CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021116Orig1s012

Trade Name:	THYRO-TABS
Generic or Proper Name:	(levothyroxine sodium)
Sponsor:	Alvogen Inc.
Approval Date:	January 13, 2015
Indication:	THYRO-TABS is L-thyroxine (T4) indicated for: • Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. • Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. Limitations of Use: - Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients. - Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

CENTER FOR DRUG EVALUATION AND RESEARCH

021116Orig1s012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021116Orig1s012

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21116/S-012

APPROVAL LETTER

LLOYD, Inc. of Iowa
Attention: W. Eugene Lloyd DVM, PhD, Chairman
604 W. Thomas Ave.
P.O. Box 130
Shenandoah, IA 51601

Dear Dr. Lloyd:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 12, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Thyro-Tabs® (levothyroxine sodium) Tablet.

We acknowledge receipt of your amendment dated July 19, 2013, November 21, 2014 and December 22, 2014.

The July 19, 2013, submission constituted a complete response to our April 17, 2012, action letter.

This "Prior Approval" supplemental new drug application provides for the modification to the formulation ingredients to improve release values and overall shelf life.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

Ramesh Raghavachari, Ph.D.
Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021116Orig1s012

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-116/S-012

COMPLETE RESPONSE

Lloyd, Inc. of Iowa
Attention: W Eugene Lloyd, DVM, Ph.D.
CEO
604 West Thomas Avenue
Shenandoah, IA 51601

Dear Dr. Lloyd:

Please refer to your Supplemental New Drug Application (sNDA) dated December 12, 2011 and received December 21, 2011 submitted under to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Thyro-Tabs® (levothyroxine sodium) USP Tablets.

We acknowledge receipt of your amendment dated February 27, 2012.

This Prior Approval Supplement provides for the modification to the formulation ingredients to improve release values and overall shelf-life.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. Your prior approval supplement S-012 submitted on December 12, 2011, requesting approval of a proposed reformulation (b) (4) (b) (4)

   - Your proposed reformulation includes (b) (4) as a new excipient. This excipient is (b) (4) included in your approved formulation. Your proposed changes (b) (4) of excipient (b) (4) (b) (4)
   - According to the SUPAC-IR guidance, Section COMPONENTS and COMPOSITION - Level 3 Changes, specifically Section III.C.1a., indicates "*any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.*" (i.e., filler ± 5%), require the submission of supportive *in vivo* bioequivalence (BE) data.
   - (b) (4)

2. Therefore, to support the approval of supplement S-012, conduct the required BE study for your proposed reformulation. The study should assess the BE of the 300µg highest strength of the proposed new formulation vs. the currently approved 300µg tablet formulation. We recommend that you submit the protocol of this BE study for review and

3.

Within
under 2
request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

James D. Vidra, Ph.D.
Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES D VIDRA
04/17/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021116Orig1s012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use THYRO-TABS® safely and effectively. See full prescribing information for THYRO-TABS.

THYRO-TABS® (levothyroxine sodium) tablets, for oral use
Initial U.S. Approval: 2002

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

See full prescribing information for complete boxed warning

- **Thyroid hormones, including THYRO-TABS should not be used for the treatment of obesity or for weight loss.**
- **Doses beyond the range of daily hormonal requirements may produce serious or even life threatening manifestations of toxicity (6, 10).**

----------INDICATIONS AND USAGE----------

THYRO-TABS is L-thyroxine (T4) indicated for:

- Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. (1)
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. (1)

  Limitations of Use:

  - Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients.
  - Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

----------DOSAGE AND ADMINISTRATION----------

- Administer once daily, preferably on an empty stomach, one-half to one hour before breakfast. (2.1)
- Administer at least 4 hours before or after drugs that are known to interfere with absorption. (2.1)
- Evaluate the need for dose adjustments when regularly administering within one hour of certain foods that may affect absorption. (2.1)
- Starting dose depends on a variety of factors, including age, body weight, cardiovascular status, and concomitant medications. Peak therapeutic effect may not be attained for 4-6 weeks. (2 2)
- See full prescribing information for dosing in specific patient populations. (2 3)
- Adequacy of therapy determined with periodic monitoring of TSH and/or T4 as well as clinical status. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg (3)

----------CONTRAINDICATIONS----------

- Uncorrected adrenal insufficiency. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease* Initiate THYRO-TABS at less than the full replacement dose because of the increased risk of cardiac adverse reactions, including atrial fibrillation. (2.3, 5.1, 8.5)
- *Myxedema coma* Do not use oral thyroid hormone drug products to treat myxedema coma. (5.2)
- *Acute adrenal crisis in patients with concomitant adrenal insufficiency* Treat with replacement glucocorticoids prior to initiation of THYRO-TABS treatment. (5.3)
- *Prevention of hyperthyroidism or incomplete treatment of hypothyroidism* Proper dose titration and careful monitoring is critical to prevent the persistence of hypothyroidism or the development of hyperthyroidism. (5.4)
- *Worsening of diabetic control* Therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing thyroid hormone therapy. (5.5)
- *Decreased bone mineral density associated with thyroid hormone over-replacement* Over-replacement can increase bone resorption and decrease bone mineral density. Give the lowest effective dose. (5.6)

----------ADVERSE REACTIONS----------

Adverse reactions associated with THYRO-TABS therapy are primarily those of hyperthyroidism due to therapeutic overdosage: arrhythmias, myocardial infarction, dyspnea, muscle spasm, headache, nervousness, irritability, insomnia, tremors, muscle weakness, increased appetite, weight loss, diarrhea, heat intolerance, menstrual irregularities, and skin rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact LLOYD, Inc. at 1-800-831-0004 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

See full prescribing information for drugs that 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 THYRO-TABS. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy may require the use of higher doses of THYRO-TABS. (2.3, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

Thyroid hormones, including THYRO-TABS, 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 *[see Adverse Reactions (6), Drug Interactions (7.7), and Overdosage (10)]*.

