Title: Energy Metabolism in Thyroidectomized Patients

Protocol #: HM20016169

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Funding Sponsor:

NIH National Institute of Health

Investigational Agent(s):	**Levothyroxine** **Liothyronine** **Placebo**
Document Version:	**Final 5.0**
Document Version Date:	02/02/2023

PROTOCOL SUMMARY

Title:	Energy Metabolism in Thyroidectomized Patients
Protocol Number:	**HM20016169**
IND Sponsor:	Not applicable.
Principal Investigator /Study Chair/Coordinating Center/Sponsor-Investigator:	Angeliki Stamatouli, M.D.
Study Sites:	Virginia Commonwealth University Division of Endocrinology Diabetes and Metabolism Department of Internal Medicine 1101 East Marshall Street Sanger Hall, 7th floor Richmond, Virginia 23298 Virginia Commonwealth University Health System Clinical Research Services Unit North Hospital 8th floor 1300 East Marshall Street Richmond, Virginia 23219
Clinical Trial Phase:	Pilot Study
Study Disease:	Surgical hypothyroidism, Weight gain, Energy Expenditure
Main Eligibility Criteria:	Age ≥18-89 years of age Clinical indication for total thyroidectomy TSH at screening >0.45 <4.5 mIU/ml Total Thyroidectomy for benign goiter or thyroid cancer not requiring suppressive thyroid hormone therapy Ability to understand and the willingness to sign a written informed consent document.
Primary Objectives:	**To characterize changes in energy metabolism following thyroidectomy in response to LT3/LT4 vs. LT4 therapy**.

	We will perform dense phenotyping including energy expenditure and substrate utilization during a up to 24-hour stay in a whole-room indirect calorimeter before, and at three and six months following the surgery. These data will enable us to define in detail the changes in weight and energy metabolism due to the lack of endogenous thyroid hormone production, and the response to LT3/LT4 therapy.
Secondary Objectives:	**To determine the effects of thyroidectomy and response to therapy on cardiovascular and endothelial function.** This aim will provide novel information on the effects of hypothyroidism on cardiovascular function, in a well-defined experimental model, and of the potential for LT3/LT4 therapy in preventing hypothyroidism-associated myocardial dysfunction and excess of cardiovascular risk.
Tertiary Objectives	**To characterize the changes in lipid metabolism following thyroidectomy.** In this aim, we will be able to define the changes in serum lipids as a consequence of post-surgical hypothyroidism, and to estimate whether LT3/LT4 is superior to LT4 therapy with respect of this important endpoint associated with cardiovascular risk.
Endpoints:	**Primary**. Differences in weight between LT4 alone or LT3/LT4 therapy. **Primary**. Differences in Energy Expenditure between LT4 alone or LT3/LT4 therapy. **Secondary.** Differences in echocardiogram parameters between LT4 alone or LT3/LT4 therapy. **Secondary**. Differences in Lipid levels between LT4 alone or LT3/LT4 therapy. **Exploratory**. Effects of the Thr92Ala D2 variant on the primary and secondary endpoints. **Exploratory**. Differences in QoL (ThyPRO-39) between LT4 alone or LT3/LT4 therapy.
Study Design:	**This is a pilot, randomized, double-blind, controlled, parallel study** in which thirty patients will be phenotypically characterized at baseline before surgery, 3 and 6 months following surgery. There will be one 6 week post-surgery dose adjustment visit. Both groups will receive active therapy for the treatment of hypothyroidism: either LT4 and placebo or LT4/LT3 combination therapy.
Study Agent/ Intervention Description:	Levothyroxine and placebo or Levothyroxine/Liothyronine combination.

Number of Subjects: 30

Subject Participation Duration: 6 Months

Estimated Time to Complete Enrollment: 1 year

Statistical Methodology:

Our preliminary estimate is based on the findings of our cross-over study with a population of 14 patients (13 female, weight (kg) = 69.7±12.5, age (years) =49.3±8.0. After substitution of LT3 for LT4 a decrease in weight was 1.8±1.9 kg, and in LDL-cholesterol was 13%. In this study LT3 treatment resulted in 85% higher morning serum T3 level as compared to LT4. From our recent study, the estimated increase in serum T3 level on LT3/LT4 combination therapy adopted in the current proposal would be about 44% as compared to LT4 alone, approximately half of the increase in serum T3 observed with full LT3 substitution. Using the point estimates of our recent meta-analysis, the predicted weight gain occurring after thyroidectomy is 1.4 to 2.2 Kg. Similarly, no study has measured changes in energy expenditure using WRIC in similar study populations, and our crossover intervention did not show significant differences in REE between LT3 only and LT4 treatments despite a significant change in body weight.

We hypothesize that LT3/LT4 therapy will be superior to LT4, likely to a smaller effect than LT3 alone. We do not expect that the effect would be larger than that of pure LT3 therapy. On the other hand, the complex interaction of LT4 and LT3 means that an optimal combination ratio may exist theoretically that outperforms the pure LT3 therapy. Based on our empirical observations and extrapolations, we enumerate a few possible effect size to estimate the required sample sizes in a two-arm, randomized, cross-sectional design, given a significance level of 0.05. The following sample size calculation and statistical power estimation are obtained based on two-sample, one-sided t-test based on weight loss in LT3/LT4 as compared to LT4 alone.

Weight Loss LT3/LT4	SD (kg)	Power (%)	Sample Size per	Weight Loss LT3/LT4	SD (kg)	Power (%)	Sample Size per
1.4	1.9	62.7	15	1.4	1.9	80.8	24
1.6	1.9	72.7	15	1.6	1.9	81.6	19
1.8	1.9	81.2	15	1.8	1.9	81.2	15
2.0	1.9	87.8	15	2.0	1.9	80.3	12
2.2	1.9	92.6	15	2.2	1.9	80.1	10
1.4	2.3	49.3	15	1.4	2.3	80.9	35
1.6	2.3	58.5	15	1.6	2.3	81.0	27
1.8	2.3	67.2	15	1.8	2.3	80.2	21
2.0	2.3	75.1	15	2.0	2.3	81.9	18
2.2	2.3	81.9	15	2.2	2.3	81.9	15

Power and sample size calculation for weight differences following thyroidectomy between LT4 and LT4/LT3 combination therapy. The left columns indicate the power of the study on the current sample size (dictated by the time and funding constrains of the R21 funding mechanism). The right columns indicate the sample size calculations necessary to assure an 80% power with a significance of 0.05.

Similarly, power and sample size calculations for changes in lipids were based on our original cross-over study which was associated with 13% reduction in LDL and 12% reduction in non-HDL. From our preliminary study, the estimated increase in serum T3 level on LT3/LT4 combination therapy would be about 44% as compared to LT4 alone. With linear extrapolation, a 5% to 8% reduction in LDL or non-HDL for this study is hypothesized. We also provide the sample size calculation and power estimation for the hypothesized percent reduction in LDL/non-HDL given the LDL of 122.6±25.2 (mg/dl) for LT4 group.

% reduction in LDL LT3/LT4 vs LT4	SD (%)	Power (%)	Sample Size per Arm	% reduction in LDL LT3/LT4 vs LT4	SD (%)	Power (%)	Sample Size per Arm
5%	10	49.7	15	5%	10	80.4	34
6%	10	62.6	15	6%	10	80.7	24
7%	10	74.2	15	7%	10	81.0	18
8%	10	83.5	15	8%	10	81.1	14
5%	12	39.9	15	5%	12	80.7	49
6%	12	49.7	15	6%	12	80.4	34
7%	12	60.5	15	7%	12	80.2	25
8%	12	70.5	15	8%	12	81.4	20

Power and sample size calculation for differences in LDL-cholesterol following thyroidectomy between LT4 and LT4/LT3 combination therapy. The left columns indicate the power of the study on the current sample size (dictated by the time and funding constrains of the R21 funding mechanism). The right columns indicate the sample size calculations necessary to assure an 80% power with a significance of 0.05.

Given the sample size of 15, we further estimate the statistical power of detecting differences in energy expenditure. Based on our recent pilot study on assessing resting metabolic rate (RMR) across 12 healthy, normal weight subjects (including both sexes, BMI: 24.1 ± 2.9, age: 25~71), we estimated that the within-subject variation in RMR is less than 0.15 kcal/min, whereas our instrument variation is less than 0.05 kcal/min within a day. Therefore, using the same cross-sectional design of 15 patients per arm, assuming we can detect a difference in RMR of 0.14 kcal/min (which is more than two times of the instrument precision), we can achieve a sufficient power of 80% with a significance level of 0.05 using a one-sided two-sample t-test.

For the exploratory aims, we plan to assess if the response to ThyPRO-39, a QoL questionnaire/instrument would yield significant difference between subjects on LT4/LT3 vs LT4 alone. We are also interested in

assessing potential genetic heterogeneity underlying the treatment group effect. More specifically, we would model the QoL endpoints using the ANOVA models incorporating treatment effect (LT4/LT3 vs LT4 alone), Thr92Ala D2 polymorphism (Thr/Thr, Thr/Ala, vs Ala/Ala), and their interaction effects. This would depict a better picture of which genetic group might benefit the most from LT4/LT3 combo therapy. This ANOVA modeling strategy can be extended in a straightforward manner to ANCOVA to assessing changes in other outcomes of interest, adjusting for potential genetic heterogeneity, as well as serum T3 level, and other important covariates.

Notice that even if the primary endpoints are expressed as differences between baseline and end of the study, in the LT3/LT4 vs LT4 alone groups, we are collecting phenotypic data at each follow-up time point. This will offer great opportunities to characterize the longitudinal profiles of these phenotypic data and to estimate the effect size as well as the standard deviation over time, essentially the trajectory of these measured endpoints over the 6-month time period. Ultimately, this would help size a much more powerful study that analyzes the repeated measures of the phenotypic data, or design a sufficiently powered study with a limited number of subjects due to the elimination of inter-subject variation. For example, with 4 time points planned for the study, even if the power to assess the treatment effect difference on the weight loss of 1.4 (SD=1.9) is 62.7% given a sample size of 15 vs 15 (LT4/LT3 vs LT4 alone), the power to detect the treatment by time effect could range from 80% up to 95% depending on mean trajectory change, and the correlation structures between measurements at different time points from a repeated measures ANOVA/ANCOVA modeling. We believe this is a significant strength in our dense phenotyping approach with multiple time points, particularly in consideration of the exploratory scope of the R21 funding mechanism.

SCHEMA

Table 1: Schedule of Events.

Procedures	Screening	Baseline	6 Weeks**	3 Months**	6 Months**
Informed Consent	X				
Confirm Inclusion/Exclusion	X				
Medical History	X	X	X	X	X
Physical Examination	X	X	X	X	X
Weight	X				
Vital Signs	X				
TSH [a]	X	X	X	X	X
HbA1c [a] or Fructosamine	X				
TPO Antibodies[a]	X				
24 Hour Resting Energy Expenditure (Whole Room Indirect Calorimeter) [b]		X		X	X
Genomic DNA*		X			
Free T4*		X		X	X
Free T3*		X		X	X
Lipids*a		X		X	X
Serum Storage*		X	X	X	X
Echocardiogram		X		X	X
ThyPro-39 Quality of Life Questionnaire		X		X	X
DXA scan		X			X
Randomization		X			
Study drug dispensation		X	X	X	
Dosing Adjustments			X	X	

- * Analyses run in the Department of Endocrine Lab
- ** +/- 7 days
- a Analyses run in the VCU Health Department of Pathology
- b Visit in Whole Room Indirect Calorimeter may be up to 24 hours

REVISION HISTORY

Revision history is presented in reverse order so that the information pertaining to the most current version of the protocol is presented first in this section.

