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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-402

Medical Review(s)

MEDICAL OFFICER REVIEW
Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	21-402	**Application Type:**	NDA
Sponsor:	Abbott Labs	**Proprietary Name:**	Synthroid
Investigator:		**USAN / Established Name:**	Levothyroxine sodium
Category:	Thyroid hormone replacement	**Route of Administration:**	oral
Medical Reviewer:	Jean Temeck, M.D.	**Review Date:**	4/18/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 31, 2001	August 2, 2001	NDA	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
August 19, 1999	NDA 21-116	Thyro-Tabs (Levothyroxine sodium): Lloyd
October 19, 1999	NDA 21-210	Unithroid: Jerome Stevens Pharm.
June 27, 2001	NDA 21-292	[redacted] (levothyroxine tabs): Genpharm
July 28, 2000	NDA 21-301	Levoxyl: Jones Pharma, Inc.
April 30, 2001	NDA 21-342	Levo-T: Mova Pharm. Corp.

REVIEW SUMMARY:

This NDA was submitted as a 505(b)(2) application in response to FDA's August 14, 1997 Federal Register Notice (FRN). This FRN declared oral levothyroxine sodium products new drugs due to variations in the stability and potency of a given dosage strength from batch-to-batch produced by a given manufacturer and across different manufacturers. This variability has resulted in numerous recalls due to release of subpotent or superpotent tablets with their attendant adverse clinical consequences.

The sponsor has fulfilled the clinical requirements of the NDA as specified in the Notice by referencing representative articles from the published literature to support the safety and efficacy of levothyroxine sodium for the approved labeled indications. These indications are replacement or supplemental therapy of hypothyroidism and suppression of TSH in the treatment of goiter, nodules and thyroid cancer. These articles have been summarized in detail in previous reviews of related levothyroxine sodium applications (see above).

A levothyroxine labeling template has also been prepared by the Agency and is attached.

From a clinical standpoint, an approval letter may be issued to Abbott Laboratories for their levothyroxine sodium tablets provided they submit draft labeling which conforms to FDA's proposed labeling template for this class of products.

OUTSTANDING ISSUES: Submit to the sponsor a copy of FDA's levothyroxine sodium labeling template.

RECOMMENDED REGULATORY ACTION:

New Clinical Studies:	_____ Clinical Hold	_____ Study May Proceed
NDA, Efficacy/ Label Supplement:	X Approvable	_____ Not Approvable

SIGNATURES: Medical Reviewer: Jean Temeck M.D. Date: 4/18/02

Medical Team Leader: _____ Date: _____

Executive Summary:

This NDA was submitted as a 505(b)(2) application in response to FDA's August 14, 1997 Federal Register Notice (FRN). This FRN declared oral levothyroxine sodium products new drugs due to variations in the stability and potency of a given dosage strength from batch-to-batch produced by a given manufacturer and across different manufacturers.

The drug product itself, levothyroxine sodium, is unstable in the presence of light, temperature, air and humidity. Manufacturers have reformulated levothyroxine drug products over the years, and these reformulations may affect the potency of the product. Hennessey (ref. 127) reported that the downward trend in levothyroxine replacement dose paralleled modifications in formulation with resultant increases in product potency and bioavailability.

The variability in stability and potency from batch-to-batch for a given levothyroxine sodium drug product and across those made by various manufacturers of this drug, has resulted in numerous recalls due to the release of subpotent or superpotent tablets with their attendant adverse clinical consequences.

Subtherapeutic drug concentrations will result in inadequate efficacy. Inadequate treatment of congenital hypothyroidism will adversely affect IQ and linear growth. Inadequate treatment of acquired hypothyroidism will also compromise the child's growth, affect pubertal development (usually delaying puberty) and may result in poor school performance (due to impaired concentration and slowed mentation). Inadequate treatment of hypothyroidism in adults may also adversely affect mentation (slowness of thought and memory loss) and may be associated with decreased cardiac contractility, hypercholesterolemia and infertility. In addition, there is an increased likelihood of miscarriage, stillbirth and premature delivery. Even if the pregnancy is successful, the growth of the fetus and subsequent growth and development of the child may be retarded. Inadequate suppression of TSH by levothyroxine in a patient with well-differentiated thyroid cancer, may stimulate thyroid tumor growth and growth of metastases.