1 INDICATIONS AND USAGE

Hypothyroidism

THYRO-TABS is indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression

THYRO-TABS is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Limitations of Use:

- THYRO-TABS is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with THYRO-TABS may induce hyperthyroidism *[see Warnings and Precautions (5.4)]*.
- THYRO-TABS is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Information

Administer THYRO-TABS as a single daily dose, on an empty stomach, one-half to one hour before breakfast.

Administer THYRO-TABS at least 4 hours before or after drugs known to interfere with THYRO-TABS absorption *[see Drug Interactions (7.1)]*.

Evaluate the need for dose adjustments when regularly administering within one hour of certain foods that may affect THYRO-TABS absorption *[see Drug Interactions (7.9)* and *Clinical Pharmacology (12.3)]*.

Administer THYRO-TABS to infants and children who cannot swallow intact tablets by crushing

the tablet, suspending the freshly crushed tablet in a small amount (5 to 10 mL or 1 to 2 teaspoons) of water and immediately administering the suspension by spoon or dropper. Do not store the suspension. Do not administer in foods that decrease absorption of THYRO-TABS, such as soybean-based infant formula *[see Drug Interactions (7.9)]*.

2.2 General Principles of Dosing

The dose of THYRO-TABS for hypothyroidism or pituitary TSH suppression depends on a variety of factors including: the patient's age, body weight, cardiovascular status, concomitant medical conditions (including pregnancy), concomitant medications, co-administered food and the specific nature of the condition being treated *[see Dosage and Administration (2.3), Warnings and Precautions (5),* and *Drug Interactions (7)]*. Dosing must be individualized to account for these factors and dose adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters *[see Dosage and Administration (2.4)]*.

The peak therapeutic effect of a given dose of THYRO-TABS may not be attained for 4 to 6 weeks.

2.3 Dosing in Specific Patient Populations

Primary Hypothyroidism in Adults and in Adolescents in Whom Growth and Puberty are Complete

Start THYRO-TABS at the full replacement dose in otherwise healthy, non-elderly individuals who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of THYRO-TABS is approximately 1.6 mcg per kg per day (for example: 100 to 125 mcg per day for a 70 kg adult).

Adjust the dose by 12.5 to 25 mcg increments every 4 to 6 weeks until the patient is clinically euthyroid and the serum TSH returns to normal. Doses greater than 200 mcg per day are seldom required. An inadequate response to daily doses of greater than 300 mcg per day is rare and may indicate poor compliance, malabsorption, drug interactions, or a combination of these factors.

For elderly patients or patients with underlying cardiac disease, start with a dose of 12.5 to 25 mcg per day. Increase the dose every 6 to 8 weeks, as needed until the patient is clinically euthyroid and the serum TSH returns to normal. The full replacement dose of THYRO-TABS may be less than 1 mcg per kg per day in elderly patients.

In patients with severe longstanding hypothyroidism, start with a dose of 12.5 to 25 mcg per day. Adjust the dose in 12.5 to 25 mcg increments every 2 to 4 weeks until the patient is clinically euthyroid and the serum TSH level is normalized.

Secondary or Tertiary Hypothyroidism

Start THYRO-TABS at the full replacement dose in otherwise healthy, non-elderly individuals. Start with a lower dose in elderly patients, patients with underlying cardiovascular disease or patients with severe longstanding hypothyroidism as described above. Serum TSH is not a reliable measure of THYRO-TABS dose adequacy in patients with secondary or tertiary hypothyroidism and should not be used to monitor therapy. Use the serum free-T4 level to monitor adequacy of therapy in this patient population. Titrate THYRO-TABS dosing per above instructions until the patient is clinically euthyroid and the serum free-T4 level is restored to the upper half of the normal range.

Pediatric Dosage - Congenital or Acquired Hypothyroidism

The recommended daily dose of THYRO-TABS in pediatric patients with hypothyroidism is based on body weight and changes with age as described in Table 1. Start THYRO-TABS at the full

daily dose in most pediatric patients. Start at a lower starting dose in newborns (0-3 months) at risk for cardiac failure and in children at risk for hyperactivity (see below). Monitor for clinical and laboratory response *[see Dosage and Administration (2.4)]*.

Table 1. THYRO-TABS 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
Greater than 12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.6 mcg/kg/day
a. The dose should be adjusted based on clinical response and laboratory parameters *[see Dosage and Administration (2.4)* and *Use in Specific Populations (8.4)]*.	

Newborns (0-3 months) at risk for cardiac failure: Consider a lower starting dose in newborns at risk for cardiac failure. Increase the dose every 4 to 6 weeks as needed based on clinical and laboratory response.

Children at risk for hyperactivity: To minimize the risk of hyperactivity in children, start at one-fourth the recommended full replacement dose, and increase on a weekly basis by one-fourth the full recommended replacement dose until the full recommended replacement dose is reached.