Version Number	**Date of Issue**	**Type of Revision**	**Brief Description of the Revision**
Version 1,	01/22/2020	Initial Protocol submission	
Version 2	**03/18/2020**	**Revised version of the initial submission**	**Added 10.7 added End of Study Directions**
Version 3	11/03/2020	Revise version 2.0	Revise Exclusion criteria 2 **Current:** Graves' disease or thyroid autoimmunity defined by anti-thyroid peroxidase (TPO) antibodies titer > 35 IU/mL **Changed to:** Graves' disease or thyroid autoimmunity **Clarify**: TPO antibodies to be analyzed in VCU Pathology Central Lab **Current:** **9.12 ClearSight System** This device consists of a small cuff that will be applied over two fingers, and based on the principle of plethysmography records blood pressure, cardiac output, endothelial function and systemic vascular resistance. The measurements will be performed at baseline, 3-months, and 6-months visits.

			Change to: Deleted Deleted ClearSight procedures for **Study visits Baseline, 3 month and 6 month** will not be done **Current:** **Study visits Baseline, 3 month and 6 month** You will be fitted with five accelerometers (one on each limb plus chest) to record spontaneous movements **Changed to :** **Study visits Baseline, 3 month and 6 month** You will be fitted with five accelerometers (one on each limb plus chest) to record spontaneous movements (maybe done based upon availability) **Study visits Baseline, 3 month and 6 month** Accelerometers Fitting - subject will be fitted with five (one on each limb plus chest) to record spontaneous movements. **Changed to:** **Study visits Baseline, 3 month and 6 month** Accelerometers Fitting - subject will be fitted with

			five (one on each limb plus chest) to record spontaneous movements (maybe done depending upon availability) **Current:** **Study visits Baseline, 3 month and 6 month** Each of the three phenotyping visits will include a 24-hour recording of energy expenditure in the whole room calorimeter. **Change to:** **Study visits Baseline, 3 month and 6 month** Each of the three phenotyping visits will include an up to 24-hour recording of energy expenditure in the whole room calorimeter. **Current:** **Study visits Baseline, 3 month and 6 month** Standardized Meals will be served at 13:00, and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat. Approximate total energy needs for weight maintenance will be

			calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at 11:00 of the following day, **Changed:** **Study visits Baseline, 3 month and 6 month** Standardized Meals will be served at 13:00 (if already entered in the WRIC), and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat. Approximate total energy needs for weight maintenance will be calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at approximately 11:00 of the following day, **Current:** **Study visits Baseline, 3 month and 6 month** EE recording will be completed at approximately 11:00 of the following day, **Change** **Study visits Baseline, 3 month and 6 month**

			EE recording will be completed at 11:00 of the following day, **Current:** Volunteers will enter the WRIC at 11:00 and will receive standardized meals at 13:00 **Change:** Volunteers will enter the WRIC at the earliest at11:00 and will receive standardized meals at 13:00 (if already entered in the WRIC), **Current: Exclusion Criteria** Uncontrolled diabetes (HbA1c > 8% at screening) **Change: Exclusion Criteria** Uncontrolled diabetes (HbA1c > 8% or fructosamine < 325 mcmol/l in substitution of HbA1c to reflect recent improvement in diabetes control at screening **Current: Exclusion Criteria** **Weight** <50 or >100 Kg; **Change: Exclusion Criteria** **Weight** <50 or >150 Kg;

Version 4	**03/13/2022**	**Revision to Version 3 to include provisions to address drug-drug interactions**	Advice to contact study team in case of new medications, or dose changes in current medications. Reduction to 1.2 mcg/Kg (-25 mcg in case of randomization to the levothyroxine/liothyronine group) of initial study drug dose in patients taking oral semaglutide
Version 5.0	2/2/2023	Revision to address change in Principle Investigator Changed the name of the Laboratory where samples are separated, aliquot and stored to Department of Endocrine Laboratory	**Current** Principle investigator: Francesco Celi, MD MHSc **Change**Deleted Francesco Celi, MD, MHSc. as PI and changed the Principle investigator to to Angeliki Stamatouli, MD **Current** Serum will be separated by centrifugation, aliquot in 1 mL cryoviales and stored in -80ºC freezers In Dr. Celi's Lab in Sanger Hall changed to **Change** Serum will be separated by centrifugation, aliquot in 1 mL cryoviales and stored in -80ºC freezers In the Department of Endocrine Lab in Sanger Hall

		Added a Sub investigator Add an unblinded physician	Added a Sub investigator Ritu Madan. MD **Current** Dose adjustments will be performed at the 6-week and 3-month follow up visits by an unblinded endocrinologist (Dr. Yavuz) aiming to achieve and maintain a target TSH within the normal range and within ± 0.5 mcIU/ml from the baseline (pre-surgery) TSH, according to the scheme in Table 1. **Change** Dose adjustments will be performed at the 6-week and 3-month follow up visits by an unblinded endocrinologist (Dr. Madan) aiming to achieve and maintain a target TSH within the normal range and within ± 0.5 mcIU/ml from the baseline (pre-surgery) TSH, according to the scheme in Table 1. Doses will be rounded to the nearest available formulation **Current** a physician who is board-certified in Endocrinology and Internal Medicine. Additionally, the unblinded physician (Yavuz) **Change** a physician who is board-certified in Endocrinology and Internal Medicine.

		Analysis of Lipids samples	Additionally, the unblinded physician (Madan) **Current** Analyses run in Dr Celi's Lab **Change** Analysis run in VCU Health Department Pathology Laboratory

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LIST OF ABBREVIATIONS

Abbreviations	Description of abbreviations
AE	Adverse Event
AM	Morning
BIA	Bio-electrical Impedance Analysis
BMI	Body Mass Index
BMR	Basal Metabolic Rate
°C	Celsius
Cmax	Maximum Plasma Concentration
CRF	Case Report Form
CRSU	Clinical Research Service Unit
CT	Computerized Tomography
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
Echo	Echocardiogram
EE	Energy Expenditure
ENT	Ears, Nose, and Throat
° F	Fahrenheit
FOA	Funding Opportunity Announcement (NIH)
GWAS	Genome-wide association study
HgA1c	Glycated Hemoglobin
IU	International Units
IRB	Institutional Review Board
Kg	Kilogram
kca	kilocalories

LT3	Liothyronine
LT4	Levothyroxine
mcg	micrograms
ml	**milliliter**
Na-EDTA	Ethylenediamine Tetraacetic Acid
NIH	National **Institutes** of **Health**
PET	Positron Emission Tomography
PHI	Protected Health Information
PK	Pharmacokinetics
PM	Night
QOL	Quality of Life
SAE	Serious Adverse Event
Tmax	Time to achieve Cmax
TSH	Thyroid-stimulating hormone
TPO	Thyroid peroxidase
T3	triiodothyronine
Free T4	Thyroxine
UP	Unanticipated Problem
VCU	Virginia Commonwealth University
Wi-Fi	Wireless Networking Technology
WRIC	whole room indirect calorimeter

1 BACKGROUND

Hypothyroidism is a common condition, particularly among women (1, 2). Weight gain despite optimal levothyroxine (LT4) replacement therapy is a common and distressful occurrence in hypothyroidism (3), leading to frequent modifications in therapy (4) with negligible improvements and to patients' dissatisfaction. Importantly, weight gain has been consistently recognized as a driver of poor quality of life in hypothyroid patients (3, 5-8). Additionally hypothyroidism is associated with dyslipidemia (9-11) and myocardium dysfunction and increased cardiovascular risk (12-16). There is a need to characterize in detail the changes in energy metabolism in hypothyroidism, and to study the effects of alternative treatment modalities directed to minimize the prevalence and severity of hypothyroid symptoms. Previous studies directed to assess the efficacy of combination liothyronine (LT3)/LT4 therapies aimed to supplement for the loss of endogenous T3 were underpowered, with heterogeneous study populations, and often with inadequate treatment scheme (17-29). Virtually all the professional organizations lament the lack of high quality, definitive data to support or deny the use of combination therapy for the treatment of hypothyroidism (30-32). Post-surgical hypothyroidism represents an ideal model to study the effects of loss of endogenous production of thyroid hormone and of therapeutic modalities because of the absence of confounders due to residual endogenous hormone production and long transition from eu- to hypothyroidism. By combining the study population characteristics with our ability to perform dense phenotyping, and a rigorous study design, we will conduct a proof-of-concept study to characterize the changes in energy metabolism, cardiovascular function, and lipid metabolism before and after thyroidectomy in response to LT4 or LT3/LT4 combination therapy. The results of this study, within the scope of the R21 funding mechanism will define the point estimates of our intervention. This in turn will enable us to: a) define whether a larger study is scientifically warranted, b) provide for the effect size for post-thyroidectomy weight gain to adequately power a large trial which definitely will address the role of combination therapy for the treatment of hypothyroidism, and c) define effect size for secondary and exploratory aims to be applied to a large clinical trial.

Irrespective of the etiology, the treatment of hypothyroidism is based on the replacement of the lack of endogenous production of thyroid hormone. This is commonly accomplished with LT4, which is metabolized by the deiodinase enzymes into T3 that ultimately delivers the hormonal signal to the tissues (30). This strategy is based on the assumption that the action of the deiodinase enzymes is able to deliver adequate T3 to all the tissue targets of thyroid hormone. Experimental and *in vivo* observations have challenged this axiom. The landmark experiments of Morreale d'Escobar in a rodent model of hypothyroidism demonstrated that LT4 alone is not sufficient to restore hypothyroidism in all tissues (33), and only administration of a combination of LT3 and LT4 could provide adequate restoration of T3 (34). On the clinical side, a significant number of patients, estimated in up to 40%, complain of residual symptoms attributed to hypothyroidism despite achieving the therapeutic goal of normalization of the Thyroid Stimulating Hormone (TSH) (3). Common symptoms include weight gain, cold intolerance, sluggishness, and "mental fog" (35). The persistence of hypothyroid symptoms has been attributed to an insufficient delivery of T3 to the target tissues because of the loss of

the T3 produced by the thyroid (estimated to be 20-30 mcg/day) (36) or to a deficit in peripheral conversion of T4 into T3, possibly due to a common polymorphism of the type 2 deiodinase gene (37). Importantly, weight gain is considered the major driver of patients' dissatisfaction (3, 5-8). The use of LT3/LT4 combination therapy was proposed to provide a more "physiologic" replacement and several clinical trials have been conducted (17-29); however, the results are inconsistent and no clear evidence has emerged. This is likely due to low power, different therapeutic regimens, and to the heterogeneity of the study populations, which were mostly composed of individuals with hypothyroidism secondary to autoimmune thyroid disease, which often have residual endogenous thyroid hormone production. In a crossover study, the substitution of desiccated thyroid extracts (DTE) for LT4 resulted in 1.27 Kg weight loss (38). Importantly, patients who lost weight on DTE therapy had a significant improvement in symptoms. Moreover, a secondary analysis of the largest LT3/LT4 trial indicated that carriers of the Thr92Ala D2 were more likely to have worse quality of life at baseline, and more robust response to LT3/LT4 combination therapy (39). In a crossover intervention, we observed that the substitution of LT3 alone for LT4 resulted in significant weight loss and lowering of cholesterol (40). Collectively, these data support the hypothesis that increased serum T3 levels as result of T3-containing therapeutic regimens enables weight loss, reduction in cholesterol, and possibly improvement in quality of life in hypothyroid patients.