Toxic blood levels may adversely affect the drug's safety profile. Overtreatment for long periods of time has been associated with premature craniosynostosis in infants and may adversely affect the tempo of brain maturation in children; psychomotor retardation has been reported with overtreatment. In addition overtreatment may accelerate the bone age and prematurely close the epiphyses, thereby compromising final adult height. In adults, overtreatment has adverse effects predominately on the heart and bone. Patients overtreated with levothyroxine may have increased heart rates and cardiac contractility as well as left ventricular hypertrophy and arrhythmias. Elderly patients have an increased risk of atrial fibrillation. In addition, long-term treatment with levothyroxine sodium has been associated with decreased bone mineral density, particularly in postmenopausal women receiving suppressive doses of L-T4.

Therefore, it is essential that drugs with a narrow therapeutic index demonstrate consistent potency and stability from lot to lot. It has been reported (Hennessey, ref. 127) that levothyroxine dosage guidelines have required revision over the years to reflect reformulation changes which have resulted in products with increased potency and bioavailability.

In conclusion, maintenance of a euthyroid state, with avoidance of both over- and undertreatment is critical to maintaining the health and well-being of the patient with hypothyroidism. This is best accomplished by having products with consistent potency and stability which is the purpose of the FDA's August 14, 1997 Federal Register Notice. The sponsor has fulfilled the clinical requirements of the NDA as specified in The Notice by submitting a review of the published literature pertaining to the safety and efficacy of levothyroxine sodium products. Please refer to previous reviews of related levothyroxine sodium applications for a detailed review of the published literature relating to the safety and efficacy of levothyroxine sodium in both adult and pediatric patients for the approved labeled indications. The approved indications are use of levothyroxine sodium as replacement or supplemental therapy of hypothyroidism and suppression of TSH in the treatment of goiter, nodules and thyroid cancer. Based on this review, levothyroxine sodium drug products are safe and effective for the stated above indications, provided they demonstrate consistent potency and stability and are used, as directed. A levothyroxine labeling template has also been prepared by the Agency and is attached. From a clinical standpoint, an approval letter may be issued to Abbott Laboratories for their levothyroxine sodium tablets provided they submit draft labeling which conforms to FDA's proposed labeling template for this class of products.

A waiver regarding conduct of clinical trials in pediatric patients may be granted because the published literature adequately supports the safe and effective use of levothyroxine sodium drug products for the indications specified in FDA's levothyroxine labeling template.

Recommended Regulatory Action:
Approval from a clinical perspective provided the sponsor submits draft labeling which conforms to FDA's levothyroxine sodium labeling template.

Table of Contents:

1. Review of Safety from the Bioavailability Studies:
   a. **Title of Study:** A Comparison of the Bioavailability of a Levothyroxine Sodium Tablet Formulation (Synthroid) with that of a Reference Liquid Formulation (Protocol: M01-324, Clinical Study Report: R&D/01/471).

Investigators:
Principal:
Dr. Robert O'Dea (is an employee of the sponsor)
Director, Department of Clinical Pharmacology, Center of Clinical Pharmacology and Pharmacokinetics
Abbott Laboratories
Subinvestigators who are not employees of the sponsor:

Subinvestigators who are employees of the sponsor:

Study Site:
Abbott Clinical Pharmacology Research Unit
Waukegan, Il

Study Design:
This was an open-label, single dose, randomized, 2-way crossover comparing 600 ug (two 300 ug Synthroid tablets) to Synthroid reconstituted solution containing 600 ug levothyroxine sodium. A 40 day washout interval separated the doses of the two study periods.

Results:
32 healthy adult subjects, aged 18-50 years of both sexes (16 males and 16 females) entered the study. 29 subjects completed the study.
There were no deaths or other serious adverse events.
2 subjects (#'s 107 and 209) prematurely discontinued the study due to adverse events (#107: erythematous papular rash on trunk and extremities developing 48h post-dosing with the tablets, resolving 3 days later, assessed as probably related; and, in #209: iron-deficiency anemia, assessed as not related to the Synthroid solution). One subject, #212, prematurely discontinued due to positive nicotine on urine screen and received the solution only.
The percentage of subjects reporting at least one treatment-emergent adverse event was slightly higher among patients who received the tablets (10/30= 33.3%)