Pregnancy

Pre-existing Hypothyroidism: THYRO-TABS dose requirements may increase during pregnancy. Measure serum TSH and free-T4 as soon as pregnancy is confirmed and, at minimum, during each trimester of pregnancy. In patients with primary hypothyroidism, maintain serum TSH in the trimester-specific reference range. For patients with serum TSH above the normal trimester-specific range, increase the dose of THYRO-TABS by 12.5 to 25 mcg/day and measure TSH every 4 weeks until a stable THYRO-TABS dose is reached and serum TSH is within the normal trimester-specific range. Reduce THYRO-TABS dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure THYRO-TABS dose is appropriate.

New Onset Hypothyroidism: Normalize thyroid function as rapidly as possible. In patients with moderate to severe signs and symptoms of hypothyroidism, start THYRO-TABS at the full replacement dose (1.6 mcg per kg body weight per day). In patients with mild hypothyroidism (TSH < 10 IU per liter) start THYRO-TABS at 1.0 mcg per kg body weight per day. Evaluate serum TSH every 4 weeks and adjust THYRO-TABS dosage until a serum TSH is within the normal trimester specific range *[see Use in Specific Populations (8.1)]*.

TSH Suppression in Well-differentiated Thyroid Cancer

Generally, TSH is suppressed to below 0.1 IU per liter, and this usually requires a THYRO-TABS dose of greater than 2 mcg per kg per day. However, in patients with high-risk tumors, the target level for TSH suppression may be lower.

2.4 Monitoring TSH and/or Thyroxine (T4) Levels

Assess the adequacy of therapy by periodic assessment of laboratory tests and clinical evaluation. Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of THYRO-TABS may be evidence of inadequate absorption, poor compliance, drug interactions, or a combination of these factors.

Adults

In adult patients with primary hypothyroidism, monitor serum TSH levels after an interval of 6 to 8 weeks after any change in dose. In patients on a stable and appropriate replacement dose, evaluate clinical and biochemical response every 6 to 12 months and whenever there is a change in the patient's clinical status.

Pediatrics

In patients with congenital hypothyroidism, assess the adequacy of replacement therapy by measuring both serum TSH and total or free-T4. Monitor TSH and total or free-T4 in children as follows: 2 and 4 weeks after the initiation of treatment, 2 weeks after any change in dosage, and then every 3 to 12 months thereafter following dose stabilization until growth is completed. Poor compliance or abnormal values may necessitate more frequent monitoring. Perform routine clinical examination, including assessment of development, mental and physical growth, and bone maturation, at regular intervals.

While the general aim of therapy is to normalize the serum TSH level, TSH may not normalize in some patients due to in utero hypothyroidism causing a resetting of pituitary-thyroid feedback. Failure of the serum T4 to increase into the upper half of the normal range within 2 weeks of initiation of THYRO-TABS therapy and/or of the serum TSH to decrease below 20 IU per liter within 4 weeks may indicate the child is not receiving adequate therapy. Assess compliance, dose of medication administered, and method of administration prior to increasing the dose of THYRO-TABS *[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.4)]*.

Secondary and Tertiary Hypothyroidism

Monitor serum free-T4 levels and maintain in the upper half of the normal range in these patients.

3 DOSAGE FORMS AND STRENGTHS

THYRO-TABS tablets are available as follows:

Tablet Strength	Tablet Color/Shape	Tablet Markings
25 mcg	Orange/Caplet	"T|4" and "25"
50 mcg	White/Caplet	"T|4" and "50"
75 mcg	Violet/Caplet	"T|4" and "75"
88 mcg	Mint Green/Caplet	"T|4" and "88"
100 mcg	Yellow/Caplet	"T|4" and "100"
112 mcg	Rose/Caplet	"T|4" and "112"
125 mcg	Brown/Caplet	"T|4" and "125"
137 mcg	Deep Blue/Caplet	"T|4" and "137"
150 mcg	Light Blue/Caplet	"T|4" and "150"
175 mcg	Lilac/Caplet	"T|4" and "175"

Tablet Strength	Tablet Color/Shape	Tablet Markings
200 mcg	Pink/Caplet	"T|4" and "200"
300 mcg	Green/Caplet	"T|4" and "300"

4 CONTRAINDICATIONS

THYRO-TABS is contraindicated in patients with uncorrected adrenal insufficiency *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Adverse Reactions in the Elderly and in Patients with Underlying Cardiovascular Disease

Over-treatment with levothyroxine may cause an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias, particularly in patients with cardiovascular disease and in elderly patients. Initiate THYRO-TABS therapy in this population at lower doses than those recommended in younger individuals or in patients without cardiac disease *[see Dosage and Administration (2.3), Use in Specific Populations (8.5)]*.

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive THYRO-TABS therapy. Monitor patients receiving concomitant THYRO-TABS and sympathomimetic agents for signs and symptoms of coronary insufficiency.

If cardiac symptoms develop or worsen, reduce the THYRO-TABS dose or withhold for one week and restart at a lower dose.

5.2 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. Use of oral thyroid hormone drug products is not recommended to treat myxedema coma. Administer thyroid hormone products formulated for intravenous administration to treat myxedema coma.

5.3 Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency

Thyroid hormone increases metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to initiating glucocorticoid therapy may precipitate an acute adrenal crisis in patients with adrenal insufficiency. Treat patients with adrenal insufficiency with replacement glucocorticoids prior to initiating treatment with THYRO-TABS *[see Contraindications (4)]*.

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

THYRO-TABS has a narrow therapeutic index. Over- or undertreatment with THYRO-TABS may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and glucose and lipid metabolism. Titrate the dose of THYRO-TABS carefully and monitor response to titration to avoid these effects *[see Dosage and Administration (2.4)]*. Monitor for the presence of drug or food interactions when using THYRO-TABS and adjust the dose as necessary *[see Drug Interactions (7.9) and Clinical Pharmacology (12.3)]*.