Post-surgical hypothyroidism is unique because patients become acutely devoid of endogenous thyroid hormone production, transitioning from a state of euthyroidism to hypothyroidism entirely dependent on exogenous thyroid hormone replacement. To this end, this form of hypothyroidism represents an ideal experimental platform to study the effects of loss of endogenous thyroid hormone production and of the response to therapy. Importantly, recent guidelines for the treatment of thyroid cancer have significantly reduced the need for thyroid hormone suppressive therapy, and the majority of patients undergoing total thyroidectomy for differentiated thyroid cancer are treated with replacement therapy aimed to normalization rather than suppression of the Thyroid Stimulating Hormone (TSH) (41). Surprisingly, little information is available on the changes in body weight and composition following thyroidectomy, and no thyroid hormone replacement therapy study has selectively recruited patients post-thyroidectomy. The reported weight gain within a year of thyroidectomy ranges from none to almost 3 Kg (42-47). These differences are likely due to retrospective nature of the analyses, methodological shortcomings, and inclusion of patients with pre-existing thyroid dysfunction.

2 RATIONALE

2.1 Levothyroxine/Liothyronine (LT4/LT3) combination therapy

Contrary to a smaller longitudinal study (48), Gullo and co-workers have demonstrated that patients on LT4 therapy have lower T3 levels than controls (49). We have shown that pharmacoequivalent doses of LT3, able to achieve the same TSH as LT4 (50), result in high-normal serum T3 levels and that LT4 alone results in serum T3 levels at the low end of the normal range (40). The increase in serum T3 levels (and as a consequence, its increase at the target tissue level) is a likely explanation for the beneficial metabolic effects of LT3 monotherapy. To this end, the addition of LT3 to the LT4 therapy regimen has been proposed as a means to overcome the lack of endogenous thyroid hormone production of T3. The definition of LT3 pharmacokinetics PK) is thus a necessary preliminary step to design a therapy which can provide adequate amount of exogenous T3 to maintain the serum levels within the normal range and to minimize T3 serum level fluctuations above and below the target range. The current data on the LT3 PK are not clear, with an estimated half-life ranging from 6 to 22 hours (51-53). The wide range is in part explained by different experimental protocols and dated hormonal assays. We revisited this question by assessing LT3 kinetic and terminal elimination in a group of patients treated with LT3 alone in preparation for nuclear medicine procedures for thyroid cancer (NCT01441154, PI Celi). Study patients were treated with LT3 0.6 mcg/Kg/day in three daily doses (average dose 18.8±4.5 mcg) (50) for four weeks before undergoing last dose PK analysis and terminal elimination. In this population, the kinetics of LT3 can be described by a two-component (fast distribution and slow elimination) model with a distribution half-life of 1.1 hour and an elimination half-life of 28.4 hour. The Tmax was reached at 1.8±0.5 hour from the LT3 administration, with a Cmax of 324.0±63.3 ng/dl. Based on these observations, we have developed a model to assess the effects of 10 mcg LT3 substitution for 25 mcg of levothyroxine on serum T3 levels, sufficient to increase the serum T3 levels. While a single administration would result in significant fluctuations of T3 levels, a twice daily administration regimen will provide more stable T3 serum levels, well within the normal range throughout the day. The therapeutic scheme adopted in this proposal is thus based on these preliminary data.

2.2 Experimental approach

This proposal is based on the premise that thyroidectomized patients on levothyroxine replacement therapy represent an ideal experimental model to study the pathophysiology of hypothyroidism due to the lack of endogenous thyroid hormone production. To this end, we intend to perform dense phenotyping in thirty patients with clinical indications for total thyroidectomy at baseline (pre- surgery), and while on LT4 or LT4/LT3 combination therapy for a 6-month period aimed to restore the individuals' TSH level prior to the surgery. The recruitment will be primarily performed from patients undergoing evaluation in the multidisciplinary thyroid neoplasia clinic and through ENT at Virginia Commonwealth University, but the study information will be disseminated among local endocrinologists, and self-referral will be allowed.

2.3 Whole-room indirect calorimeters

The indirect calorimeter instruments and techniques allow for non-invasive real-time recording of energy expenditure and respiratory quotient by measuring oxygen consumption and carbon dioxide production[15]. In comparison with alternate forms of measuring energy expenditure (the historically-used metabolic carts and portable calorimeters), the whole room calorimeters overcome the issues of: 1) Low accuracy due to environmental interference (relative humidity, oxygen and carbon dioxide concentration in the testing room, presence of study personnel); 2) Inconvenience of using a face mask or a canopy hood which limit the duration of the observations and the flexibility of conducting tests which require additional sensors or manipulations. Conversely, whole room calorimeters, by allowing free movement of the subject and through controlling and monitoring environmental factors (e.g. temperature, gas concentration in the inflow air), overcome the limitations of the metabolic carts and portable calorimeters. Traditionally, room calorimeters were challenged by the long equilibration period and limited ability of capturing dynamic interventions with time resolution of less than 30 minutes[16]. At VCU, we have recently built and validated a fast-response whole-room calorimeter suite, which allows a fast equilibration period (10 minutes) and recording dynamic changes within 10-15 minutes, favorably comparable to the metabolic cart methods. Additionally, the environmental temperature of our systems can be modulated between 15°C - 30°C (59°F - 86°F) while maintaining an accurate reading. Our room calorimeters are equipped with airtight ports for food administration,Television set, a toilet, and Wi-Fi connectivity, which enable more comfortable and longer studies, as well as direct observation of acute (minutes to hours) effects of pharmacologic interventions on energy expenditure and substrate utilization. The flexibility of the VCU whole-room indirect calorimeter system allows for continuous and noninvasive monitoring of energy expenditure, and other parameters such as heart rate and skin temperature, while the volunteer is in a comfortable environment.

3 TRIAL OBJECTIVES

3.1 Aim 1: To characterize changes in energy metabolism following thyroidectomy in response to LT3/LT4 vs. LT4 therapy.

Historically, the measurement of energy expenditure (EE) by indirect calorimetry has been used as an index of thyroid function (57). While overt thyrotoxicosis and hypothyroidism are associated with dramatic extremes in EE, small differences sufficient to generate significant weight changes (40) or small variations in LT4 dose fall below the detection of the ventilated hood (“metabolic cart”) technique (58). Additionally, the ventilated hood method does not allow for prolonged recordings, negating the opportunity to reliably measure the entire spectrum of the EE. Interestingly, a recent report indicated that the metabolic signature of chronic calorie restriction is low T3 and decreased sleeping EE (59). The whole room indirect calorimeter (WRIC) technique enables recordings of the entire spectrum of EE components, including resting and sleeping EE, spontaneous movements, and thermic effect of food in a near free-living environment (60). For our WRIC system, we have recently devised and validated a data

analysis algorithm to overcome the suboptimal temporal resolution issue associated with traditional WRICs. This method minimizes the latency between events and response in EE recordings and enable truly minute-by-minute real-time monitoring capability of WRIC (61). Additionally, the continuous recording of the respiratory quotient (RQ) during controlled fasting enables us to assess substrate utilization and metabolic flexibility, which correlates well with the risk of developing metabolic complications from obesity (62). The real-time monitoring capability of WRIC, coupled with precise event annotation and timestamping as well as the wearable sensors that collect other physiological data simultaneously, allows for analysis of each component of EE. For example, the thermic effect of food can be found by aggregating the post-prandial EE 4-hours after the meal time. Sleeping/wake onset times can be detected using wearable activity sensors (63) and sleeping EE can be found by aggregating EE between sleep time and wake onset time. While no exercise will be conducted in our study, we also plan to monitor minute-by-minute activity counts and assess the impact of spontaneous activities on EE in our analysis. The optimized temporal response of our WRIC system, and expertise in wearable data collection and analysis, will in turn make the VCU whole room indirect calorimeter system uniquely poised to record small differences in the EE and its components. For the purpose of this study, we will perform 24-hour recordings of EE in the VCU WRIC which has a precision of 0.05 Kcal/min. In preliminary experiments performed in a group of liver transplant patients with or without non-alcoholic fatty liver disease (NAFLD), we were able to detect a significant difference in RQ during controlled fast (Figure 4) indicating that NAFLD adversely affects metabolic flexibility in this population. These data show that the VCU WRIC system is uniquely positioned to detect small differences in EE components which over time can result in significant weight changes. In our study design, study participants will undergo a total of three 24-hour EE recordings before, three, and six months after total thyroidectomy while on LT4 alone or LT3/LT4 therapy. Weight will be measured by a stadiometer at the end of each EE recording, following 15-hour fasting, after voiding. Body composition will be measured by DXA scan at baseline and at the completion of the study.

Expected results. We predict that patients undergoing total thyroidectomy treated with LT4 alone will experience a significant weight gain over a six-month period following the procedure despite adequate replacement therapy. Treatment with LT3/LT4 combination therapy will prevent weight gain while achieving TSH levels similar to the LT4-only group. Moreover, the longitudinal assessment of EE will provide novel and clinically relevant information on the effects of surgical hypothyroidism and its treatment on EE and its components. Collectively, the data will enable us to define in detail the changes in weight and energy balance in its components, and body composition due to the lack of endogenous thyroid hormone production, and the response to therapies.

