mcg) Mean Range RSD	56% 10.4%	83% 5.0%	88% 4.6%	90% 3.7%
Thyrox® Lot 008500 (300mcg) Mean Range RSD	44% 13.0%	81% 7.5%	95% 5.7%	99% 5.3%

CONDITIONS (USP METHOD):

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate, 37°C ± 0.5°C, 500 mL
Apparatus: 2 (Paddles)
Speed: 50 rpm
Sample Times: 10, 20, 30 and 45 minutes
Limits: NLT 70% (Q) in 45 minutes

LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG,
125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

F_2 Analysis

1. Analysis of Profiles Generated at Initial Release

REFERENCE: Levothyroxine Sodium Tablets USP, 300mcg, Lot R1H0708
(Highest Strength and Lot used in Bioequivalence Studies)

LOT NUMBER	STRENGTH	TIME (minutes)				f_2
		10	20	30	45	
R1H0854	25mcg	58	78	83	87	69.40
R1H0746	50mcg	59	74	79	83	56.30
R1H0747	75mcg(bio lot)	70	78	82	85	53.64
R1H0748	88mcg	67	78	82	85	56.94
R1H0707	100mcg	59	78	82	86	66.20
R1H0749	112mcg	59	79	83	88	70.97
R1H0750	125mcg(bio lot)	63	76	80	83	56.7[illegible]
R1H0751	150mcg	53	75	80	84	58.8[illegible]
R1H0752	175mcg	56	78	82	86	67.3[illegible]
R1H0753	200mcg	58	79	83	86	69.73
R1H0708	300mcg	56	83	88	90	

Acceptance Criteria: $50 < f_2 < 100$

2. Analysis of Profiles Generated to Coincide with Testing of Innovator Non-Bio Strengths

Samples of the non-bio strengths of the referenced listed drug were not available at the time the initial dissolution profiles for Mylan's Levothyroxine Sodium Tablets, USP were performed. Additional dissolution profiles for Mylan's non-bio strengths were performed to coincide with the subsequent testing of the referenced listed drug.

REFERENCE: Levothyroxine Sodium Tablets USP, 300mcg, Lot R1H0708
(Highest Strength and Lot used in Bioequivalence Studies)

LOT NUMBER	STRENGTH	TIME (minutes)				f_2
		10	20	30	45	
R1H0854	25mcg	57	77	83	87	68.17
R1H0746	50mcg	62	76	79	83	56.54
R1H0748	88mcg	72	80	83	86	52.77
R1H0707	100mcg	73	79	82	85	50.85
R1H0749	112mcg	51	75	80	84	57.91
R1H0751	150mcg	61	79	84	86	67.89
R1H0752	175mcg	66	77	81	85	56.79
R1H0753	200mcg	60	78	82	87	66.20
R1H0708	300mcg	56	83	88	90	

Acceptance Criteria: $50 < f_2 < 100$

Dissolution Comments: The test and reference products meet the USP specification of NLT 70% of the labeled amount of levothyroxine dissolved in 45 minutes. Similarity Factor F2 calculated between the highest strength and other strengths was acceptable (greater than 50). The dissolution data are acceptable.

VII. Deficiencies: The following deficiencies have been found in the assay methodology reports of all 3 studies:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

The following information was not provided for the 3 bio studies and currently requested by the DBE:

The information on the race of all subjects who participated in the studies.

VIII. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 300 µg, lot # R1H0708, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, lot # 008500, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

2. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 125 µg, lot # R1H0750, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, lot # 003799, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

3. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 75 µg, lot # R1H0747, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, lot # 004100, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

4. The *in vitro* dissolution testing conducted by Mylan on its Levothyroxine Sodium Tablets, 300 µg, 200 µg, 175 µg, 150 µg, 125 µg, 112 µg, 100 µg, 88 µg, 75 µg, 50 µg and 25 µg, has been found **acceptable** by the Division of Bioequivalence.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% SLS at 37C using USP XXIV apparatus II(paddle) at 50 rpm. The test product should meet the following USP specifications:

Not less than 70% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The firm has demonstrated that the formulations of its Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, are proportionally similar to the formulations of the 300 µg, 125 µg and 75 µg strengths that underwent in vivo bioavailability testing. However, the biowaivers of these strengths are not considered at the present time pending acceptable biostudy results of the 300 µg, 125 µg and 75 µg strengths.