5.5 Worsening of Diabetic Control

Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing THYRO-TABS *[see Drug Interactions (7.2)]*.

5.6 Decreased Bone Mineral Density Associated with Thyroid Hormone Over-Replacement

Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly in post-menopausal women. 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. Administer the minimum dose of THYRO-TABS that achieves the desired clinical and biochemical response to mitigate this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with THYRO-TABS therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5), Overdosage (10)]*. 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, muscle spasm
- *Cardiovascular:* palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest
- *Respiratory:* dyspnea
- *Gastrointestinal:* diarrhea, vomiting, abdominal cramps, elevations in liver function tests
- *Dermatologic:* hair loss, flushing, rash
- *Endocrine:* decreased bone mineral density
- *Reproductive:* menstrual irregularities, impaired fertility

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

Adverse Reactions in Children

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.

Hypersensitivity Reactions

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

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs can exert effects on thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to THYRO-TABS (see Tables 2-5 below).

Table 2. Drugs That May Decrease T4 Absorption (Hypothyroidism)

Potential impact: Concurrent use may reduce the efficacy of THYRO-TABS by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.	
Drug or Drug Class	**Effect**
Calcium Carbonate Ferrous Sulfate	Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer THYRO-TABS at least 4 hours apart from these agents.
Orlistat	Monitor patients treated concomitantly with orlistat and THYRO-TABS for changes in thyroid function.
Bile Acid Sequestrants - Colesevelam - Cholestyramine - Colestipol Ion Exchange Resins - Kayexalate - Sevelamer	Bile acid sequestrants and ion exchange resins are known to decrease levothyroxine absorption. Administer THYRO-TABS at least 4 hours prior to these drugs or monitor TSH levels.
Other drugs: Proton Pump Inhibitors Sucralfate Antacids - Aluminum & Magnesium Hydroxides - Simethicone	Gastric acidity is an essential requirement for adequate absorption of levothyroxine. Sucralfate, antacids and proton pump inhibitors may cause hypochlorhydria, affect intragastric pH, and reduce levothyroxine absorption. Monitor patients appropriately.

Table 3. Drugs That May Alter T4 and Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism)

Drug or Drug Class	Effect
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.

Drug or Drug Class	Effect
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.
Potential impact (below): Administration of these agents with THYRO-TABS results in an initial transient increase in FT4. Continued administration results in a decrease in serum T4 and normal FT4 and TSH concentrations.	
Salicylates (> 2 g/day)	Salicylates inhibit binding of T4 and T3 to TBG and transthyretin. An initial increase in serum FT4 is followed by return of FT4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T4 levels may decrease by as much as 30%.
Other drugs: Carbamazepine Furosemide (> 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-inflammatory Drugs - Fenamtes	These drugs may cause protein-binding site displacement. Furosemide has been shown to inhibit the protein binding of T4 to TBG and albumin, causing an increase free T4 fraction in serum. Furosemide competes for T4-binding sites on TBG, prealbumin, and albumin, so that a single high dose can acutely lower the total T4 level. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and free T4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Closely monitor thyroid hormone parameters.

Table 4. Drugs That May Alter Hepatic Metabolism of T4 (Hypothyroidism)

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased THYRO-TABS requirements.	
Drug or Drug Class	**Effect**
Phenobarbital Rifampin	Phenobarbital has been shown to reduce the response to thyroxine. Phenobarbital increases L-thyroxine metabolism by inducing uridine 5'-diphospho-glucuronosyltransferase (UGT) and leads to a lower T4 serum levels. Changes in thyroid status may occur if barbiturates are added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of levothyroxine.

Table 5. Drugs That May Decrease Conversion of T4 to T3

Potential impact: Administration of these enzyme inhibitors decreases the peripheral conversion of T4 to T3, leading to decreased T3 levels. However, serum T4 levels are usually normal but may occasionally be slightly increased.	
Drug or Drug Class	**Effect**
Beta-adrenergic antagonists (e.g., Propranolol > 160 mg/day)	In patients treated with large doses of propranolol (> 160 mg/day), T3 and T4 levels change, TSH levels remain normal, and patients are clinically euthyroid. Actions of particular beta-adrenergic antagonists may be impaired when a hypothyroid patient is converted to the euthyroid state.
Glucocorticoids (e.g., Dexamethasone $\geq$ 4 mg/day)	Short-term administration of large doses of glucocorticoids may decrease serum T3 concentrations by 30% with minimal change in serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production (See above).
Other drugs: Amiodarone	Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, and decreased or normal free-T3) in clinically euthyroid patients.

7.2 Antidiabetic Therapy

Addition of THYRO-TABS therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control, especially when thyroid therapy is started, changed, or discontinued *[see Warnings and Precautions (5.5)]*.

7.3 Oral Anticoagulants

THYRO-TABS 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 THYRO-TABS dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

THYRO-TABS may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may decrease when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.

7.5 Antidepressant Therapy

Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and THYRO-TABS 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 central nervous system stimulation. THYRO-TABS may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on THYRO-TABS may result in increased THYRO-TABS requirements.

7.6 Ketamine

Concurrent use of ketamine and THYRO-TABS may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

7.7 Sympathomimetics

Concurrent use of sympathomimetics and THYRO-TABS 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.