3.2 Aim 2: To determine the effects of thyroidectomy and response to therapy on cardiovascular and endothelial function.

Hypothyroidism, even in the subclinical range, is an important cardiovascular risk factor (12-16) which is not completely eliminated by the LT4 treatment (64, 65). Experimental data indicate beneficial effects of LT3 supplementation in the recovering phase of cardiac surgery (66), and LT3 therapy has been suggested as a potential addition to the treatment of congestive heart failure (67). While overt hypothyroidism is associated with systolic dysfunction and congestive

heart failure, the effects of subclinical hypothyroidism are subtle, mostly characterized as diastolic dysfunction with distinct echocardiographic changes (14). Of note, in our original study, the LT3-only arm had a significant decrease in isovolumetric relaxation time, and a trend toward an increase in left ventricle end diastolic volume, suggesting an increase in compliance and diastolic function (40). Aside the direct effects on the heart, thyroid hormone also plays a significant role in the maintenance of vascular tone and endothelium function (68-70), and hypothyroidism is associated with an increase in systemic vascular resistance (71). To comprehensively assess the effects of surgical hypothyroidism on cardiovascular function, and to compare the effects of LT4 vs. LT3/LT4 combination therapy, we will use echocardiography . This is a non-invasive device based on the volume clamp method, which continuously measures blood pressure by clamping the artery to a constant volume by dynamically providing equal pressure on either side of the arterial wall, while the volume is measured by a photoplethysmography built into a cuff which is fitted on a hand finger. This non-invasive device is very precise and accurate when compared with measurement of cardiac output using pulmonary artery catheter thermodilution (Swan-Ganz right heart catheterization) (72, 73). The echocardiogram will measure left ventricular end diastolic and end-systolic volumes, calculate ejection fraction, and measure indirect parameters of diastolic function.. The measurements of diastolic parameters will include measuring the early velocity of the mitral annulus in diastole at pulsed wave, tissue Doppler analysis (E') which is an indirect measure of myocardial relaxation and a surrogate for the myocardial relaxation constant τ, and the ratio of the early transmitral flow velocity E to E' (E/E'), which correlates with left ventricular filling pressures (75). **Expected results.** When compared to baseline, we expect that the LT4-treated group will develop subtle evidence of diastolic dysfunction, while the LT3/LT4-treated group will show no changes, indicating that the combination therapy is able to prevent the effect of hypothyroidism on the cardiovascular system. Due to the exploratory nature of the proposal we do not expect that the results will be conclusive, but will provide a unique opportunity of estimating the effects of transition from a state of euthyroidism to full reliance on replacement therapy, and to compare the differential response to LT4 vs. LT3/LT4 therapy on the cardiovascular system. The point estimates obtained from this proposal will then enable us to design an adequately powered study to assess the effects of thyroid hormone replacement on cardiovascular function.

3.3 Aim 3: To characterize the changes in lipid metabolism following thyroidectomy.

Thyroid hormone exerts pervasive actions on lipid metabolism by directly regulating transcription of the LDL receptor, intracellular metabolism of cholesterol within the hepatocyte, cholesterol excretion and reabsorption through the biliary tract, and peripheral lipolysis (10, 76). Hypothyroidism results in significant, reversible hypercholesterolemia, which in turn contributes to increased cardiovascular risk. We have previously demonstrated that the increase in circulating levels of T3 following substitution of LT3 for LT4 results in significant decrease in total and LDL cholesterol, 10.9% and 13.3%, respectively (40). No significant differences in cholesterol or in lipoprotein levels were demonstrated as a result of LT3/LT4 therapy, presumably because of the heterogeneity of the study populations. Our study design offers the

unique opportunity to assess the effects of LT3/LT4 combination therapy in patients who transitioned from euthyroidism to hypothyroidism without the confounder of residual thyroid hormone production or a prolonged course of thyroid dysfunction. We will compare the levels of total, LDL, and HDL cholesterol at baseline and at three and six months following surgery between LT4 and LT3/LT4-treated patients. Additionally, by longitudinally assessing serum lipids in the same patient before and after thyroidectomy while on LT4 or LT3/LT4 therapy, we will be able to obtain information whether surgical hypothyroidism, despite adequate replacement results in significant changes in lipid levels, and if LT3/LT4 therapy this can be prevent these changes. The data gathered in this aim will thus provide high value (due to the strengths of the study design) point estimates to evaluate the effect size of the LT3/LT4 on lipid metabolism. **Expected results.** We predict that the LT3/LT4 therapy will result in a measurable decrease in total and LDL cholesterol compared to LT4 treatment arm, which in turn will show an increase compared to baseline.

3.4 Exploratory aims: to evaluate the changes in ThyPRO-39, a thyroid specific quality of life instrument, and the role of the Thr92Ala D2 polymorphism in post-surgical thyroidectomy patients treated with LT4 or LT3/LT4 combination therapy.

Quality of Life. A deterioration in quality of life is a common complaint of hypothyroidism (4-8), which persists despite adequate replacement therapy (3). While few studies have indicated improvement in indices of quality of life in patients treated with LT3/LT4 combination therapy, the results are far from definitive. Aside study design limitations, some studies used quality of life instruments which lack of specificity for thyroid dysfunction related symptoms. To address this shortcoming, we plan to use the ThyPRO-39, a validated thyroid-specific quality of life instrument which is considered the gold standard for the assessment of thyroid related symptoms and overall well-being (77-80). We have secured the collaboration of Dr. Watt, the creator of this instrument, who will contribute in analyzing the data (see letter of support). We are confident that we will be able to obtain a point estimate difference between the two treatment groups which will enable us to justify the development of a larger adequately powered study to detect clinically significant differences in quality of life.

D2 Polymorphism. Epidemiologic, *in vivo*, and *in vitro* data support the hypothesis that the Thr92Ala D2 polymorphism (81) causes a reduction in the hormonal signaling due to a decrease in conversion of T4 into T3 (82-86). The Thr92Ala D2 polymorphism is associated with worse quality of life at baseline in hypothyroid patients, who responded better to LT3/LT4 combination therapy (39), but the results are not conclusive (87), and no prospective study has been performed to assess its role in the response to combination therapy. The prevalence of the minor Ala92 allele (81) will enable a Mendelian randomization, and we expect that 50% of the study population will be a carrier as heterozygous or homozygous. We do not expect to be able to detect a significant difference in any of the study outcomes as a consequence of the Thr92Ala D2 status, but the data gathered in this proof-of-concept study will enable to measure the point estimate for the modulatory role of the Thr92Ala D2, and if deemed relevant and feasible to design an adequately powered study. Genomic DNA extraction and genotyping will be performed in the Department of Endocrine lab. Briefly, genomic DNA isolated from whole

blood is amplified and genotyped using a SYTO 9 based PCR master mix containing primers specific to the DIO2
rs225014 (Thr92Ala) variant. PCR amplification and genotyping by small amplicon high-resolution melting (88) will be performed on the Applied Biosystems QuantStudio 3 real-time PCR system.

4 STUDY DESIGN

This is a two arm, parallel, double blind placebo controlled (both arms will receive active medication) proof of concept study. Thirty patients will be enrolled and allocated 1:1 to the LT4 alone or to the LT3/LT4 combination regimen. Due to the exploratory and preliminary nature of the funding mechanism (R21) and FOA (Pilot and Feasibility Clinical Trials in Diabetes, and Endocrine and Metabolic Diseases), the study is geared toward gathering a large amount of preliminary data in a relatively small number of study participants (dense phenotyping). The acquisition of point estimates of the endpoints will then enable us to 1) justify the execution of a large study (go/no-go); 2) define primary and secondary outcomes; 3) adequately power a large, multicenter study able to demonstrate clinically relevant differences in the selected endpoints.

5 PATIENT SELECTION

A maximum of 60 adult patients will be screened in this study, in order to have a least 30 patients completed.

The Principal Investigator will give his approval to the participation of each subject in the study on the basis of acceptable medical history and findings in the physical examination and laboratory investigations which comply with the inclusion/exclusion criteria below.

5.1 Inclusion Criteria

A potential subject must meet all of the following inclusion criteria to be eligible to participate in the study.

5.1.1 Clinical indication for total thyroidectomy

5.1.2 Euthyroid (TSH at screening> 0.45<4.5 mIU/mL)

5.1.3 Indication to total thyroidectomy for benign goiter or thyroid cancer not requiring suppressive thyroid hormone therapy

5.1.4 Age 18-89 years of age

5.1.5 Males and females

5.2 Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

5.2.1 Weight <50 or >150 Kg;

5.2.2 Graves' disease

5.2.3 Use of thyroid hormone therapy use of thyroid hormone therapy or thyroid supplements (at screening) except for multinodular goiter;

5.2.4 Indication for thyroid hormone suppressive therapy following surgery

5.2.5 Uncontrolled arterial hypertension. (Stage 2 or greater on medication); (>140/90 mmHg at screening while on medication (patients with hypertension controlled by therapy will be allowed to participate).

5.2.6 Cardiovascular disease: congestive heart failure; unstable coronary artery disease (angina, coronary event, or revascularization within 6 months); atrial fibrillation, arrhythmia or ventricular arrhythmia,

5.2.7 Pregnancy, breastfeeding, or planned pregnancy within six months from the thyroidectomy

5.2.8 History of major depression or psychosis;

5.2.9 Uncontrolled diabetes (HbA1c > 8% or fructosamine < 325 mcmol/l in substitution of HbA1c to reflect recent improvement in diabetes control at screening

5.2.10 Conditions that in the opinion of the PI may impede the successful completion of the study

Patients on statin treatment will be allowed to participate in the study and the treatment will remain unchanged throughout the study.

6 STUDY ENTRY AND WITHDRAWAL PROCEDURES

6.1 Study Entry Procedures

6.1.1 Required Pre-Registration Screening Tests and Procedures

The study participants will be recruited primarily among patients attending the multidisciplinary endocrine tumor program at VCU, although self-referral from ClinicalTrials.gov will be allowed. The study will also be publicized among local endocrinologists and ENT surgeons. Self-referral will be allowed.

During the screening visit, the following procedures will be performed: informed consent, history and physical examination performed by a trained physician, weight and vital signs recorded by a trained physician or nurse.

Registration Process

After obtaining informed consent and all initial screening visit procedures, patients will participate in one screening visit, one dose adjustment outpatient visit, and three inpatient overnight admissions (referred as phenotyping visits)

6.2 Study Withdrawal Procedures

6.2.1 A patient is free to withdraw from the study for any reason, at any time, without reason for doing so and without any penalty of prejudice.

6.2.2 A patient may be removed from treatment for one of the following criteria:

6.2.3 The study physician thinks it is necessary for the health and safety of the patient.

6.2.4 Principal Investigator's decision to discontinue the study.

6.2.5 The patient is non-adherent with the protocol

6.2.6 If an adverse event (including worsening of the concomitant illness) develops which is considered by the Investigator as incompatible with continuation of the study

6.2.7 Administrative reasons that require the patient to withdrawal

6.2.8 If pregnancy develops

6.2.9 Lost to follow-up

6.2.10 Patient death

6.2.11 All available data will be collected if feasible. The reason for discontinuation should be documented in the case report form (CRF).

If a patient decides to withdraw from the study, any information and specimens already collected will be handled according the following algorithm. Patients who withdrew consent before the end of their involvement will not have their data used.

Table 2: Effects of Withdrawal on Data Collected.

Timing of Withdrawal	Action
After the screening visit, before baseline	Data collected will not be deleted, but no additional information regarding the patient will be obtained.
After the baseline visit before 6 week Visits	Data collected will not be deleted, but no additional information regarding the patient will be obtained. Information gathered can still be used in analyses.
After the 6 week Visit before Month 3	Data collected will not be deleted, but no additional information regarding the patient will be obtained.
After Month 3 Visit before 6 Month	Data collected will not be deleted, but no additional information regarding the patient will be obtained.