/S/
Hoanhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 8/28/2001
FT INITIALED YHUANG

/S/
Concur: _____ Date: 9/27/2001
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 76-187 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-30-01/W #76187sdw.601
Also as V:\firmsam\mylan\ltrs&rev\76187sdw.601
Attachment: None

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

In the assay methodology reports of all 3 studies:

1. [redacted]
2. [redacted]
3 [redacted]
c [redacted]
1 [redacted]

In the study clinical reports, the following information was not provided for all 3 bio studies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

Please provide the above listed items.

Sincerely yours.

/S/

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-187
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 8/28/2001
HFD-617/ K. Scardin
HFD-650/ D. Conner 8/27/2001

V:\FIRMSAM\MYLAN\LTRS&REV\76187SDW.601
Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE

Submission date: 06-05-01

1. FASTING STUDY (STF) o/c
   Clinical:
   Analyti
   Strength: 0.075 mg
   Outcome: IC

2. FASTING STUDY (STF) o/c
   Clinical:
   Analytic
   Strength: 0.125 mg
   Outcome: IC

3. FASTING STUDY (STF) o/c
   Clinical:
   Analyti
   Strength: 0.300 mg
   Outcome: IC

4. DISSOLUTION WAIVER (DIW) o/c
   (each strength is DIW and Outcome is IC)
   Strength: 0.200 mg, 0.175 mg, 0.150 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.050 mg & 0.025 mg
   Outcome: IC

OUTCOME DECISIONS: IC - Incomplete UN - Unacceptable
AC - Acceptable

WINBIO COMMENTS:

MYLAN PHARMACEUTICALS INC.

COMPARATIVE QUANTITATIVE COMPOSITIONS
LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

	25MCG		50MCG		75MCG		88MCG		100MCG		112MCG	
ACTIVE COMPONENT	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
Levothyroxine Sodium, USP	0.025	0.02	0.050	0.04	0.075	0.06	0.088	0.07	0.100	0.08	0.112	0.09
INACTIVE COMPONENTS												
Mannitol USP												
Sucrose, NF												
Butylated Hydroxyanisole, NF												
Povidone, NF												
Purified Water, USP[1]												
Alcohol, USP												
Microcrystalline Cellulose, NF												
Crospovidone, NF												
Magnesium Stearate/Sodium Lauryl Sulfate												
Colloidal Silicon Dioxide, NF												
FD&C Yellow #6 Lake HT												
FD&C Blue #2 Lake HT												
FD&C Red #40 Lake HT												
FD&C Blue #1 Lake HT												
D&C Yellow #10 Lake HT												
D&C Red #27 Lake HT												
D&C Red #30 Lake HT												
FD&C Red #40 Lake HT												
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

Purified Water USP and Alcohol USP , do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

7/2/01
pg. #

COMPARATIVE QUANTITATIVE COMPOSITIONS (continued)

LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

	125MCG		150MCG		175MCG		200MCG		300MCG	
ACTIVE COMPONENT	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
Levothyroxine Sodium, USP	0.125	0.10	0.150	0.12	0.175	0.14	0.200	0.16	0.300	0.24
INACTIVE COMPONENTS										
Mannitol USP,										
Sucrose, NF										
Butylated Hydroxyanisole, NF										
Povidone, NF										
Purified Water, USP[1]										
Alcohol, USP										
Microcrystalline Cellulose, NF										
Crospovidone, NF										
Magnesium Stearate/Sodium Lauryl Sulfate										
Colloidal Silicon Dioxide, NF										
FD&C Yellow #6 Lake HT										
FD&C Blue #2 Lake HT										
FD&C Red #40 Lake HT										
FD&C Blue #1 Lake HT										
D&C Yellow #10 Lake HT										
D&C Red #27 Lake HT										
D&C Red #30 Lake HT										
FD&C Red #40 Lake HT										
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

(1) Purified Water USP and Alcohol USP, do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

	Master	Exhibit	Made	Packaged
2[illegible] cg				
50 mcg				
75 mcg				
88 mcg				
100 mcg				
1[illegible] mcg				
125 mcg				
150 mcg				
175 mcg				
200 mcg				
300 mcg				

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : June 20, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence studies and request for waiver submitted with an ANDA for Levothyroxine Sodium Tablets USP,0.025 mg, 0.05 mg, 0.075 mg. 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, and 0.3 mg to determine if the application is substantially complete for filing.