7.8 Tyrosine-Kinase Inhibitors

Concurrent use of tyrosine-kinase inhibitors such as imatinib may cause hypothyroidism. Closely monitor TSH levels in such patients.

7.9 Drug-Food Interactions

Consumption of certain foods may affect THYRO-TABS absorption thereby necessitating adjustments in dosing *[see Dosage and Administration (2.1)]*. Soybean flour, cottonseed meal, walnuts, and dietary fiber may bind and decrease the absorption of THYRO-TABS from the gastrointestinal tract. Grapefruit juice may delay the absorption of levothyroxine and reduce its bioavailability.

7.10 Drug-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone and/or determine the free-T4 index (FT4I) in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentration. Nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, androgens, and corticosteroids decrease TBG concentration. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Experience with levothyroxine use in pregnant women, including data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages *[see Data]*. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since TSH levels may increase during pregnancy, TSH should be monitored and THYRO-TABS dosage adjusted during pregnancy *[see Clinical Considerations]*. There are no animal studies conducted with levothyroxine during pregnancy. THYRO-TABS should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, gestational hypertension, pre-eclampsia, stillbirth, and premature delivery. Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development.

Dose Adjustments During Pregnancy and the Postpartum Period

Pregnancy may increase THYRO-TABS requirements. Serum TSH levels should be monitored and the THYRO-TABS dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the THYRO-TABS dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration (2.3)]*.

Data

Human Data

Levothyroxine is approved for use as a replacement therapy for hypothyroidism. There is a long experience of levothyroxine use in pregnant women, including data from post-marketing studies that have not reported increased rates of fetal malformations, miscarriages or other adverse maternal or fetal outcomes associated with levothyroxine use in pregnant women.

8.2 Lactation

Risk Summary

Limited published studies report that levothyroxine is present in human milk. However, there is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for THYRO-TABS and any potential adverse effects on the breastfed infant from THYRO-TABS or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of THYRO-TABS varies with age and body weight. Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters *[see Dosage and Administration (2.3, 2.4)]*.

In children in whom a diagnosis of permanent hypothyroidism has not been established, discontinue THYRO-TABS administration for a trial period, but only after the child is at least 3 years of age. Obtain serum T4 and TSH levels at the end of the trial period, and use laboratory test results and clinical assessment to guide diagnosis and treatment, if warranted.

Congenital Hypothyroidism *[See Dosage and Administration (2.3, 2.4)]*

Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, initiate THYRO-TABS therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients.

Closely monitor infants during the first 2 weeks of THYRO-TABS therapy for cardiac overload, arrhythmias, and aspiration from avid suckling.

Closely monitor patients to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment is associated with craniosynostosis in infants, may adversely affect the tempo of brain maturation, and may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients

Closely monitor patients 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.

8.5 Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, initiate THYRO-TABS at less than the full replacement dose *[see Warnings and Precautions (5.1)* and *Dosage and Administration (2.3)]*. Atrial arrhythmias can occur in elderly patients. Atrial fibrillation is the most common of the arrhythmias observed with levothyroxine overtreatment in the elderly.

10 OVERDOSAGE

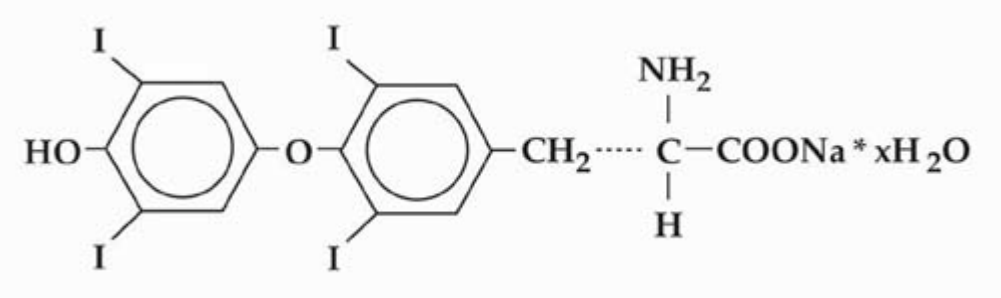
The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions (5)* and *Adverse Reactions (6)]*. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures occurred in a 3-year- old child ingesting 3.6 mg of levothyroxine. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Reduce the THYRO-TABS dose or discontinue temporarily if signs or symptoms of overdosage occur. Initiate appropriate supportive treatment as dictated by the patient's medical status.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

THYRO-TABS (levothyroxine sodium tablets, USP) contain synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T4) sodium]. Synthetic T4 is chemically identical to that produced in the human thyroid gland. Levothyroxine (T4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \bullet \mathbf{x}H_2O$ (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



THYRO-TABS tablets for oral administration are supplied in the following strengths: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg. Each THYRO-TABS tablet contains the inactive ingredients microcrystalline cellulose, calcium phosphate dibasic dihydrate, povidone, sodium starch glycolate, magnesium stearate, and butylatedhydroxy toluene. Each tablet strength meets USP Dissolution Test 1. Table 6 provides a listing of the color additives by tablet strength:

Table 6. THYRO-TABS Tablets Color Additives

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

a. Note – FD&C Yellow No. 6 is orange in color.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. Triiodothyronine (T3) and L-thyroxine (T4) 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.

The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.

12.2 Pharmacodynamics

Oral levothyroxine sodium is a synthetic T4 hormone that exerts the same physiologic effect as endogenous T4, thereby maintaining normal T4 levels when a deficiency is present.