than those who received the solution (7/31= 22.6%). On the tablets, the 10 subjects reported 21 AEs and on the solution, 7 subjects reported 10 AEs.
The most common treatment-emergent adverse events (reported by 2 or more subjects in any regimen) were headache, vasodilatation (2 subjects on tablets: hot flashes, feels flushed) and nausea (2 subjects on liquid). Those reported by only one patient were:
on the tablets: back pain, chest pain, photosensitivity reaction, palpitation, diarrhea, dyspepsia, flatulence, GI disorder, nervousness, cough increased, dyspnea, epistaxis, pharyngitis, rash and dysuria;
on the liquid: vasodilatation (hot flashes), iron deficiency anemia, anxiety, dizziness, syncope and pharyngitis.
The majority of AEs were assessed by the investigator as possibly or probably related to study drug and mild in severity with the exception of one that was rated as moderate (dizziness in subject 109, assessed as not related to study drug).
Results of other safety assessments including individual subject changes, changes over time and individually clinically significant values for vital signs, ECGs and physical examinations were unremarkable for each regimen.

b. Title of Study: Proportionality Study of Three Different Dosage-Form Strengths of Marketed Levothyroxine Sodium Tablets (Synthroid) (Protocol: M01-323, Clinical Study Report: R&D/01/470).

Investigator:
Principal: Dr. Robert O'Dea
Subinvestigators:

[redacted] and [redacted]

Study Site:
Abbott Clinical Pharmacology Research Unit
Waukegan, Il

Study Design:
This was an open-label, single dose, randomized, three-period, six-sequence, crossover study design. The total dose of levothyroxine sodium given for each regimen in the study was 600 ug levothyroxine sodium. Subjects received 12-50ug Synthroid tablets (Regimen A), 6- 100ug Synthroid tablets (Regimen B) and 2- 300ug Synthroid tablets (Regimen C) under fasting conditions. A 35 day washout period separated the doses.

Results:
36 healthy adult subjects, aged 18-50 years of both sexes (18 males and 18 females) entered the study. 34 subjects completed the study.
There were no deaths or serious adverse events. No clinically significant physical examination results, vital signs, clinical laboratory values or adverse event profiles were observed during the course of the study.

2 subjects (#'s 115 and 205) prematurely discontinued the study. Subject #115 withdrew consent and was lost to follow-up and subject 205 was lost to follow-up (subject chose not to complete the study).
The percentage of subjects reporting at least one treatment-emergent adverse event was slightly higher for Regimens A and C (7/34= 20.6% and 6/35= 17.1%, respectively) than it was for Regimen B (5/36= 13.9%).
On Regimen A, 7 subjects reported 12 AEs; on Regimen B, 5 subjects reported 7 AEs; and on Regimen C, 6 subjects reported 13 AEs.
The most common treatment-emergent AE (reported by ≥2 subjects in any regimen) was headache. Those reported by only one patient for a regimen were:
on the 50ug tablets:
abdominal pain, asthenia, diarrhea, dyspepsia, GI hemorrhage (subject #204: single episode of small amount of blood in stool, assessed as probably not related, stool culture done), nausea, dizziness and pruritus;
on the 100ug tablets:
vasodilatation (feeling hot), flatulence, dizziness, paresthesia (tongue numbness) and pharyngitis;
on the 300ug tablets:
asthenia, pain, syncope, vasodilatation (feels hot), diarrhea, flatulence, rhinitis, contact dermatitis, pruritus and sweating.
The investigator assessed the majority of AEs as possibly or probably related to study drug and the majority were rated as mild. Only 2 AEs were rated as moderate (dizziness and feeling hot in subject #207) and one as severe (subject #216: episode of fainting which occurred 12 minutes post-dose blood collection, assessed as probably not related to study drug but a vasovagal response associated with blood drawing).
There were no clinically significant changes in laboratory values, vital signs, ECGs or physical examinations.

c. Per volume 19 of the Human Pharmacokinetics and Bioavailability Section of the NDA, the sponsor conducted additional bioavailability studies of Synthroid and in healthy females. FDA requested none of the following studies. Per Table 2, page 13 of volume 19 these studies were:
Protocol #BP1 2020: BA, 2-way crossover, fasting, Synthroid vs. Levothyroxine sample size: n= 29, dose: 2 x 300ug;
BP1 2021: BA, 2-way crossover, fasting, Synthroid vs. Levothroid sample size: n= 27, dose: 2 x 300ug;
BP1 2022: BA, 2-way crossover, fasting, Synthroid vs. Levothroid sample size: n= 28, dose: 4 x 150ug;
BP1 2036: BA, 2-way crossover, Synthroid slower (A) vs. faster (B) dissolving tablets, sample size: n= 30, dose: 4 x 150ug;
FL1 2002: BA, 2-way crossover, fasting, Synthroid vs. Levoxine sample size: n= 30, dose: 24 x 300ug.