7 PREMATURE TERMINATION

7.1 The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination, which must be documented.

8 TREATMENTS

8.1 Investigational /non Investigational Products

The following medications will be used in this study:

- Levothyroxine (LT4)
- Liothyronine (LT3)
- Placebo (sugar pill)
  (Medisca empty gelatin capsules size 00 manufactured by CapsuleDepot)

The VCU Investigational Drug Pharmacy will over-encapsulate the Investigational Pharmacy will over-encapsulateLT4 plus placebo, or LT4 plus 5 mcg LT3 in “AM” and “PM” color coded capsules.

The pharmacy will create the over-encapsulating tablets and making matching placebo capsule placebo distinguish the AM and PM doses They will use; dextrose, USP (anhydrous) manufactured by Medisca empty gelatin capsules size 00 manufactured by CapsuleDepot
The placebo capsules is used to assist in the blinding process, It will allow that two capsules to be given as one of the randomized study drug is one drug Levothyroxine alone. The placebo will make the number of capsules (2) the same dose Levothyroxine and Lithothyroxine dose combination

8.2 Study Dosing Group

In this study, Levothyroxine (LT4) and placebo (a look-alike inactive substance, a "sugar pill") will be compared to Liothyronine/levothyroxine (LT3/LT4) combination therapy. Levothyroxine (LT4) and Liothyronine (LT3) are drugs approved by the U. S. Food and Drug Administration (FDA).

There will be thirty (30) subjects enrolled into the study. They will be randomly assigned 1:1 into one of two study-dosing groups:

Table 3: Randomization Dosing Table

Study Group	Number of Subjects
LT4 group + Placebo	Fifteen Subjects
LT4/LT3 group	Fifteen Subjects

8.3 Dosage and administration

Study Dosing

Patients in the LT4 group will be started at a dose of 1.6 mcg/Kg (52), while patients assigned to LT4/LT3 group will have 25 mcg of LT4 substituted with 5 mcg LT3 twice daily, to mimic the average daily T3 production form the thyroid (36). For patients taking oral Semaglutide the initial levothyroxine dose will be reduced to 1.2 mcg/Kg (-25 mcg in case of randomization to the levothyroxine/liothyronine group) to correct for increase in absorption. The VCU Investigational Pharmacy will over-encapsulate LT4 plus placebo, or LT4 plus 5 mcg LT3 in "AM" and "PM" color coded capsules. Patients will be instructed to take the AM drug first thing in the morning with water only, and to wait at least 30 minutes before taking other medications coffee or breakfast. The PM dose will be taken at least 30 minutes before dinner. Dose adjustments will be performed at the 6-week and 3-month follow up visits by an unblinded endocrinologist (Dr. Madan) aiming to achieve and maintain a target TSH within the normal range and within ± 0.5 mcIU/ml from the baseline (pre-surgery) TSH, according to the scheme in Table 1. Doses will be rounded to the nearest available formulation. No changes will be made in LT3.

Patients and their healthcare providers will be encouraged to inform the study team of any change in medications. An information card containing a basic description of the protocol, study medications, and contact information of the PI and study coordinator will be given to the study. participants with instructions to show it at any encounter with healthcare providers for the duration of the study.

Table 4: Dose Adjustment Table

Table 1. Dose Titration	
TSH µIU/ml	**Adjustment**
Baseline ± 0.5	No change
Baseline >0.5-7.0	Increase by 10%
>7.0	Increase by 20%
Baseline <0.5-0.1	Decrease by 10%
<0.1	Decrease by 20%

9 STUDY PROCEDURES

STUDY VISIT PROCEDURES

The entire protocol consists of five visits: one screening visit, one baseline visit, one dose adjustment visit, and three inpatient overnight admissions (referred as “phenotyping visits”). The follow up study visits will occur in a +/- 7-day window. Study participants will be admitted for their baseline phenotyping visit before surgery. Randomization will be performed at the time of the baseline visit. On discharge from the hospital, (postoperative day 1 or 2) patients will start the study drugs. An outpatient visit for dose adjustment will occur six weeks following surgery. Three months after surgery, patients will have a second overnight phenotyping visit and therapy adjustment. A third phenotyping visit (end of study) will be performed six months after surgery. The overnight phenotyping visits will be identical, except no DXA scan will be performed at baseline and during the 6-month post-op visit.

The summary of the procedures is presented in the table 2 (study scheme)

9.1 Informed Consent

Prior to performing any study-related procedures, the patient must sign and date an Institutional Review Board (IRB)-approved informed consent form (ICF). The informed consent process must be thoroughly documented in the patient's record.

9.2 Medical History:

The following information will be gathered from the patient and from the review of the medical records:

- Age
- Self-reported race/ethnicity
- Medical History
- Prior history of cardiovascular disease, diabetes, hypertension, dyslipidemia.
- Prior surgical history
- Social history (use of tobacco or alcohol)
- History of Medication usage
- Female subjects will be asked to provide a menstrual history,
    - use of contraception, and
    - self-reported pregnancy status planning for the study period.

9.3 Physical Examination

An abbreviated physical examination will be performed, and the following organ systems will be evaluated:

- Vital signs: oral temperature and blood pressure
- Neurological exam: focal deficit, resting tremor, reflexes
- Lungs: sounds
- Cardiovascular: rate, rhythm, murmur, peripheral pulses
- Abdomen: tenderness, organomegaly

9.4 Energy Expenditure Recordings

Each of the three phenotyping visits will include an up to 24-hour recording of energy expenditure in the whole room calorimeter. The room calorimeter is a 10' x 10' x7'6" room with a window and transparent plexiglass wall. The room is fitted with TV, phone, hospital bed, small desk, a toilet behind a privacy screen and a vanity. Meals are passed through an air lock port. The room is fitted with Wi-Fi and the door has no lock. The enclosed space may cause some minimal discomfort and the ventilation can be noisy, non-dissimilar to a commercial airplane. Study volunteers will be instructed they can step out the room and withdraw from the study at any time, and there is no lock in the calorimeter's door. Volunteers will enter the WRIC at the earliest at11:00 and will receive standardized meals at 13:00 (if already entered in the WRIC), and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat.

Approximate total energy needs for weight maintenance will be calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at approximately 11:00 of the following day.

9.5 Anthropometric data

Height and weight will be recorded using a calibrated stadiometer. Temperature, heart rate, and blood pressure will be recorded by a research nurse.

9.6 Blood Collection

Venous Blood Sample Collection
We will insert a needle in a vein to collect blood samples at specified times. Study subjects will undergo one venipuncture during each of the study visits. Altogether, five blood samples will be collected throughout the study for a total of approximately one and a half cup of blood. All the samples collected will be for the research study, except for the measurement of TSH that will be used to adjust the therapy. We will store and analyze your samples for lipids (cholesterol, HDL, triglycerides), Thyroid stimulating Hormone TSH (determinations for dose adjustments), Free T4 and total T3. TPO antibodies and HbA1c or fructosamine < 325 mcmol/l in substitution of HbA1c to reflect recent improvement in diabetes control (the latter for patients with diabetes) will be collected at the screening visit to help determine the presence of autoimmune thyroid disease and, limited to patients with diabetes, the control of the disease. Blood samples will be collected at screening, baseline (pre-surgery), 3-month and 6-month study visits.

We will collect two 5 mL of blood will be collected in a Na-EDTA tube (purple top) at the baseline visit to obtain HbA1c and to extract genomic DNA. Approximately 20 mL of blood will be collected in SST tubes with (no additives except serum separator) each session for TSH, thyroid hormones (total T3 and free T4), serum lipids and storage. No more than 320 mL of blood will be collected over the course of the five sessions. Serum will be separated by centrifugation, aliquoted in 1 mL cryovials and stored in -80ºC freezers in the Department of Endocrine laboratory in Sanger Hall. Samples will be stored as described above for future analyses for studies. The Thr92Ala D2 polymorphism will be analyzed in the Department of Endocrine laboratory. Dr. Ni will supervise the performance of these analyses.

9.7 Accelerometers

The accelerometers are sensing devices that measure a moving object's acceleration and can detect frequency and intensity of human movement. They are very similar to “Fitbit” or other exercise recording devices. Maybe done depending upon availability

9.8 Genetic Material

Genetic material will be collected during the study to study whether common gene variations called “Single Nucleotide Polymorphisms” (SNPs) in gene that regulate the thyroid hormone

signaling affect the response to the therapy. We do not plan to screen for genetic disease, and the information collected are without clinical interest, thus the information will not be provided to the volunteers. No genome wide association study will be performed, and the genetic material will be disposed of at the end of the study. Study volunteers can opt out the collection of genetic material.

9.9 Quality of Life assessment

Study participants will be administered ThyPRO-39, a thyroid specific quality of life instrument at the baseline (pre-surgery), 3-month and 6-month visit. This questionnaire helps the researchers to measure the intensity of the symptoms associated with hypothyroidism, and their changes in relation to the therapy. Some individual may experience discomfort by gaining introspection in their condition.

9.10 DXA Scan (Dual-energy x-ray Absorptiometry):

DXA stands for dual-energy x-ray absorptiometry (also known as a **DEXA scan**). A simple, 10-minute test takes a comprehensive snapshot of your exact breakdown of bone, fat tissue, and muscle mass. The DXA scan is the most accurate and precise body fat test available. There are not any special preparations needed, except to stop taking any calcium supplements for 24 hours before the test. Study participants are requested to lay still on a table while a sensor (similar to an X-ray machine) moves over the body from the head to the feet. Wear comfortable clothing. Study volunteers will undergo (DXA scan) at the baseline and six-month visits. The only potential risk associated with DXA scan is the exposure to radioactivity.

9.11 Echocardiogram (echo)

An echocardiogram will be performed at the baseline, three and six-month visits to assess the myocardial structure and ejection fraction.

10 STUDY VISITS

10.1 Overall study schedule

Study schedule summarized (Table 1)

10.2 Screening/Inclusion

(Screening Visit)

Trained Endocrinologists and study staff will conduct the screening Visit

Study Identifiers

At screening, each volunteer will be assigned a sequential volunteer ID number (EMT-01M25, EMT-02F27, etc) that will indicate study identifier, sequential number of screening, sex, age). The suffix "E" will be applied to volunteer who met the inclusion criteria and were enrolled in the study. The volunteer ID number will be used for all study related procedures. The key to the volunteer ID number will be maintained by the study coordinator and will be kept in a secure location behind a locked door (Sanger Hall, 8th Floor, Room 8-066). Only allowed investigators on the study roster will have access to the key (upon request). The key will be destroyed at the end of study following VCU policy.