12.3 Pharmacokinetics

Absorption

Absorption of orally administered T4 from the gastrointestinal tract ranges from 40% to 80%. The majority of the THYRO-TABS dose is absorbed from the jejunum and upper ileum. The relative bioavailability of THYRO-TABS tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 94%. T4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases bioavailability of T4. Absorption may also decrease with age. In addition, many drugs and foods affect T4 absorption *[see Drug Interactions (7)]*.

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 T4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T4 compared to T3. 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 Drug Interactions (7)]*. Thyroid hormones do not readily cross the placental barrier *[see Use in Specific Populations (8.1)]*.

Elimination

Metabolism

T4 is slowly eliminated (see Table 7). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T3 is derived from peripheral T4 by monodeiodination. The liver is the major site of degradation for both T4 and T3, with T4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T4 is deiodinated to yield equal amounts of T3 and reverse T3 (rT3). T3 and rT3 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.

Excretion

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 T4 is eliminated in the stool. Urinary excretion of T4 decreases with age.

Table 7. Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[a]
Levothyroxine (T4)	10 - 20	1	6-7[b]	99.96
Liothyronine (T3)	1	4	≤ 2	99.5

a. Includes TBG, TBPA, and TBA
b. 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine.

16 HOW SUPPLIED/STORAGE AND HANDLING

THYRO-TABS (levothyroxine sodium, USP) tablets are supplied as follows:

Strength (mcg)	Color/Shape	Tablet Markings	NDC# for bottles of 90	NDC# for bottles of 1,000
25 mcg	Orange/Caplet	"T|4" and "25"	61690-280-40	61690-280-20
50 mcg	White/Caplet	"T|4" and "50"	61690-281-40	61690-281-20
75 mcg	Violet/Caplet	"T|4" and "75"	61690-282-40	61690-282-20
88 mcg	Mint Green/Caplet	"T|4" and "88"	61690-283-40	61690-283-20
100 mcg	Yellow/Caplet	"T|4" and "100"	61690-284-40	61690-284-20
112 mcg	Rose/Caplet	"T|4" and "112"	61690-285-40	61690-285-20
125 mcg	Brown/Caplet	"T|4" and "125"	61690-286-40	61690-286-20
137 mcg	Deep Blue/Caplet	"T|4" and "137"	61690-291-40	61690-291-20
150 mcg	Light Blue/Caplet	"T|4" and "150"	61690-287-40	61690-287-20
175 mcg	Lilac/Caplet	"T|4" and "175"	61690-288-40	61690-288-20
200 mcg	Pink/Caplet	"T|4" and "200"	61690-289-40	61690-289-20
300 mcg	Green/Caplet	"T|4" and "300"	61690-290-40	61690-290-20

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. THYRO-TABS tablets should be protected from light and moisture.

17 PATIENT COUNSELING INFORMATION

Inform the patient of the following information to aid in the safe and effective use of THYRO-TABS:

Dosing and Administration

- Instruct patients to take THYRO-TABS only as directed by their healthcare provider.

- Instruct patients to take THYRO-TABS as a single dose, preferably on an empty stomach, one-half to one hour before breakfast.
- Inform patients that agents such as iron and calcium supplements and antacids can decrease the absorption of levothyroxine. Instruct patients not to take THYRO-TABS tablets within 4 hours of these agents.
- Instruct patients to notify their healthcare provider if they are pregnant or breastfeeding or are thinking of becoming pregnant while taking THYRO-TABS.

Important Information

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in THYRO-TABS is intended to replace a hormone that is normally produced by the thyroid gland. Generally, replacement therapy is to be taken for life.
- Inform patients that THYRO-TABS should not be used as a primary or adjunctive therapy in a weight control program.
- Instruct patients to notify their healthcare provider if they are taking any other medications, including prescription and over-the-counter preparations.
- Instruct patients to notify their physician of any other medical conditions they may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems, as the dose of medications used to control these other conditions may need to be adjusted while they are taking THYRO-TABS. If they have diabetes, instruct patients to monitor their blood and/or urinary glucose levels as directed by their physician and immediately report any changes to their physician. If patients are taking anticoagulants, their clotting status should be checked frequently.
- Instruct patients to notify their physician or dentist that they are taking THYRO-TABS prior to any surgery.

Adverse Reactions

- Instruct patients to notify their healthcare provider if they 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.
- Inform patients that partial hair loss may occur rarely during the first few months of THYRO-TABS therapy, but this is usually temporary.

LLOYD, Inc.

Shenandoah, IA 51601, U.S.A.

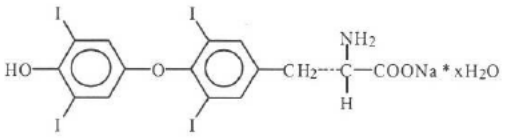
August 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021116Orig1s012

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW # 1	1. ORGANIZATION: PME	2. NDA Number 21-116
3. Name and Address of Applicant (City & State) Lloyd Incorporated P.O. Box 130 604 West Thomas Avenue Shenandoah, Iowa 51601-0130		**4. Supplement(s)** **Number(s)** **Date(s)** S-012 12/12/11
5. Drug Name Thyro-Tabs®	**6. Nonproprietary Name** Levoxythyroxine sodium, USP	**7. Amendments - Dates** S-012 (BC) 2/27/12
8. Supplement Provides For: change in the formulation: [redacted] addition of [redacted] sodium starch glycolate; and [redacted] of butylated hydroxytoluene.		
9. Pharmacological Category Hypothyroidism, Thyroid Goiter, Thyroid Cancer	**10. How Dispensed** Rx	**11. Related NDAs**
12. Dosage Form(s) Tablet	**13. Potencies** 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 µg	
14. Chemical Name and Structure: Levoxythyroxine Sodium, USP  Mol. Formula: $C_{15}H_{10}O_4I_4NNa$ (anhydrous) Mol. Weight: 798 798.85 (calculated on the anhydrous basis) Levoxythyroxine sodium is also known as T_4.		**15. Records/Reports** **Current** **Yes X No** **Reviewed** **Yes No X**

16. Comments: This is a '***Prior Approval***' supplement proposes a modification to the formulation. The proposed formulation of Thyro-Tabs® Human is very similar to the currently approved [redacted] manufacturing method.