Brief Overview of Safety of the Above Studies:

BP1 2020:

There were no study discontinuations due to adverse events. The most frequently reported adverse event was headache. Other AEs were diarrhea (2 events) and one each of abdominal cramps and acid indigestion. These AEs ranged from mild to moderate in severity, all were judged to be possibly related to study medication and all events resolved.

During this study, there were no apparent clinically significant changes from baseline in any of the vital signs.

BP1 2021:

There were no apparent clinically significant changes from baseline in vital signs or laboratory parameters.

No adverse events were reported.

BP1 2022:

There were no apparent clinically significant changes from baseline in vitals. None of the evaluable subjects had any clinically significant laboratory abnormalities. The most common AE was headache. Additional AEs were URI (2 events) and faintness (1 event).

BP1 2036:

None of the subjects had any clinically significant laboratory abnormalities. There were no differences in the incidence of AEs between the 2 formulations (10 subjects or 31% experienced at least one adverse event on each formulation). The most common adverse event was headache. Additional AEs (1-2 events each) included asthenia, flu syndrome, anorexia, diarrhea, nausea, lymphadenopathy, dizziness, somnolence, sweating and conjunctivitis. There were no clinically significant changes from baseline or between the two formulations in vital signs.

FL1 2002:

No patient experienced a serious adverse event and no patient was discontinued from the study due to an adverse event. The predominant AEs reported in this study were headache and asthenia.

2. Financial Disclosure:
   As noted above, the principal investigator of the bioavailability studies, Dr. Robert O'Dea, as well as the following subinvestigators: [redacted] are employees of the sponsor.

3. The following are additional articles of interest from the published literature categorized by topic:
   a. Efficacy: Nontoxic Goiter and Thyroid Nodules:
   Gharib and Mazzaferri (ref. 111) review thyroxine suppressive therapy in patients with nodular thyroid disease. They state that recent studies suggest that spontaneous decrease in size with complete disappearance of the thyroid nodules is not uncommon. Thyroxine suppressive therapy fails to shrink most nodules with only 10-20% of nodules responding to this treatment. The optimal level of TSH suppression has not yet been defined, but complete suppression of TSH to <0.1 mIU/L is probably not necessary in patients with benign thyroid disease. They recommend moderate suppression of TSH to 0.1-0.5 mIU/L for most patients and reserve suppression to <0.1 mIU/L for the occasional patient with a malignant thyroid condition. They mention that the major adverse effects of thyroxine suppressive therapy are on the skeleton (osteopenia) and heart (increased pulse rate, LV mass and frequency of atrial arrhythmias) particularly with long-term TSH suppression in post-menopausal women. This is the rationale for choice of a TSH suppression level between 0.1-0.5 mIU/L: to minimize the side effects of thyroxine therapy. They caution against use of thyroxine suppressive therapy if the pre-treatment TSH is <0.1 mIU/L because subclinical hyperthyroidism may already be present and thyroxine therapy may potentiate thyrotoxicosis, especially in elderly patients. They recommend continued follow-up and monitoring of patients with cytologically benign nodules rather than thyroxine suppressive therapy because most remain stable and benign and, therefore, the potential risks outweigh the potential benefits of long-term suppressive therapy in most patients, particularly postmenopausal women.