Screening Visit will include:

- Informed Consent (section 9 (9.1))
- Anthropometric information, which include measures of height, weight, temperature, and body composition and blood pressure.(section 9 (9.5))
- A physical exam will be performed by the study physician (section 9 (9.3))
- The study team will collect the following information (section 9 (9.2))
    - demographics,
    - Medical history
    - Prior surgical history,
    - social history,
    - history of medication usage;
- Female subjects will be asked to provide a menstrual history,
    - use of contraception, and
    - Self-reported pregnancy status for the study period.
- Blood sampling: (section 9(9.6))
    - Thyroid peroxidase antibody (TPO antibodies)
    - Thyroid Stimulating Hormone (TSH)
    - HgA1c (for subjects with a history of diabetes)
- Review the inclusion /exclusion to determine eligibility section (5 5.1 and 5.2)

The Endocrinologist will determine study eligibility. Eligible subjects will proceed to three identical overnight **Phenotyping Visits and one outpatient Dose Adjustment Visit:**

- (Visit 1) Baseline

- (Visit 2) Three month after surgery and
- 6 Week Dose Adjustment Visit
- (Visit 3) Six month Visit End of study

10.3 Phenotype Visit 1 (Baseline)

Once the surgical thyroidectomy date has been determined, subjects will be scheduled for the Phenotype (Visit 1) Baseline Visit

10.3.1 **Two (2) days prior to the Phenotype Visit 1 Baseline**

Subjects will be instructed to:

- refrain from strenuous exercise
- Remain on a regular diet

10.3.2 **Prior to Surgery Phenotype Visit 1 Baseline**

Subjects will be admitted to the hospital on the Clinical Research Services Unit for an inpatient stay in the whole room indirect calorimeter (WRIC) prior to Thyroidectomy surgery (Standard of care)

- **Randomization** will be performed

- **The following will be performed in the am Prior to Entry into the WRIC**
  - An abbreviated history and physical examination.
  - Echocardiogram recorded,
  - Administration of ThyPRO-39.
  - Accelerometers Fitting - subject will be fitted with five (one on each limb plus chest) to record spontaneous movements. (maybe done depending upon availability)
  - DXA scan
  -

- **The subject will enter the WRIC at 11:00 am**

- **Dietary Meals**
  - The study will provide Standardized Meals.

  - Standardized Meals will be served at 13:00 (if already entered in the WRIC), and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat. Approximate total energy needs for weight maintenance will be calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at approximately 11:00 of the following day,

- EE recording will be completed at approximately 11:00 of the following day,

- Blood sampling: TSH, Genomic DNA, Free T4, Free T3, Lipids, serum for storage
- Dispense Study Medication prior to discharge

On discharge from the hospital, (postoperative day 1 or 2) patients will start the study drugs

10.4 Six Week Post Surgery

An outpatient visit for dose adjustment will occur six weeks following surgery.

- An abbreviated history and physical examination.
- Blood sampling: TSH, serum for storage
- Dose Adjustment
- Dispense Study Medication prior to discharge

10.5 Phenotype Visit 2 (Month 3)

Three months after surgery, patients will have a second overnight phenotyping visit and Medication adjustment.

- **The following will be performed in the am Prior to Entry into the WRIC**
  - An abbreviated history and physical examination
  - Pill count
  - Echocardiogram recorded,
  - Administration of ThyPRO-39.
  - Accelerometers Fitting - subject will be fitted with five (one on each limb plus chest) to record spontaneous movements. (maybe done depending upon availability)
  -

- **The subject will enter the WRIC at 11:00 am**

- **Dietary Meals**
  - The study will provide Standardized Meals.

  - Standardized Meals will be served at 13:00 (if already entered in the WRIC), and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat. Approximate total energy needs for weight maintenance will be calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at approximately 11:00 of the following day,

- EE recording will be completed at approximately 11:00 of the following day,

- Blood sampling: TSH, Free T4, Free T3, Lipids, serum for storage
- Dispense Study Medication prior to discharge

Note: No DXA scan will be performed during the 3-month post-op visit.

10.6 Phenotype Visit 3 (Month 6)

Six months after surgery a third phenotyping visit (end of study).

- **The following will be performed in the am Prior to Entry into the WRIC**
  - An abbreviated history and physical examination
  - Pill count
  - Echocardiogram recorded
  - Administration of ThyPRO-39
  - Accelerometers Fitting - subject will be fitted with five (one on each limb plus chest) to record spontaneous movements. (maybe done depending upon availability)
  - DXA scan
  -

- **The subject will enter the WRIC at 11:00 am**

- **Dietary Meals**
  - The study will provide Standardized Meals.

  - Standardized Meals will be served at 13:00 (if already entered in the WRIC), and at 18:00, each representing 1/3 of the estimated EE with the following macronutrient composition: 50% carbohydrate, 20% protein, 30% fat. Approximate total energy needs for weight maintenance will be calculated using the Mifflin-St. Jeor equation (89). EE recording will be completed at approximately 11:00 of the following day,

  - EE recording will be completed at approximately 11:00 of the following day,

  - Blood sampling: TSH, Free T4, Free T3, Lipids, serum for storage

  - Collect Medication prior to discharge

10.7 End of study Treatment

At the end of the trial the subjects care will be transferred to their endocrinologist or primary care provider. We will prescribe three-month supply of the levothyroxine or levothyroxine-

liothyronine combination therapy, based on the subject's preference since both drugs are approved for the treatment of hypothyroidism. The subjects insurance will be responsible for the cost of the prescription since the study is completed.

11 STUDY RECRUITMENT AND RETENTION

11.1 Recruitment

11.1.1 Recruitment of Women, children and minority individuals study

In this study, we will recruit exclusively adult women and men (age > 21). This choice is driven by scientific reasons because the prevalence of hypothyroidism is highest in the adult population. The study design precludes the recruitment of children since the differences in the biomarkers between adults and children would impede the interpretation of the data collected. Furthermore, since this proof-of-principle study the participation of minors in the study would provide little additional information. We expect an overrepresentation of women in the study, reflecting the higher prevalence of hypothyroidism in females. We will encourage the recruitment of minorities, and the ethnic composition of the accrual table reflect the population attending the outpatient clinics of Virginia Commonwealth University Medical Center.

11.1.2 Recruitment and retention plan

The recruitment will be primarily performed from patients undergoing evaluation in the multidisciplinary thyroid neoplasia clinic and through ENT at Virginia Commonwealth University, but the study information will be disseminated among local endocrinologists, and self-referral will be allowed. Additionally, the study will be disseminated through Adult Endocrinologists and Surgeons performing thyroidectomy at VCU (ENT and Endocrine Surgeons) will be made aware of the study hypothesis, design, and potential benefits for the participants.

11.2 Retention

Study participants will not receive compensation, but the study visits, including TSH assay for therapy adjustment will be performed free of charge. Additionally, the study medications will be dispended free of charge for the duration of the study (six months). Patients will be provided with meal and parking coupons for the study visits. Patients will also be informed of the results of their phenotype studies, including body composition, energy expenditure, and echocardiogram. These benefits should provide sufficient incentive to assure retention of the study participants.

12 DATA AND SAFETY MONITORING PLAN (DSMP)

Data and Safety Monitoring Plan (DSMP):
The research team will develop a complete DSMP for review by the NIH. The PI, Dr. Angeliki Stamatouli, a physician board-certified Endocrinology, Diabetes and Metabolism, and Internal Medicine will assume responsibility to ensuring the overall safety of protocol participants.

An independent Data and Safety Monitoring Board (DSMB) will be responsible for monitoring the safety of participants and the data associated with the proposed study.
The DSMB will be comprised of a physician, a pharmacist, and biostatistician. One member of the DSMB will be selected as the Committee Chair and will be responsible for generating a written summary of the content of each quarterly meeting. Potential adverse events will be listed in the IRB-approved protocol and in the consent form. A record of adverse events will be retained in a study binder for review by the study team, the independent DSMB, and the IRB. The classification of adverse events will be as follows: 1) Mild Severity, discomforts that do not disrupt daily activities, or adverse events in which no therapy or only symptomatic therapy is required); 2) Moderate Severity (discomfort sufficient to modify normal daily activity, or adverse events requiring specific therapy that is more than symptomatic; 3) Serious Severity (illness or injury resulting in inability to work or to perform normal daily activities, life-threatening events or death). All adverse events will initially be evaluated by the PIStamatouli), a physician who is board-certified in Endocrinology and Internal Medicine. Additionally, the unblinded physician (Madan) and the Cardiologist (Abbate) will be available to provide insight on the severity and the potential association with the study drugs and dosage. Those events classified as moderate or severe will be reported to DSMB Committee Chair for review within 24 hours. The entire DSMB will meet to review all serious adverse events, should they occur. In addition, all serious adverse events, both anticipated and unanticipated, will be reported to the IRB within 48 hours (and to the NIH within a timeframe consistent with the policy of the institute). Additionally, a summary of all adverse events will be submitted to the Institution IRB annually as part of the protocol's continuing review.

13 CLINICALTRIALS.GOV REQUIREMENTS:

This application includes a trial which requires registration in ClinicalTrials.gov. As is required, this trial will be registered upon approval from the institution's IRB.
Dissemination of study results through ClinicalTrials.gov registration and reporting at a minimum will include the following components: The Principle Investigator (PI) will be responsible for ensuring compliance with ClinicalTrials.gov requirements for this project. The PI or his/her designee will register the trial prior to enrolling the first subject. Once a record is established, the PI will confirm accuracy of record content; resolve problems; and maintain records including content update and modifications. The PI will also be responsible for aggregate results reporting and Adverse Event reporting at the conclusion of the project. I certify that this submission contains an Applicable Clinical Trial (ACT) and that I will ensure compliance with registration and results reporting submissions to ClinicalTrials.gov as required under the FDA Amendment Act of 2007 (FDAAA) and the Final Rule (42CFR Part 11). For all clinical trials in scope of the Policy, the informed consent will include the FDA- required statement related to

ClinicalTrials.gov: “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

14 ADVERSE EVENTS

Any adverse reaction occurring during the study either observed by the physicians or nurses or reported by the patient will be recorded. Anticipated adverse events that will not be reported to the IRB include the pain and bruise associated with needle stick, and abnormal laboratory results that are found as a part of the screening blood work and lead to exclusion from the study, but will receive appropriate follow-up and referral to the primary care provider. Also other incidental serious adverse events unrelated to the study (such as trauma resulting from motor vehicle accidents or sport activities) will not be reported to the IRB. Serious adverse events: All serious adverse events related or possibly related to the research protocol, i.e. cardiovascular events, psychiatric events, intravenous catheter or venipuncture site infection/bleeding, and thrombophlebitis will be reported to the IRB as soon as possible, but no later than seven days of death or life threatening serious adverse event or within fifteen days after the occurrence of all other forms of serious adverse events. A serious adverse event is any adverse drug experience that: 1) Results in death; 2) Is life threatening; 3) Results in hospitalization or prolongs hospitalization; 4) Results in persistent or significant disability or incapacity; 5) Results in congenital anomaly or birth defect; 6) Results in a condition, which in the judgment of the investigator represents a significant hazard.

15 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

15.1 Definitions

15.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

15.1.2 Serious AE (SAE)

An AE is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE is consider “life-threatening” if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

15.1.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

15.1.4 AE Description and Grade

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

15.1.5 AE Expectedness

AEs can be 'Unexpected' or 'Expected'.

Expected AEs are listed in section 8.2 below.

Unexpected AEs are those AEs occurring in one or more subjects participating in the research protocol, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

15.1.6 AE Attribution

- Definite – The AE *is clearly related* to the study treatment.

- Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

15.2 Known AEs List

Table 3: Known AEs/Risks.