Replacing a [redacted], addition of a small amount of sodium starch glycolate [redacted] and addition of a very small amount of BHT [redacted] did not impact the hardness, moisture, and dissolution of the tablets. In addition the stability data also meets all the specification limits.

17. Conclusions and Recommendations: From CMC perspective the supplement is approvable; however, from the Biopharmaceutics perspective the supplement is not recommended for approval at this time.

A **COMPLETE RESPONSE** to the following Biopharmaceutics (refer to Biopharm review in DARRTS, Tien-Mien Chen, Ph.D., dated 3/25/2012) comments should be communicated to the Applicant in the action letter:

1. Your prior approval supplement S-012 submitted on December 12, 2011, requesting approval of a proposed reformulation [redacted] cannot be approved at this time due to the following reasons:

- Your proposed reformulation includes [redacted] This excipient [redacted] in your approved

formulation. Your proposed changes (b) (4)

(b) (4)

- According to the SUPAC-IR guidance, Section COMPONENTS and COMPOSITION - Level 3 Changes, specifically Section III.C.1a., indicates "*any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.*" (i.e., filler ± 5%), require the submission of supportive *in vivo* bioequivalence (BE) data.
- (b) (4)

2. Therefore, to support the approval of supplement S-012, conduct the required BE study for your proposed reformulation. The study should assess the BE of the 300µg highest strength of the proposed new formulation vs. the currently approved 300µg tablet formulation. We recommend that you submit the protocol of this BE study for review and comments.

3. When you submit the report for the completed BE study for the 300µg highest strength, the results should demonstrate that the current and proposed formulations are bioequivalent. Also, (b) (4)

(b) (4)

18. Reviewer:		
Name: Kris Raman, Ph.D.	**Signature:**	**Date Completed:** 4/3/12

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISHNA P RAMAN
04/16/2012

JAMES D VIDRA
04/17/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	21-116/PAS-012
Submission Date:	12/12/11
Brand Name:	Thyro-Tab Human
Generic Name:	Levothyroxine Sodium
Formulation:	Immediately Release (IR) tablets
Strength:	0.025, 0.050, 0.075, 0.088, 0.100, 0.112, 0.125, 0.137, 0.150, 0.175, 0.200, and 0.300 mg (12 strengths)
Applicant:	Lloyd
Type of submission:	PAS (Prior Approval Supplement)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background: LLOYD's Thyro-Tabs® Human (levothyroxine sodium, USP) IR tablets, twelve (12) strengths: 25µg, 50µg, 75µg, 88µg, 100µg, 112µg, 125µg, 137µg, 150µg, 175µg, 200µg, and 300µg, were approved under NDA 21-116 on 10/24/02 (for eleven strengths) and the strength 137µg was approved later on 12/07/04. Thyro-Tabs® Human tablets are intended as a replacement or supplemental therapy in patients with hypothyroidism. Levothyroxine is considered as a narrow therapeutic drug.

A proposed reformulation (a Level-3 formulation change) to the approved Thyro-Tabs® Human IR tablet was previously submitted on (b) (4). Due to a missing bioequivalence (BE) study, PA (b) (4) was not recommended for approval. (b) (4) (b) (4)

Current Submission

On 12/12/11, the Applicant submitted PAS-012 providing a similar modification to the approved formulation. Included in this PAS, there are 1) *In vitro* comparative dissolution data between the batches of the 300µg proposed formulation and the most recently manufactured batches of the currently approved 300µg strength and 2) *In vitro* comparative dissolution data between the reformulated 300µg and three lower strengths (b) (4)

However, the supplement did not include an *in vivo* BE study supporting the approval of the highest 300µg strength.

Biopharmaceutics Review

The above proposed reformulation is considered a Level 3 formulation change (b) (4) according to the SUPAC-IR guidance. Therefore, it requires an *in vivo* BE study. However, the needed BE study was not submitted for review to support this PAS/S-012.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 21-116/PAS-012 for Thyro-Tabs® Human (levothyroxine sodium) IR tablets is not recommended for approval at this time. The following Biopharmaceutics comments should be conveyed to the Applicant.

COMMENTS: (Need to be sent to the Applicant)

1. Your prior approval supplement S-012 submitted on December 12, 2011, requesting approval of a proposed reformulation [redacted] (b) (4) product cannot be approved at this time due to the following reasons:

   - Your proposed reformulation include [redacted] (b) (4) (b) (4)
   - According to the SUPAC-IR guidance, Section COMPONENTS and COMPOSITION - Level 3 Changes, specifically Section III.C.1a., indicates "*any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.*" (i.e., filler ± 5%), require the submission of supportive *in vivo* bioequivalence (BE) data.