   b. Singer (ref. 261) states that the use of levothyroxine suppression for benign thyroid nodules (solitary nodules and euthyroid multinodular goiter) remains controversial both from the efficacy and safety standpoints. Evidence is accumulating to suggest that thyroid hormone administration in doses sufficient to suppress TSH levels, causes subclinical thyrotoxicosis, resulting in a greater likelihood of developing osteoporosis, especially in postmenopausal women. In addition, chronic TSH suppression may be associated with the development of some degree of reversible cardiac hypertrophy (although the clinical significance of this is unknown) and, in the elderly, a greater risk of atrial fibrillation. The efficacy of levothyroxine suppressive therapy in decreasing nodule size is controversial. Likewise, it is unclear to what level TSH should be suppressed and for how long if this mode of therapy is chosen. The author mentions a level of TSH suppression to between 0.1-1.0 mIU/L for approximately 6-12 months. He mentions that avoiding maximum TSH suppression may minimize the potential adverse skeletal and cardiac effects of chronic administration of excess levothyroxine, especially in postmenopausal women and the elderly. He cautions against the use of levothyroxine suppressive therapy in patients with low serum TSH levels which suggests autonomy.

c. Burgi et al (ref. 49) state that thyroid hormone therapy is contraindicated in patients with nontoxic diffuse and nodular goiter who are already subclinically thyrotoxic (i.e. serum TSH is suppressed while serum T_3 and T_4 levels are still normal) because of the risk of development of iatrogenic thyrotoxicosis. The authors state that treatment of these conditions with thyroid hormone rarely gives satisfactory long-term results . It is potentially dangerous in elderly patients who may develop tachyarrhythmias, CHF, MI and angina due to iatrogenic thyrotoxicosis.

d. Cooper (ref. 66) states that with the use of ever more sensitive TSH assays, clinicians can avoid excessive quantities of T_4. The author mentions that there is no evidence that judicious use of T_4, wherein the TSH level is maintained within the normal range, has any deleterious effect on the skeleton or CV system.
In patients with solitary benign thyroid nodules, he recommends aiming for a TSH below normal but above the limit of detection
in a sensitive assay (i.e. >0.1 mU/L). He states there is little justification for full TSH suppression (i.e. to undetectable levels) in patients with a benign thyroid disorder.
The author points out that that autonomous thyroid tissue, if present in a multinodular goiter, will not respond to TSH suppression, but will lead to iatrogenic hyperthyroidism. He also points out that many patients with multinodular goiter are elderly and may have underlying cardiac disease or osteoporosis. Patients in whom the TSH is already at the lower end of the normal range, are not candidates for suppression therapy. Likewise, the presence of significant underlying disease may militate against treatment. In contrast to solitary nodules, there is a high likelihood of regrowth after discontinuation of therapy for multinodular goiter. Therefore, he recommends continuous therapy of multinodular goiter to maintain the TSH in the lower part of the normal range.

4. I have added additional information to the following articles which have been included in my previous reviews:
   a. <u>Safety: Long-term Adverse Cardiovascular Effects:</u>
   Sawin (ref. 247) reported that elderly patients ($\geq$ 60 years) with low serum TSH (suppressed TSH to $\leq$ 0.1 mIU/L) due either to subclinical hyperthyroidism or overtreatment with levothyroxine had ~3 fold increased incidence of atrial fibrillation over a 10 year period compared to those with normal TSH levels.

   b. <u>Safety: Long-term Adverse Effects on Bone:</u>
   Uzzan (ref.) performed a meta-analysis of all controlled cross-sectional studies of the effects of thyroid hormone therapy on bone mineral density that were published between 1982 and 1994. This analysis demonstrated substantial decreases (5-9%) in bone mineral density at the lumbar spine, the proximal femur, and the radius in post-menopausal women receiving long-term suppression therapy with thyroid hormone. No negative effect of therapy on bone mineral density was found in pre-menopausal women on suppressive therapy or in men.

Conversely, replacement therapy was associated with bone loss at the lumbar spine and femoral neck in pre- but not post-menopausal women. However, the authors conclude that only a large long-term prospective placebo-controlled trial of thyroid hormone therapy (e.g. in benign nodules) evaluating bone mineral density and, ideally fracture rate, will provide further insight into these issues.

Faber (ref. 86) performed a meta-analysis of the results of 13 studies of bone density in several hundred women who were receiving long-term (5-15 years) T4 treatment, most of whom had low serum TSH concentrations. Bone loss was measured in the distal forearm, femoral neck and lumbar spine. Premenopausal women, treated on average with 164 mcg L-T4/day for 8.5 years, had 2.67% less bone mass than controls (not statistically significant= NS), corresponding to an excess annual bone loss of 0.31% after 8.5 yrs.of treatment (NS). In contrast, postmenopausal women, treated on average with 171 mcg/day L-T4 for 9.9 yrs. had 9.02% less bone mass than controls, corresponding to a significant excess annual loss of 0.91% after 9.9 yrs. of treatment. Therefore, the meta-analysis did not find any statistically significant reduction in bone mass during prolonged L-T4 treatment in premenopausal women with reduced serum TSH. However, L-T4 treatment in postmenopausal women in doses leading to decreased serum TSH below the lower reference range did result in significant excess annual bone loss compared to controls.