Research-related risks in this study include those associated with study procedures, namely blood drawing, study medications, radiation exposure, and dissemination of PHI, including genetic data.
No significant risk can be expected from the whole room indirect calorimeter, echocardiogram. Some individuals may experience anxiety during the stay in the indirect calorimeter. Potential additional risks are associated with the collection of genetic material and the possible

infringement of the study participants' privacy with dissemination of protected health information (PHI).

Table 5 Study Risk Assessment

Assessment/Procedure	Possible AEs/risks
Energy Expenditure recording	The only risk is anxiety or discomfort due to extended period of fasting. 06:00 PM until the end of the whole room indirect calorimeter recording at 11:00 AM of the next day), about 8-hours overnight fasting and 4 hours fasting during the study) Anxiety space available in the whole room indirect calorimeter. claustrophobia
Echocardiograph	Allergy or sensitive to adhesive or latex and may experience skin rash (dermatitis) from the electrodes.
DXA Scan	A low dose of X-ray radiation comparable to 1/10 of the radiation from a chest x-ray.
Blood collection	There may be pain at the site where the catheter is inserted, and some bruising and very rarely infection may occur. Some people may experience nausea or faint when the catheter is inserted or when they see blood. Bandages used to cover the catheter site may cause a skin rash (dermatitis) in some people who are allergic or sensitive to adhesive or latex
Quality of Life (QoL) questionnaires	Participants may experience some emotional discomfort as they assess their perceived quality of life
Genetic Risk	Infringement of the study participants' privacy with dissemination of protected health information (PHI). Breech of confidentiality

Pregnancy: Pregnancy is not considered an AE, although a patient will be withdrawn from the study if a pregnancy occurs and the visit will be completed. The pregnancy must be immediately reported to the Principle investigator. Additional follow-up may be required.

15.3 Time Period and Grade of AE Capture

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study. Illnesses present before the patient signs the informed consent form (ICF) are considered pre-existing conditions and are documented on the medical history worksheet and in the Case Report Form. Pre-existing conditions that worsen during the study are entered on the AE case report form.

Table 6 Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events

Grade	Description
1	**Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate**: minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	**Severe:** severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	**Life-threatening:** Life-threatening consequences; urgent intervention indicated
5	**Death:** Death related to AE

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010).

Table 7: Adverse Event Grading For Known AE/Risks Using CTCAE Guidelines

Adverse Event	Description	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anxiety	A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	N/A
Palpitation	A disorder characterized by an unpleasant sensation of	Mild symptoms; intervention not indicated	Intervention indicated	N/A	N/A	N/A

	irregular and/or forceful beating of the heart.					
Pre-syncope	A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.	N/A	Present (e.g., near fainting)	N/A	N/A	N/A
Syncope	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.	N/A	N/A	Fainting; orthostatic collapse	N/A	N/A
Pain of Skin	A disorder characterized by a sensation of marked discomfort in the skin.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	N/A	N/A
Contact Dermatitis	A disorder characterized by a rash and/or itching of the skin where adhesive or latex was in contact with the skin.	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	N/A	N/A	N/A
Bruising	A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.	Localized or in a dependent area	Generalized	N/A	N/A	N/A

Vascular access complication		TPA administration into line with no intent for systemic therapy indicated	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Pulmonary embolism, deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Nausea	A disorder characterized by a queasy sensation and/or the urge to vomit.	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	N/A	N/A
Vomiting	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death

15.4 Procedures for Recording AEs, SAEs, and Ups

All AEs will be documented on the AE case report form and in the patient's medical record. The following attributes must be assigned: (1) description, (2) dates of onset and resolution, (3) severity, (4) "serious" criteria if applicable, and (5) action taken. The investigator will actively solicit this information and assess the AEs in terms of severity and relationship to the study. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. The treatment may extend beyond the duration of the study. The investigator will record treatment and medications required for treatment on the appropriate CRF(s).

In the event that a patient is withdrawn from the study because of an AE, the event must be recorded on the Termination CRF as the reason for discontinuation.

All serious adverse events related or possibly related to the research protocol, i.e. cardiovascular events, psychiatric events, intravenous catheter or venipuncture site infection/bleeding, and thrombophlebitis will be reported to the IRB as soon as possible, but no later than seven days of death or life threatening serious adverse event or within fifteen days after the occurrence of all other forms of serious adverse events.

15.5 Routine Reporting Procedures for AEs

Each event will be reported to the Principle Investigator once becoming aware of the occurrence. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, whichever occurs first. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts, where the designation may remain ongoing. The investigator will ensure that the follow-up includes any supplemental investigation as may be indicated to elucidate at the nature and/or causality of the SAE. This may include additional laboratory test or investigations, histopathological examinations, or consultation with other health care professionals. SAEs that are ongoing at the time of the subjects final study visit/contact will be documented as ongoing.

15.6 Expedited Reporting Procedures for SAEs, UPs, and DLTs

Expedited Reporting Requirements (Events, Report Recipients, and Time Frames)	
SAEs	**UPs**
Principal Investigator[1]	Principal Investigator[1]
	DSMB[1]
	IRB[2]

[1] Report event within 5 business days of becoming aware of the occurrence.

[2] Each UP must be reported to the VCU IRB within 5 business days of becoming aware of the occurrence. The report must be prepared using the "VCU IRB PROMPT REPORTING FORM," found on the VCU IRB Forms Page.

Principal Investigator	**Massey Cancer Center DSMB**
Angeliki Stamatouli, M.D. 804-828- 3495 Angeliki.stamatouli@vcuhealth.org	FAX: 804-828-5406 E-mail: masseydsmb@vcu.edu

15.7 Resource sharing plan

The data generated by this proof-of-principle proposal will be limited due to the small number of patient recruited, and by the exploratory nature of the investigation. Nonetheless, the information gathered may be of use to other investigators who are involved in thyroid pathophysiology or in the development of efficacy/effectiveness trials.
In accordance to the new Rigor and Reproducibility guidelines, we will clearly describes the experimental protocols in the material and methods section of the publications and maintain a clear and readily accessible documentation of the experimental procedures. Any research resources developed through this proposal will be made readily available for research purposes to qualified individuals within the scientific community in accordance with the NIH Grants Policy Statement and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources. Virginia Commonwealth University (Technology transfer office) has established policies for Material Transfer Agreements that identify what intellectual property rights will be retained by the University to distributed resources.

16 REGULATORY COMPLIANCE AND ETHICS

16.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

16.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards), and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children)

16.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the Office for Human Research Protections (OHRP). Any amendments to the protocol or consent materials must also be approved. In the United States and in other countries, only institutions holding a current US Federal wide Assurance issued by OHRP may participate.

16.4 Informed Consent Process

Informed consent is an ongoing process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/ products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

16.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

17 DATA HANDLING AND RECORD KEEPING

17.1 Data Management Responsibilities

The principal investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating sites of any UPs.

Any laboratory conducting correlative studies must maintain the laboratory records and documentation (laboratory notebooks, laboratory protocols, print-outs, recordings, photographs, etc.).

17.2 Source Documents

Paper based source documents will be kept in secure location and only accessed by authorized study personnel. Electronic records will be made available only to those personnel in the study through the use of access controls and encryption. Identifiers will be removed from study-related data (data is coded with a key and stored in a separate and secure location).

17.3 Case Report Forms

Patient information will be collected and documented in paper based case report forms. All hand written entries on the case report forms (CRFs) should be made legibly in black ink. Errors, when made, should be corrected by drawing a single line through the incorrect entry (do not erase, white-out, or tape over errors) and then entering the correct data above the original entry. Entry corrections should be initialed and dated. Explain missing data with “ND” for “not determined” and “NA” used for “not applicable.”

17.4 Study Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond: (i) the publication of any abstract or manuscript reporting the results of the protocol; (2) the submission of any sponsored research final report; or (iii) submission of a final report to clinicaltrials.gov. Those patients who consent to be a part of the data registry will have all personal identifiers kept indefinitely. Information in the databases will only be accessible to individuals working on the study or VCU/VCUHS officials who have access for specific research-related tasks.

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Appendix A

BMR formula is as follows:

BMR (kcal / day) = 10 * weight (kg) + 6.25 * height (cm) – 5 * age (y) + s (kcal / day) , where s is +5 for males and -161 for females.

Appbendix B

H LIGHTS OF PRESCRIBING INFORMATION

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

LEVO-T® (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 Levo-T 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---------- LEVO-T is L-thyroxine (T_4) 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 LEVO-T 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 LEVO-T 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 LEVO-T 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 Neolpharma, Inc. at 1-844-200-4163 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 LEVO-T. (7)

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

Pregnancy may require the use of higher doses of LEVO-T. (2.3, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 FULL PRESCRIBING INFORMATION

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

Thyroid hormones, including Levo-T, 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)]*.

1.1 1 INDICATIONS AND USAGE Hypothyroidism

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

1.2 Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression

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

Limitations of Use:

- LEVO-T 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 LEVO-T may induce hyperthyroidism *[see Warnings and Precautions (5.4)].*

- LEVO-T is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

1.3 2 DOSAGE AND ADMINISTRATION

1.3.1 2.1 General Administration Information

Take LEVO-T with a full glass of water as the tablet may rapidly disintegrate.

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

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

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

Administer LEVO-T 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 LEVO-T, such as soybeanbased infant formula *[see Drug Interactions (7.9)]*.

1.3.2 2.2 General Principles of Dosing

The dose of LEVO-T 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 LEVO-T may not be attained for 4 to 6 weeks.

2.3 Dosing in Specific Patient Populations

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

Start LEVO-T 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 LEVO-T 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 LEVO-T 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.

1.3.4 *Secondary or Tertiary Hypothyroidism*

Start LEVO-T 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 LEVO-T 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 LEVO-T 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.

1.3.5 *Pediatric Dosage - Congenital or Acquired Hypothyroidism*

The recommended daily dose of LEVO-T in pediatric patients with hypothyroidism is based on body weight and changes with age as described in Table 1. Start LEVO-T 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)]*.

1.4 Table 1. LEVO-T 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.

1.4.1 *Pregnancy*

Pre-existing Hypothyroidism: LEVO-T 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 LEVO-T by 12.5 to 25 mcg/day and measure TSH every 4 weeks until a stable LEVO-T dose is reached and serum TSH is within the normal trimesterspecific range. Reduce LEVO-T dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure LEVO-T 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 LEVO-T 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 LEVO-T at 1.0 mcg per kg body weight per day. Evaluate serum TSH every 4
weeks and adjust LEVO-T dosage until a serum TSH is within the normal trimester specific range *[see Use in Specific Populations (8.1)]*.

1.4.2 *TSH Suppression in Well-differentiated Thyroid Cancer*

Generally, TSH is suppressed to below 0.1 IU per liter, and this usually requires a LEVO-T 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.

5.2.2.1 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 LEVO-T may be evidence of inadequate absorption, poor compliance, drug interactions, or a combination of these factors.

1.4.3 *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.

1.4.4 *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 LEVO-T 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 LEVO-T *[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.4)]*.

1.4.5 *Secondary and Tertiary Hypothyroidism*
Monitor serum free-T4 levels and maintain in the upper half of the normal range in these patients.