   [redacted] (b) (4)

2. Therefore, to support the approval of supplement S-012, conduct the required BE study for your proposed reformulation. The study should assess the BE of the 300µg highest strength of the proposed new formulation vs. the currently approved 300µg tablet formulation. We recommend that you submit the protocol of this BE study for review and comments.

3. When you submit the report for the completed BE study for the 300µg highest strength, the results should demonstrate that the current and proposed formulations are bioequivalent. Also [redacted] (b) (4) (b) (4)

_____ 03/24/12

Tien-Mien Chen, Ph.D. Date
ONDQA Biopharmaceutics Reviewer

_____ 03/25/12

Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

CC: DARRTS/NDA 21-116/PAS-012

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

LLOYD's Thyro-Tabs® Human levothyroxine sodium, USP, tablets, twelve (12) strengths: 25µg, 50µg, 75µg, 88µg, 100µg, 112µg, 125µg, 137µg, 150µg, 175µg, 200µg, and 300µg, were approved under NDA 21-116 on 10/24/02 (for eleven strengths) and the strength 137µg was approved later on 12/07/04. Thyro-Tabs® Human tablets (NDA 21-116) is intended as a replacement or supplemental therapy in patients with hypothyroidism. Levothyroxine is considered as a narrow therapeutic drug.

A proposed reformulation (a Level-3 formulation change) was submitted previously on (b) (4). Due to a missing BE study, th (b) (4) was not recommended for approval. (b) (4)

CURRENT SUBMISSION

Under this PAS-012, the Applicant is proposing a similar modification to the formulation (b) (4) The Applicant reported that the proposed formulation of Thyro-Tabs® Human is nearly identical to the currently approve (b) (4)
The changes proposed involve:

- Replacing (b) (4) (b) (4)
- Adding (b) (4) sodium starch glycolate, NF,
- Addin (b) (4) butylated hydroxytoluene NF (BHT – 2,6-di-t-butyl-4-methylphenol), and (b) (4)

An identical change will be made to all twelve dosage strengths marketed. All other aspects of manufacturing remain unchanged.

In vitro comparative dissolution data of two batches of the most recently manufactured tablets of the currently approved formulation at the highest strength (300µg) were compared to that of three batches of the 300µg proposed tablet formulation. *In vitro* comparative dissolution between the proposed 300µg and three lower strengths (b) (4) (b) (4) were also provided (b) (4) (b) (4)

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the data supporting the approval of the reformulated produc (b) (4) (b) (4) The submission included in vitro dissolution data but it did not include the *in vivo* BE data for the highest strength.

FORMULATION COMPARISONS

The proposed formulation changes are summarized below.

Table 1. The Currently Approved and Newly Proposed Formulation of Thyro-Tab Human (Levothyroxine Na) IR 300µg Tablets

	Theoretical (mg/tablet)	
Ingredient	**Currently Approved**	**Reformulated**
Levothyroxine Sodium		(b) (4)
Microcrystalline Cellulose	(b) (4)	
BHT		
(b) (4)		
Calcium Phosphate Dibasic Dihydrate		
Polyvinylpyrrolidone		
Sodium Starch Glycolate		
Magnesium Stearate		
FD & C Blue #1 Aluminum Lake		
FD & C Yellow #6 Aluminum Lake		
D & C Yellow #10 Aluminum Lake		
Total Tablet		

The changes in the formulation are summarized below:

1 (b) (4)

2. Sodium Starch Glycolate to be added
3. BHT (antioxidant) to be added.

4 (b) (4)

The above proposed reformulation is considered a Level 3 chang (b) (4) according to the SUPAC-IR guidance. Therefore, it requires an *in vivo* BE study. However, the required BE study was not submitted.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The currently approved dissolution method and acceptance criterion for levothyroxine sodium tablets are shown below.

Apparatus:	**USP2 (paddle) with 50 rpm**
Medium:	**0.01 N HCl containing 0.2% Sodium Lauryl Sulfate (SLS), 500 mL at 37°C**
Acceptance Criterion:	**Q= 70.0% at 45 minutes**

Two batches of the most recently manufactured tablets of the currently approved formulation at the highest strength (300µg) were compared to three batches of the 300µg proposed tablet formulation. *In vitro* dissolution profile and f2 data comparing the

proposed 300µg and the proposed lower strength [redacted]

Reviewer's Comments:
NDA 21-116/PAS-012 is not recommended for approval because the *in vivo* BE study needed to support the proposed reformulation is missing in the submission. [redacted]. Therefore, the dissolution data/profiles and f2 data included in this supplement will not be reviewed at this time.

Complete dissolution data to support all the 11 lower strengths vs. the highest strength 300µg tablet (the biobatch to be used in the needed BE study) should be provided when the final report for the BE study is submitted.

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/s/

TIEN MIEN CHEN
03/25/2012

ANGELICA DORANTES
03/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021116Orig1s012

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-116/S-012 **PRIOR APPROVAL SUPPLEMENT**

Lloyd, Inc. of Iowa
Attention: W Eugene Lloyd, DVM, Ph.D.
CEO
604 West Thomas Avenue
Shenandoah, IA 51601

Dear Dr. Lloyd:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Thyro-Tabs® (levothyroxine sodium) USP Tablets
NDA Number:	21-116
Supplement number:	S-012
Date of supplement:	December 12, 2011
Date of receipt:	December 21, 2011

This supplemental application proposes the following changes: modification to the formulation ingredients to improve release values and overall shelf-life.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2012, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 21, 2012.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-4085.

Sincerely,

Swati Patwardhan
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SWATI A PATWARDHAN
01/18/2012