5. Pediatric Waiver:
The sponsor has requested a pediatric waiver on the basis that there are adequate data in the scientific literature to support the safe and effective use of levothyroxine in pediatric patients. This waiver may be granted because it is justified on this basis.

6. Conclusions and Recommendations:
Levothyroxine sodium tablets are safe and effective for the indications stated in the draft labeling for this product. However, it is important to bear in mind that levothyroxine sodium is a drug with a narrow therapeutic index and there may be serious adverse consequences if the dose is not specifically titrated to the needs of the individual patient. Specifically, undertreatment of an infant with congenital hypothyroidism may have adverse consequences on intellectual development and growth. Undertreatment of a child with acquired hypothyroidism may adversely affect school performance, as well as growth and pubertal development. Undertreatment of hypothyroidism in an adult may adversely affect mentation (slowness of thought and memory loss), myocardial performance (impaired myocardial contractility) and lipid levels. Inadequate suppression of TSH by levothyroxine in a patient with well-differentiated thyroid cancer, may stimulate tumor growth and growth of metastases. Conversely, overtreatment is to be avoided. Overtreatment of congenital hypothyroidism with levothyroxine sodium may disrupt the tempo of brain maturation and may result in premature craniosynostosis. Excess T4 replacement in children may accelerate the bone age leading to premature closure of the epiphyses and compromised final adult height. In the adult, overtreatment may have adverse consequences on the myocardium and bone. Therefore, it is critical to

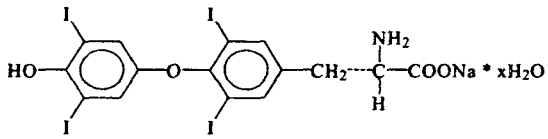
precisely titrate the dose of levothyroxine sodium to achieve and maintain the euthyroid state clinically and biochemically, thus avoiding the adverse consequences of under- and overtreatment, unless TSH suppression is the objective as in patients with well-differentiated thyroid cancer. To achieve this goal, it is essential to have levothyroxine drug products that demonstrate consistent potency and stability.
In addition, a 25 mcg dosage strength that meets chemistry and biopharm criteria for approval, is essential for proper labeling of the product for safe and effective use given that in certain clinical situations, levothyroxine sodium dosing is initiated at — 25 mcg/day and increased in — -25 mcg dosing increments.
From a clinical standpoint, an approval letter may be issued to Abbott Laboratories for their levothyroxine sodium tablets provided they submit draft labeling which conforms to FDA's proposed labeling template for this class of products.

7. Recommended Revisions to FDA's Levothyroxine Labeling Template:
   a. WARNINGS
      Second paragraph, second sentence after the boxed warning, the word "suppressed" and "precipitating" are misspelled.

   b. DOSAGE AND ADMINISTRATION:
      TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules:
      First paragraph, third sentence: the word "individualized" has been misspelled.
      Third paragraph, first sentence: revise the parenthesis to read: (e.g. 0.1 to either 0.5 or 1.0 mU/L)...

8. Levothyroxine Labeling Template Prepared by FDA (note: this is the most recent version of the template and it incorporates the above changes):

TRADEMARK ™ (levothyroxine sodium tablets, USP) 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 an empirical formula of $C_{15}H_{10}I_4N\ NaO_4$ x H_2O, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



Inactive Ingredients

[Product-specific information supplied by applicant]

Strength (mcg)	Color additive(s)

	[Product-specific information supplied by applicant]

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 ANDADMINISTRATION**).