Mylan Pharmaceuticals Inc. has submitted ANDA 76-187 for Levothyroxine Sodium Tablets USP. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence studies and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the studies and request for waiver submitted by Mylan on June 5, 2001 for its Levothyroxine Sodium product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

____ Study does **NOT** meet statutory requirements

Reason:

CONCUR:
6/21/01

✓ Waiver meets statutory requirements

____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

6/25/01
Date

6/14/01

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310

Reference Number: OGD# 00-472

Dear Mr. Sisto:

This letter is in response to your correspondence dated November 2, 2000. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Levothyroxine Tablets, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 175 mcg, 200 mcg, and 300 mcg. OGD provides the following comments:

1. The labeling for the reference listed drug (RLD), Unithroid™ Tablet (Levothyroxine Sodium), states that it should be taken on an empty stomach. Therefore, the Division of Bioequivalence (DBE) requests that you conduct only a single-dose fasting *in-vivo* bioequivalence study comparing your Levothyroxine Tablets, 300 mcg, to the RLD. This recommendation is consistent with the Guidance for Industry, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations," issued on October 27, 2000. The DBE recommends that you use a 35-day washout period for a two-way crossover design. Alternatively, you may use a parallel design with equal numbers of male and female subjects in each treatment group.

2. The DBE recommends that you measure only levothyroxine (T4). A 600 mcg dose is recommended to detect T4 above baseline levels. Blood samples should be collected up to 48 hours.

3. The lower strengths of the Levothyroxine Sodium Tablets are eligible for a waiver of in-vivo bioequivalence study requirements based on (1) acceptable bioequivalence study on the 300 mcg strength, (2) acceptable dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths.

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Gary J. Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Bartle, Margo L

Warzala, Ruth A; Sponaugle Jr, Richard G
Scardina, Krista; Mazzella, Steven; Nwaba, Nina
Subject: 30 DAY EVA 76-187 REC 6-6-2001

76-187 LEVOTHYROXINE SODIUM TABLETS USP, 11 STRENGTHS MYLAN RECEIVED 6-6-2001

DISKETTES PROVIDING THE BIO ELECTRONIC SUBMISSION ESD BA/BE EVA WILL BE FORWARDED WITHIN 30 DAYS

THANKS,

MARGO

Bartle, Margo L

Patel, Rashmikant M; Fang, Florence S
Beers Block, Patricia M; Holcombe Jr, Frank O; Sayeed, Vilayat A; Smela Jr, Michael
Subject: FIRST GENERIC 76-187

FIRST GENERIC 76-187 LEVOTHYROXINE SODIUM TABLETS USP, 11 STRENGTHS
MYLAN RECEIVED 6-6-2001

TEAM LEADER IS MIKE SMELA

THANKS,

MARGO

November 7, 2001

ORIG AMENDMENT
N/AB

AB

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 76-187; LEVOTHYROXINE SODIUM TABLETS, USP
25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg

Dear Mr. Buehler,

Reference is made to Mylan Pharmaceuticals' Abbreviated New Drug Application identified above for Levothyroxine Sodium Tablets, USP. Reference is also made to the Agency's October 10, 2001 correspondence to Mylan providing comments regarding the bioequivalence studies submitted in the referenced application. The Agency requested a copy of the SOP's for the analytical method used in the conduct of the bioequivalence studies. It is our pleasure to provide to you the SOP's for the analytical method of the above study that were requested. The analytical method is [redacted] therefore

If you have any questions please do not hesitate to contact me at [redacted]

CENTER FOR DRUG
NOV 0 9 2001
OGD
EVALUATION AND RESEARCH

c.c. Scott W. Chervenick, Ph.D., Mylan Pharmaceuticals Inc.

-COMM. JOURNAL- DATE MAR-28-2002 TIME 08:20

MODE = MEMORY TRANSMISSION START=MAR-28 08:18 END=MAR-28 08:20

FILE NO.=149

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK		913042856407	002/002	00:00:38

-FDA CDER OGD CHEMI -

ANDA 76-187

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

DATE: March 28, 2002 PAGES: 1 (excluding cover page)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

Reference is also made to your amendments dated November 7, and November 12, 2001.

SPECIAL INSTRUCTIONS:
Bioequivalency comments provided.

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ANDA 76-187

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

DATE: March 28, 2002 PAGES: 1 (excluding cover page)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

Reference is also made to your amendments dated November 7, and November 12, 2001.

SPECIAL INSTRUCTIONS:
Bioequivalency comments provided.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCY COMMENTS

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

#3

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-187 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Levothyroxine Sodium Tablets USP
STRENGTH(S) : 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
TYPES OF STUDIES : Fasting SD Studies (for 0.075mg, 0.125 mg & 0.300 mg)
CINICAL STUDY SITE(S) : ——
ANALYTICAL SITE(S) : ——

STUDY SUMMARY : Acceptable
DISSOLUTION: Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ——— DATE : 11-29-01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ——— DATE : 11/30/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : ——— DATE : 12/31/2001

James Fan

LEVOTHYROXINE SODIUM TABLETS USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
ANDA 76-187
Reviewer: Hoainhon Nguyen
W #76187an01.doc

Mylan Pharmaceuticals
Morgantown, WV

Submission Date: 11/07/01 & 11/12/01

Review of a Study Amendment

The firm has submitted the current amendment in response to the DBE deficiency letter dated October 10, 2001. The deficiency comments were as follows:

The demographic information concerning the race of all subjects who were enrolled in the studies."

The firm's responses are summarized below.

I. Firm's Responses:

5. The demographic information including the race of all subjects was provided. The information is summarized below.

For Study LEVO-0057 (Fasting Study for the 75 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (18)	27 (18-45)	166 (150-178)	64 (54-75)
Male (16)	22 (18-29)	181 (165-190)	80 (62-98)

Race: Black (0), Caucasian (34), Hispanic (0), Asian (0)

For Study LEVO-0054 (Fasting Study for the 125 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (15)	33 (20-48)	167 (152-188)	68 (58-95)
Male (15)	26 (18-44)	181 (168-193)	78 (67-100)

Race: Black (0), Caucasian (29), Hispanic (0), Asian (0), Native American (1)

For Study LEVO-0062 (Fasting Study for the 300 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (11)	29 (18-46)	182 (173-196)	67 (58-90)
Male (25)	25 (18-50)	182 (173-196)	78 (60-93)

Race: Black (0), Caucasian (35), Hispanic (0), Asian (0), Native American (1)

II. Comments: All of the firm's responses are adequate and acceptable. The bioequivalence studies, Nos. LEVO-0057, LEVO-0054 and LEVO-0062, as reviewed in the current amendment and the original submission (06/05/01), are found acceptable. The studies demonstrate that the test and reference products are equivalent in the rate and extent of absorption as measured by log-transformed CMAX and AUC of T4.

From the review of the original submission, the following was also addressed:

1. **Formulation Comments:** All inactive ingredients in the formulations of all strengths were reviewed and found to be present at or below levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products. The formulations are proportionally similar by Definition 2 of the current general BA/BE guidance.

2. **Dissolution Comments:** The test and reference products meet the USP specification of NLT 70% of the labeled amount of levothyroxine dissolved in 45 minutes. Similarity Factor F2 calculated between the highest strength and other strengths was acceptable (greater than 50). The dissolution data are acceptable.

III. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 300 µg, lot # R1H0708, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, lot # 008500, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 300 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, under fasting conditions.

2. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 125 µg, lot # R1H0750, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, lot # 003799, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 125 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, under fasting conditions.

3. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 75 µg, lot # R1H0747, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, lot # 004100, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 75 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, under fasting conditions.

4. The *in vitro* dissolution testing conducted by Mylan on its Levothyroxine Sodium Tablets, 300 µg, 200 µg, 175 µg, 150 µg, 125 µg, 112 µg, 100 µg, 88 µg, 75 µg, 50 µg and 25 µg, has been found **acceptable** by the Division of Bioequivalence.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% SLS at 37C using USP XXIV apparatus II(paddle) at 50 rpm. The test product should meet the following USP specifications:

Not less than 70% of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

5. The firm has demonstrated that the formulations of its Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, are proportionally similar to the formulations of the 300 µg, 125 µg and 75 µg strengths that underwent in vivo bioavailability testing. The biowaiver request of these strengths is granted. The test product, Mylan's Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, is deemed bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, respectively.

Hoaimhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG \S\ + 11/30/2001

Concur. \S\ Date: 12/31/2001
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 76-187 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-30-01/W #76187an01.doc
Also as V:\firmsam\mylan\ltrs&rev\76187an01.doc
Attachment: None

BIOEQUIVALENCY COMMENTS

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-187
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 11/30/2001
HFD-617/ K. Scardini 3/4/02
HFD-650/ D. Conner 12/31/2001

V:\FIRMSAM\MYLAN\LTRS&REV\76187AN01.DOC

Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 11-07-01
11-12-01

1. STUDY AMENDMENT (STA)

Strength: 0.075 mg, 0.125 mg & 0.300 mg
Outcome: AC

2. STUDY AMENDMENT (STA)

Strength: 0.075 mg, 0.125 mg & 0.300 mg
Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable
AC - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-187 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Levothyroxine Sodium Tablets USP
STRENGTH(S) : 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
TYPES OF STUDIES : Fasting SD Studies (for 0.075mg, 0.125 mg & 0.300 mg)
CINICAL STUDY SITE(S)
ANALYTICAL SITE(S)

STUDY SUMMARY : Acceptable
DISSOLUTION: Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : /S/ DATE : 11-29-01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : /S/ DATE : 11/30/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for INITIAL : /S/ DATE : 12/31/2001