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 TRADEMARK tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately [***Product-specific information supplied by applicant***] %. 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 in Thyroglobulin	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	10 - 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 **WARNINGS** and **PRECAUTIONS**), including thyroid nodules (see **WARNINGS** and **PRECAUTIONS**), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see **WARNINGS** and **PRECAUTIONS**) 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 subclinical (suppressed serum TSH level with normal T_3 and T_4 levels) or overt 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**). TRADEMARK is contraindicated in patients with hypersensitivity to any of the inactive ingredients in TRADEMARK tablets. (See **DESCRIPTION, Inactive Ingredients.**)

WARNINGS

WARNING: Thyroid hormones, including TRADEMARK, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. 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.

In patients with nontoxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see **Contraindications**). If the serum TSH level is not suppressed, Trademark should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

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. Many drugs interact with levothyroxine sodium necessitating adjustments in dosing to maintain therapeutic response (see **Drug Interactions**).

Effects on bone mineral density- In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. 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 **WARNINGS; 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 nontoxic diffuse goiter or nodular thyroid disease - Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see **WARNINGS.**). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see **Contraindications**).

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 TRADEMARK:

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 TRADEMARK. 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 TRADEMARK 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 TRADEMARK 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 TRADEMARK 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 TRADEMARK. It is likely that your dose of TRADEMARK will need to be increased while you are pregnant.
9. Notify your physician or dentist that you are taking TRADEMARK prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of TRADEMARK therapy, but this is usually temporary.
11. TRADEMARK should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep TRADEMARK out of the reach of children. Store TRADEMARK 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 $\leq$ 0.1 mIU/L or third generation assay sensitivity $\leq$ 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 TRADEMARK 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 6-8 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 8-12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6-12 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 TRADEMARK (see **WARNINGS, 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 TRADEMARK 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 TRADEMARK.

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 1-2 months during the first year of life; every 2-3 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 TRADEMARK 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 TRADEMARK. 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 ($\geq$ 1 µg/kg/min); Glucocorticoids (hydrocortisone $\geq$ 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 pharmacological 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 - but FT_4 concentration remains normal; and, therefore, the patient remains euthyroid	
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 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.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol > 160 mg/day) Glucocorticoids - (e.g., Dexamethasone $\geq$ 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)	Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac Glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-α - Interleukin-2	Therapy with interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-β and -γ have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic Agents	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and / or TSH level alterations by various mechanisms.

Oral anticoagulants- Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the TRADEMARK dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see **Table 2**).

Digitalis glycosides- The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 2**).

Drug-Food Interactions – Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

Drug-Laboratory Test Interactions – Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T_4 index (FT_4I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also **Table 2**). Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

Carcinogenesis, Mutagenesis, and Impairment of Fertility – Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine. The synthetic T_4 in TRADEMARK is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed. Patients receiving TRADEMARK for appropriate clinical indications should be titrated to the lowest effective replacement dose.

Pregnancy – Category A – Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. TRADEMARK should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking TRADEMARK should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of TRADEMARK. Since postpartum TSH levels are similar to preconception values, the TRADEMARK dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.

Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

Nursing Mothers – Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when TRADEMARK is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatric Use

General

The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see **DOSAGE AND ADMINISTRATION, Table 3**). Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see **PRECAUTIONS, Laboratory Tests**).

In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that levothyroxine administration be discontinued for a 30-day trial period, but only after the child is at least 3 years of age. Serum T_4 and TSH levels should then be obtained. If the T_4 is low and the TSH high, the diagnosis of permanent hypothyroidism is established, and levothyroxine therapy should be reinstituted. If the T_4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20mU/L, levothyroxine treatment should be discontinued for another 30-day trial period followed by repeat serum T_4 and TSH.

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see **PRECAUTIONS**).

Congenital Hypothyroidism (see **PRECAUTIONS, Laboratory Tests and DOSAGE and ADMINISTRATION**)

Rapid restoration of normal serum T_4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, TRADEMARK therapy should be initiated immediately upon diagnosis and is generally continued for life.

During the first 2 weeks of TRADEMARK therapy, infants should be closely monitored for cardiac overload, arrhythmias, and aspiration from avid suckling.

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients

The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage (see **PRECAUTIONS** and **OVERDOSAGE**). They include the following:
General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating;
Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia;
Musculoskeletal: tremors, muscle weakness;
Cardiovascular: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest;
Respiratory: dyspnea;
Gastrointestinal: diarrhea, vomiting, abdominal cramps and elevations in liver function tests;
Dermatologic: hair loss, flushing;
Endocrine: decreased bone mineral density;
Reproductive: menstrual irregularities, impaired fertility

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Seizures have been reported rarely with the institution of levothyroxine therapy.

Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see **PRECAUTIONS** and **ADVERSE REACTIONS**). In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a child ingesting 18 mg of levothyroxine. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Treatment of Overdosage

Levothyroxine sodium should be reduced in dose or temporarily discontinued if signs or symptoms of overdosage occur.

Acute Massive Overdosage – This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. If not contraindicated (e.g., by seizures, coma, or loss of the gag reflex), the stomach should be emptied by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption. Central and peripheral increased sympathetic activity may be treated by administering B-receptor antagonists, e.g., propranolol, provided there are no medical contraindications to their use. Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hypoglycemia, and fluid loss as necessary. Large doses of antithyroid drugs (e.g. methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T_4 to T_3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T_4 is highly protein bound, very little drug will be removed by dialysis.

DOSAGE AND ADMINISTRATION

General Principles:

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of TRADEMARK that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see **WARNINGS** and **PRECAUTIONS**). Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualized and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (see **PRECAUTIONS, Laboratory Tests**).

TRADEMARK is administered as a single daily dose, preferably one-half to one-hour before breakfast. TRADEMARK should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see **PRECAUTIONS, Drug Interactions**).

Due to the long half-life of levothyroxine, the peak therapeutic effect at a given dose of levothyroxine may not be attained for 4-6 weeks.

Caution should be exercised when administering TRADEMARK to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see **PRECAUTIONS**).

Specific Patient Populations:

Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (see **WARNINGS** and **PRECAUTIONS, Laboratory Tests**)

Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). 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). Older patients may require less than 1 mcg/kg/day. Levothyroxine doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses $\geq$ 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 **25-50 mcg/day** of levothyroxine is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose of levothyroxine in elderly patients with cardiac disease is **12.5-25 mcg/day**, with gradual dose increments at 4-6 week intervals. The levothyroxine dose is generally adjusted in 12.5-25 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 **12.5-25 mcg/day** with increases of 25 mcg/day every 2-4 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**).

TRADEMARK 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 (5-10 ml or 1-2 teaspoons) 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 **10-15 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 4-6 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 2-4 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[a]
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 but growth and puberty incomplete	**2-3 mcg/kg/day**
Growth and puberty complete	**1.7 mcg/kg/day**

[a] 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 **PREGNANCY**).

Subclinical Hypothyroidism- If this condition is treated, a lower levothyroxine dose (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 –The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of TRADEMARK used for TSH suppression should be individualized based on the specific disease and the patient being treated.

In the treatment of well-differentiated (papillary and follicular) thyroid cancer, levothyroxine is used as an adjunct to surgery and radioiodine therapy. Generally, TSH is suppressed to <0.1 mU/L, and this usually requires a levothyroxine dose of **greater than 2 mcg/kg/day**. However, in patients with high-risk tumors, the target level for TSH suppression may be <0.01 mU/L.

In the treatment of benign nodules and nontoxic multinodular goiter, TSH is generally suppressed to a higher target (e.g. 0.1 to either 0.5 or 1.0 mU/L) than that used for the treatment of thyroid cancer. Levothyroxine sodium is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (see **CONTRAINDICATIONS, WARNINGS** and **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 thyroid hormone drug products are not recommended to treat this condition. Thyroid hormone drug products formulated for intravenous administration should be administered.

HOW SUPPLIED

—TRADEMARK™ (levothyroxine sodium tablets, USP) are *[Product-specific information supplied by applicant]*

Strength (mcg)	Color	NDC # for bottles of (count)	NDC # for bottles of (count)

STORAGE CONDITIONS

[Product-specific information supplied by applicant]

Rx ONLY

MANUFACTURER

[Product-specific information supplied by applicant]

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NDA Division file
HFD-510: Dr. Ahn, Dr. Johnson, Dr. Davis-Bruno, Dr. David Lewis, Dr. Markofsky and Mr. McCort

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NDA: 21,402
Drug: Synthroid (levothyroxine sodium tablets)
Sponsor: Abbott Pharm Products Division

Date submitted: 10/18/01
Date received: 10/19/01
Date reviewed: 10/25/01

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Mr. S. McCort, Project Manager:

Please send to Abbott a copy of our latest revised levothyroxine labeling template which can be found in my review of the .

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