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 12, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

RE: ANDA 76-187; LEVOTHYROXINE SODIUM TABLETS, USP
0.025MG, 0.050MG, 0.075MG, 0.088MG, 0.100MG, 0.112MG, 0.125MG
0.150MG, 0.175MG, 0.200MG AND 0.300MG
RESPONSE TO AGENCY CORRESPONDENCE DATED OCTOBER 10, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalency comments pertaining to this application which were provided to Mylan by facsimile on October 10, 2001 (refer to Attachment 1). In response to the October 10, 2001 comments, Mylan would like to amend this application as follows:

Regarding Assay Methodology Reports (all 3 studies):

FDA COMMENT 1:

MYLAN RESPONSE:

FDA COMMENT 2:

MYLAN RESPONSE:

NOV 13 2001
OGD
EVALUATION AND RESEARCH

G:\PROJECT\ANDA\LEVOTHYROXINE\AGENCY-BIO-LETTER-DATED-101001.doc

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-
Label Control (800) 848-
Legal Services (304) 598-6
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

FDA COMMENT 3:

MYLAN RESPONSE:

FDA COMMENT 4.

MYLAN RESPONSE:

REGARDING CLINICAL STUDY REPORTS

FDA COMMENT: In the study clinical reports, the following information was not provided for all 3 biostudies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

MYLAN RESPONSE: The demographic summary tables that were previously submitted in the original application have been updated to provide race information. The revised demographic tables are provided in Attachments 11, 12, and 13 for LEVO-0057, LEVO-0054 and LEVO-0062, respectively.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

CENTER FOR DRUG
NOV 13 2001
EVALUATION AND RESEARCH

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

G:\PROJECT\ANDA\LEVOTHYROXINE\AGENCY-BIO-LETTER-DATED-101001.doc

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Correspondence

'16-101

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 12, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: **LEVOTHYROXINE SODIUM TABLETS, USP 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG**

BIOEQUIVALENCE ELECTRONIC SUBMISSION ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) for the referenced product that was submitted to the Agency on June 5, 2001. Please find enclosed a diskette providing the electronic submission, ESD, for the bioequivalence studies [fasting studies LEVO-0057 (75mg), LEVO-0054 (125mg) and LEVO-0062 (300mg)] that were submitted in the ANDA. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Should you have any questions or require additional information, please contact the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Marlane Juran for

Frank R. Sisto
Vice President
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 16 2001
OGD

Enclosures

G:\PROJECT\ANDA\LEVOTHYROXINE\EVA.doc

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Business Development	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
		Medical Unit	(304) 598-5446		

MYLAN PHARMACEUTICALS INC.
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 5, 2001

Concur.
11-JUL-2001

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 06 2001
OGD

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG,
125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed Abbreviated New Drug Application for:

Proprietary Name: None
Established Name: Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg
This application consists of a total of 37 volumes.
Archival Copy - 16 volumes.
Review Copy - 17 volumes.
Technical Section For Chemistry - 8 volumes.
Technical Section For Pharmacokinetics - 9 volumes.
Analytical Methods - 2 extra copies; 2 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

G:\PROJECT\ANDA\LEVOTHYROXINE\SECTIONS-01THRU07.doc

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

We certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

CENTER FOR DRUG
RECEIVED
JUN 06 2001
OGD
EVALUATION AND RESEARCH

G:\PROJECT\ANDA\LEVOTHYROXINE\SECTIONS-01THRU07.doc

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Establishment Evaluation Request

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 76187/000
Stamp: 06-JUN-2001
Regulatory Due:
Applicant: MYLAN PHARMS
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310
Priority:
Org Code: 600

Action Goal:
District Goal: 06-MAY-2002
Brand Name:
Estab. Name: LEVOTHYROXINE SODIUM
Generic Name:
Dosage Form: (TABLET)
Strength: ALL 11 STRENGTHS

Application Comment:
FDA Contacts: M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:
Establishment:

DMF No:
AADA:
Responsibilities:
Profile: CSN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment:

DMF No:
AADA:
Responsibilities:
Profile: CTL
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment: 1110315
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCM
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment:

DMF No:
AADA:
Responsibilities:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: ANDA 76187/000
Stamp: 06-JUN-2001 Regulatory Due:
Applicant: MYLAN PHARMS
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority:
Action Goal:
Brand Name:
Established Name: LEVOTHYROXINE SODIUM
Generic Name:
Dosage Form: TAB (TABLET)
Strength: ALL 11 STRENGTHS

Org Code: 600
District Goal: 06-MAY-2002

FDA Contacts: M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 01-AUG-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JUL-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUL-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

Establishment: 1118315
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310
DMF No:
AADA No:

Profile: TCM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JUL-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUL-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

2

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

Reason:

___b(4) Confidential Commercial Information

___b(4) Trade Secret Information

✓ b(5) Deliberative Process; Attorney- Client and Attorney Work Product Privileges

___b(6) Personal Privacy

___b(7) Law Enforcement Records

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 76187/000
Stamp: 06-JUN-2001 Regulatory Due:
Applicant: MYLAN PHARMS
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority:
Action Goal:
Brand Name:
Established Name: LEVOTHYROXINE SODIUM
Generic Name:
Dosage Form: TAB (TABLET)
Strength: ALL 11 STRENGTHS

Org Code: 600
District Goal: 06-MAY-2002

FDA Contacts: M. DILLAHUNT (HFD-613) 301-827-5848 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 01-AUG-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-JUL-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUL-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

Establishment: 1118315
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JUL-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: [redacted]
[redacted]
[redacted]
[redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUL-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]
[redacted]
[redacted]
[redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Chemistry Review / CMC
Labeling Def Corresp

1. CHEMISTRY REVIEW NO. 1 (one)

2. ANDA # 76-187

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug for this ANDA is Unithroid® (Levothyroxine Sodium) Tablets manufactured by Jerome Stevens Pharmaceuticals, Inc.
There are no patents that claim the listed drug referred to in this application.
The referenced product is not covered by any exclusivity provisions.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Levothyroxine Sodium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Date of submission: June 5, 2001

10. PHARMACOLOGICAL CATEGORY
Levothyroxine is effective as replacement or supplement therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.
Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters.

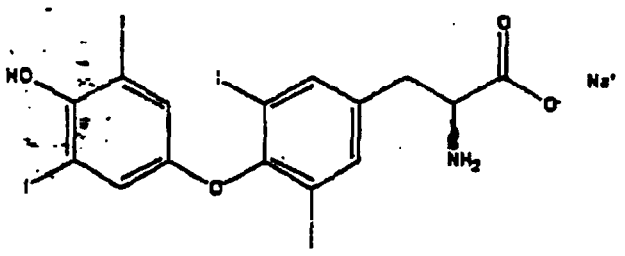
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 21210 Jerome Stevens' Unithroid® tablets

13. DOSAGE FORM
Tablet

14. POTENCY
25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

15. CHEMICAL NAME AND STRUCTURE



Levothyroxine sodium [25416-65-3]
Chemical name: L-Tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-mono-sodium salt
Synonyms: L-3,3',5,5'-tetraiodothyronine, sodium salt (pentahydrate)

$C_{15}H_{10}I_4NNaO_4$
798.85607 (anhydrous)

16. RECORDS AND REPORTS
None

17. COMMENTS

This application is not approvable due to the deficiencies in the following areas.
(1) drug substance (2) analytical method

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

19.

REVIEWER:	DATE COMPLETED:
Liang-Lii Huang, Ph.D.	10/11/01;11/5/01
Endorsed by James Fan	10/11/01;11/5/01

22

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

Reason:

✓ b(4) Confidential Commercial Information

✓ b(4) Trade Secret Information

___ b(5) Deliberative Process; Attorney- Client and Attorney Work Product Privileges

___ b(6) Personal Privacy

___ b(7) Law Enforcement Records

1. CHEMISTRY REVIEW NO. 2 (two)

2. ANDA # 76-187

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug for this ANDA is Unithroid® (Levothyroxine Sodium) Tablets manufactured by Jerome Stevens Pharmaceuticals, Inc.
There are no patents that claim the listed drug referred to in this application.
The referenced product is not covered by any exclusivity provisions.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Levothyroxine Sodium Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Date of submission: June 5, 2001
Minor amendment: January 18, 2002
Telephone amendment: April 19, 2002

10. PHARMACOLOGICAL CATEGORY
Levothyroxine is effective as replacement or supplement therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.
Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters.

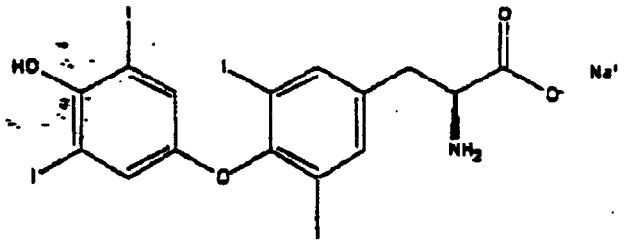
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 21210 Jerome Stevens' Unithroid® tablets

13. DOSAGE FORM
Tablet

14. POTENCY
25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

15. CHEMICAL NAME AND STRUCTURE



Levothyroxine sodium [25416-65-3]
Chemical name: L-Tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-mono-sodium salt
Synonyms: L-3,3',5,5'-tetraiodothyronine, sodium salt (pentahydrate)

$C_{15}H_{10}I_4NNaO_4$
798.85607 (anhydrous)

16. RECORDS AND REPORTS
None

17. COMMENTS

This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

19.

REVIEWER:	DATE COMPLETED:
Liang-Lii Huang, Ph.D.	4/23/02
Endorsed by James Fan	4/23/02

15

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

Reason:

✓ b(4) Confidential Commercial Information

✓ b(4) Trade Secret Information

___ b(5) Deliberative Process; Attorney- Client and Attorney Work Product Privileges

___ b(6) Personal Privacy

___ b(7) Law Enforcement Records

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 19, 2002

ANDA SUPP AMEND
N/Am

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG
ANDA 76-187
RESPONSE TO AGENCY TELEPHONE CALL OF APRIL 18, 2002

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review. Reference is also made to an April 18, 2002 telephone conference held between Dr. Paul Schwartz, Mr. James Fan, Dr. Sarah Ho and Mr. Liang Lii Huang of your Office, and representatives from our firm pertaining to the review of this application. As agreed during the telephone conference, Mylan wishes to amend the application by revising the finished drug product stability specifications for related compounds as follows:

Not More Than — Individual Known Impurities
Not More Than — Other Individual Impurity
Not More Than — Total Impurities (excluding Liothyronine sodium)

The drug product specifications and post-approval stability protocols have been revised to reflect the agreed upon stability specifications for related compounds. The revised specifications and stability protocols are provided in Attachments A and B, respectively.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, is also being forwarded to the FDA's Baltimore District Office.

This amendment, which was submitted via facsimile on the date noted above, is also submitted in duplicate hard copy via Federal Express mail. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talbott for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn
Enclosures

RECEIVED
APR 22 2002
OGD / CDER

Department—Fax Number
Accounting (304) 599-6406
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 599-6406
Information Systems (304) 285-6404
Legal Services (304) 599-5408
Maintenance & Engineering (304) 599-5411
Medical Unit (304) 599-5445
Purchasing (304) 599-5401
Quality Control (304) 599-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 599-3232

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-187
Date of Submission	Jan. 18, 2002
Applicant	Mylan Pharmaceuticals Inc.
Drug Name	Levothyroxine Sodium Tablets USP
Strength(s)	0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

FPL Approval Summary

Container Labels		
0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.3 mg	100s	Submitted January 18, 2002 vol. 4.1blue
Package Insert Labeling	LVTX:R1 Rev. Date Nov. 2001	Submitted January 18, 2002 vol. 4.1

BASIS OF APPROVAL:

No Patent Data For NDA 21-210.

No Exclusivity Data For NDA 21-210.

Reference Listed Drug

RLD on the 356(h) form	Unithorid Tablets
NDA Number	21-210
RLD established name	Levothyroxine sodium
Firm	Jerome Stevens Pharmaceuticals
Currently apprvoved PI	S-001
AP Date	8/21, 2000.

Note:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	[illegible]	[illegible]	[illegible]
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	

Do you find the name objectionable? List reasons in FTR. If so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for the route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does the applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and data study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 21210/ S-001, JSP; Unithyroid, ; approved 8/21/01 .
2. Patent/ Exclusivities: no unexpired patents or exclusivity, firm file a paragraph PI
3. Storage Conditions:
   NDA - 20-25 C (68-77 F) with escursion between 15-30 C (59-86 F)
   ANDA - store at CRT
   USP - None
4. Dispensing Recommendations:
   NDA - none
   ANDA - Dispense in a tight, light resistant container as defined in UDP. Using a child resistant closure.
   USP - tight light resistant container
5. Scoring:
   NDA - partial bisected.
   ANDA - scored
   USP - none
6. Product Line:
   The innovator markets their product in bottles of 100s and 1000s
   The applicant proposes to market their product in HDPE bottles of 100s with CRC.
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).
8. Inactive ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 4441-4470 section VII (Volume 10.1) .
9. Mylan, at Morgantown, will perform all operations in the manufacturing package and labeling.

Date of Review: February 06, 2002

Date of Submission: January 18, 2002

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cc: ANDA: 76-187
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:firmsam/mylan/lets&revs/76187ap.L
Review

2/06/02
2/6/2002

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 18, 2002

N/AM

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG
ANDA 76-187
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 9, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's November 9, 2001 correspondence pertaining to this application (provided in Attachment I). In response to the Agency's comments of November 9th, Mylan wishes to amend this application as follows.

A. DEFICIENCIES

FDA COMMENT 1: Please include D_{10} or D_{50} particle size specification in addition to the present limit for the Levothyroxine Sodium USP drug substance.

MYLAN RESPONSE: Mylan acknowledges the Agency's request for an additional particle size specification at the level for the drug substance. Therefore, Mylan has revised the particle size specifications for the drug substance as follows:

ess than or equal to —
ess than or equal to —

The revised drug substance specifications are provided in Attachment A.

FDA COMMENT 2: Please indicate the method to be used for the moisture determination for the final (pages 6626-6636).

MYLAN RESPONSE: The moisture content of — will be determined via —

CENTER FOR DRUG
JAN 2 2 2002
AND RESEARCH

1/24/02

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

4

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

Reason:

✓ b(4) Confidential Commercial Information

✓ b(4) Trade Secret Information

___ b(5) Deliberative Process; Attorney- Client and Attorney Work Product Privileges

___ b(6) Personal Privacy

___ b(7) Law Enforcement Records

C. REGARDING LABELING DEFICIENCIES

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment L contains twelve (12) copies of the following final printed bottle labels and outsert for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg.

BOTTLE LABELS

25mcg
Code RM1800A – Bottles of 100 Tablets

50mcg
Code RM1803A – Bottles of 100 Tablets

75mcg
Code RM1805A – Bottles of 100 Tablets

88mcg
Code RM1807A – Bottles of 100 Tablets

100mcg
Code RM1809A – Bottles of 100 Tablets

112mcg
Code RM1811A – Bottles of 100 Tablets

125mcg
Code RM1813A – Bottles of 100 Tablets

150mcg
Code RM1815A – Bottles of 100 Tablets

175mcg
Code RM1817A – Bottles of 100 Tablets

200mcg
Code RM1819A – Bottles of 100 Tablets

300mcg
Code RM1821A – Bottles of 100 Tablets

OUTSERT
Code LVTX:R1, Revised November 2001

The enclosed labeling incorporates the revisions requested in the Agency's letter of November 9, 2001. A copy of this correspondence is provided in Attachment I for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment J contains a side-by-side comparison of the final printed bottle labels to those draft bottle labels that were previously submitted and Attachment K contains a side-by-side comparison of the final printed outsert (LVTX:R1) to the draft outsert that was previously submitted. It is noted that prior to approval of this application, the Agency may find the color or other factors in the final printed labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosure

G:\PROJECT\ANDA\LEVOTHYROXINE\AGENCY-LETTER-DATED-110801.DOC

MINOR AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV - 9 2001

TO: APPLICANT: Myland Pharmaceuticals Inc — TEL: 304-599-2595

ATTN: Frank R. Sisto — FAX: 304-285-6407

FROM: Sarah Ho — PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC and Labeling comments provided.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
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-COMM. JOURNAL- DATE NOV-09-2001 TIME 14:31

MODE = MEMORY TRANSMISSION START=NOV-09 14:30 END=NOV-09 14:31

FILE NO.=488

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-CDER OGD DOC RM

MINOR AMENDMENT

ANDA 76-127

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV - 9 2001

Center for Drug Evaluation and Research • FDA •

TO: APPLICANT: Mylan Pharmaceuticals Inc TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-187 Date of Submission: 6/5/01
Applicant's Name: Mylan Pharmaceuticals
Established Name: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg
Labeling Deficiencies:

1. CONTAINER - 100s for each strength.
   a. We acknowledge your comment that each product strength will have a unique color scheme.
   b. Satisfactory in draft.
   c. Ensure that the lot and expiration information are on the labels.
2. INSERT - Please make the following minor changes.
   a. DESCRIPTION - changes " empirical" to "molecular".
   b. PRECAUTION, Information for Patients, number 5 and number 12 - ...sodium tablet... (note- add tablet)
   c. DOSAGE AND ADMINISTRATION
      i. General Principles, 2nd paragraph - revise to read "Levothyroxine sodium tablets" rather than "levothyroxine sodium". (Two occurrences)
      ii. Pediatric Dosage, General Prinicipies , 3rd paragraph - revise "teaspoons" to read teaspoonful.
      iii. TSH Suppression in Well-differentiated Thyroid cancer and Thyroid Nodules, 1st paragraph - place " greater than" in bold print, as does the innovator.
   d. HOW SUPPLIED - revise "capsule shaped" to read "caplet shaped".

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rid/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research