1.5 3 DOSAGE FORMS AND STRENGTHS

LEVO-T tablets are available as follows:

Tablet Strength	**Tablet Color/Shape**	**Tablet Markings**
25 mcg	Orange/Caplet	“25” and “GG/331”
50 mcg	White/ Caplet	“50” and “GG/332”
75 mcg	Violet/ Caplet	“75” and “GG/333”
88 mcg	Olive Green/ Caplet	“88” and “GG/334”
100 mcg	Yellow/ Caplet	“100” and “GG/335”
112 mcg	Rose/ Caplet	“112” and “GG/336”
125 mcg	Brown/ Caplet	“125” and “GG/337”
137 mcg	Turquoise/ Caplet	“137” and “GG/330”
150 mcg	Blue/ Caplet	“150” and “GG/338”
175 mcg	Lilac/ Caplet	“175” and “GG/339”
200 mcg	Pink/ Caplet	“200” and “GG/340”
300 mcg	Green/ Caplet	“300” and “GG/341”

1.6 4 CONTRAINDICATIONS

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

1.7 5 WARNINGS AND PRECAUTIONS

1.7.1 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 LEVO-T 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 LEVO-T therapy. Monitor patients receiving concomitant LEVOT and sympathomimetic agents for signs and symptoms of coronary insufficiency.

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

1.7.2 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 LEVO-T *[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism LEVO-T has a narrow therapeutic index. Over- or undertreatment with LEVO-T 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 LEVO-T 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 LEVO-T and adjust the dose as necessary *[see Drug Interactions (7.9) and Clinical Pharmacology (12.3)]*.

1.7.3 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 LEVO-T *[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 LEVO-T that achieves the desired clinical and biochemical response to mitigate this risk.

1.8 ADVERSE REACTIONS

Adverse reactions associated with LEVO-T 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

1.8.1 • *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.

1.9 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.

1.10 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.

1.11 7 DRUG INTERACTIONS

1.11.1 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 LEVO-T (see Tables 2-5 below).

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

Potential impact: Concurrent use may reduce the efficacy of LEVO-T 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 LEVO-T at least 4 hours apart from these agents.
Orlistat	Monitor patients treated concomitantly with orlistat and LEVO-T 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 LEVO-T 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.
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.

Potential impact (below): Administration of these agents with LEVO-T 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 -Fenamates	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 LEVO-T 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 ≥ 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 LEVO-T 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

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

7.4 Digitalis Glycosides

LEVO-T 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 LEVO-T 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. LEVO-T may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on LEVO-T may result in increased LEVO-T requirements.

7.6 Ketamine

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

7.7 Sympathomimetics

Concurrent use of sympathomimetics and LEVO-T 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 LEVO-T 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 LEVO-T 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 LEVO-T dosage adjusted during pregnancy *[see Clinical Considerations]*. There are no animal studies conducted with levothyroxine during pregnancy. LEVO-T 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 LEVO-T requirements. Serum TSH levels should be monitored and the LEVO-T dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the LEVO-T 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 LEVO-T and any potential adverse effects on the breastfed infant from LEVO-T or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of LEVO-T 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 LEVO-T 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 LEVO-T therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients.

Closely monitor infants during the first 2 weeks of LEVO-T 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 LEVOT 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

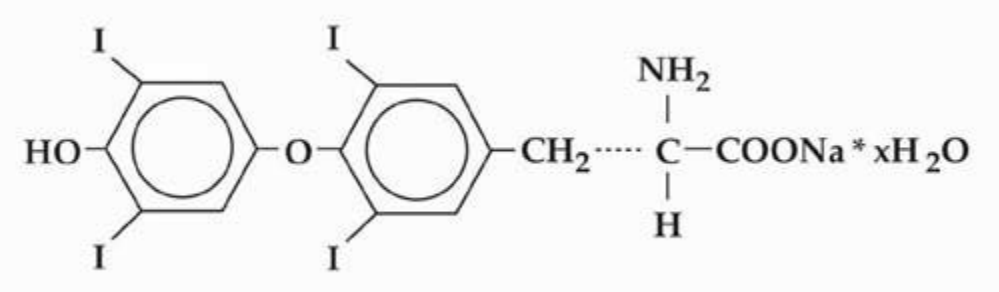
The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions (5)* and *Adverse Reactions (6)]*. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures occurred in a 3-year old child ingesting 3.6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

Reduce the LEVO-T 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

LEVO-T (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 $C_{15}H_{10}I_4NNaO_4$•**x**H_2O (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



LEVO-T 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 LEVO-T tablet contains the inactive ingredients Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Colloidal Silicone Dioxide, NF; and Sodium Starch Glycolate, NF. Each tablet strength meets USP Dissolution Test 2. Table 6 provides a listing of the color additives by tablet strength:

Table 6. LEVO-T Tablets Color Additives

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

300	D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake

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 LEVO-T dose is absorbed from the jejunum and upper ileum. The relative bioavailability of LEVO-T tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%. 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)]*.

1.11.2 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

LEVO-T (levothyroxine sodium, USP) tablets are supplied as follows:

Strength (mcg)	Color/Shape	Tablet Markings	NDC# for bottles of 90	NDC # for bottles of 1000
25	Orange/Caplet	“25” and “GG/331”	55466-104-11	55466-104-19
50	White/ Caplet	“50” and “GG/332”	55466-105-11	55466-105-19

75	Violet/ Caplet	“75” and “GG/333”	55466-106-11	55466-106-19
88	Olive Green/ Caplet	“88” and ‘GG/334”	55466-107-11	-
100	Yellow/ Caplet	“100” and “GG/335”	55466-108-11	55466-108-19
112	Rose/ Caplet	“112” and “GG/336”	55466-109-11	-
125	Brown/ Caplet	“125” and “GG/337”	55466-110-11	55466-110-19
137	Turquoise/ Caplet	“137” and “GG/330”	55466-111-11	-
150	Blue/ Caplet	“150” and “GG/338”	55466-112-11	-
175	Lilac/ Caplet	“175” and “GG/339”	55466-113-11	-
200	Pink/ Caplet	“200” and “GG/340”	55466-114-11	-
300	Green/ Caplet	“300” and “GG/341”	55466-115-11	-

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. LEVO-T 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

LEVO-T*:*

Dosing and Administration

- Instruct patients that LEVO-T should be taken with a full glass of water since the tablet may rapidly disintegrate.
- Instruct patients to take LEVO-T only as directed by their healthcare provider.
- Instruct patients to take LEVO-T 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 LEVO-T 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 LEVO-T.

Important Information

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in LEVO-T 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 LEVO-T 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 LEVO-T. 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 LEVO-T 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 LEVO-T therapy, but this is usually temporary.

Manufactured and Distributed by:
Neolpharma, Inc.
Caguas, Puerto Rico 00725

December 2017

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Appendix C

LEVOTHYROXINE SODIUM- levothyroxine sodium tablet Mylan Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVOTHYROXINE SODIUM TABLETS safely and effectively. See full prescribing information for LEVOTHYROXINE SODIUM TABLETS.

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 levothyroxine sodium tablets 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

Levothyroxine sodium tablets are levothyroxine sodium (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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-8774-INFO-RX) 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 levothyroxine sodium tablets. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of levothyroxine sodium tablets. (2.3, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 levothyroxine sodium tablets, 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: Levothyroxine sodium tablets are indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: Levothyroxine sodium tablets are indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropindependent well-differentiated thyroid cancer.

Limitations of Use:

- Levothyroxine sodium tablets are 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 levothyroxine sodium tablets may induce hyperthyroidism *[see Warnings and Precautions (5.4)]*.
- Levothyroxine sodium tablets are not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Information

Administer levothyroxine sodium tablets as a single daily dose, on an empty stomach, one-half to one hour before breakfast.

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

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

Administer levothyroxine sodium tablets 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 levothyroxine sodium tablets, such as soybean-based infant formula *[see Drug Interactions (7.9)]*.

2.2 General Principles of Dosing

The dose of levothyroxine sodium tablets 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 levothyroxine sodium tablets may not be attained for 4 to 6 weeks.

2.3 Dosing in Specific Patient Populations

2 PRIMARY HYPOTHYROIDISM IN ADULTS AND IN ADOLESCENTS IN WHOM GROWTH AND PUBERTY ARE COMPLETE

Start levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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.

3 *SECONDARY OR TERTIARY HYPOTHYROIDISM*

Start levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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.

4 *PEDIATRIC DOSAGE-CONGENITAL OR ACQUIRED HYPOTHYROIDISM*

The recommended daily dose of levothyroxine sodium tablets in pediatric patients with hypothyroidism is based on body weight and changes with age as described in Table 1. Start

levothyroxine sodium tablets 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)].*

5 TABLE 1. LEVOTHYROXINE SODIUM TABLETS DOSING GUIDELINES FOR PEDIATRIC HYPOTHYROIDISM

AGE	Daily Dose Per Kg Body Weight *
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
Greater than 12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.6 mcg/kg/day

* 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)]*.

5.1 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.

5.2 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.

5.3 Pregnancy

Pre-Existing Hypothyroidism

Levothyroxine sodium tablets 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 levothyroxine sodium tablets by 12.5 to 25 mcg/day and measure TSH every 4 weeks until a stable levothyroxine sodium tablets dose is reached and serum TSH is within the normal trimester-specific range. Reduce levothyroxine sodium tablets dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets at 1.0 mcg per kg body weight per day. Evaluate serum TSH every 4 weeks and adjust levothyroxine sodium tablets dosage until a serum TSH is within the normal trimester specific range *[see Use in Specific Populations (8.1)]*.

5.4 TSH Suppression in Well-Differentiated Thyroid Cancer

Generally, TSH is suppressed to below 0.1 IU per liter, and this usually requires a levothyroxine sodium tablets 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 levothyroxine sodium tablets may be evidence of inadequate absorption, poor compliance, drug interactions, or a combination of these factors.

5.5 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.

5.6 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
levothyroxine sodium tablets 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 levothyroxine sodium tablets *[see Warnings and Precautions (5.1)*and *Use in Specific Populations (8.4)]*.

5.7 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

Levothyroxine Sodium Tablets, USP are available containing 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg or 300 mcg of levothyroxine sodium, USP.

- The 25 mcg tablets are orange, capsule-shaped, scored tablets debossed with **L** to the left of the score and **4** to the right of the score on one side of the tablet and **M** on the other side.
- The 50 mcg tablets are white, capsule-shaped, scored tablets debossed with **L** to the left of the score and **5** to the right of the score on one side of the tablet and **M** on the other side.
- The 75 mcg tablets are violet, capsule-shaped, scored tablets debossed with **L** to the left of the score and **6** to the right of the score on one side of the tablet and **M** on the other side.
- The 88 mcg tablets are olive, capsule-shaped, scored tablets debossed with **L** to the left of the score and **7** to the right of the score on one side of the tablet and **M** on the other side.
- The 100 mcg tablets are yellow, capsule-shaped, scored tablets debossed with **L** to the left of the score and **8** to the right of the score on one side of the tablet and **M** on the other side.
- The 112 mcg tablets are rose, capsule-shaped, scored tablets debossed with **L** to the left of the score and **9** to the right of the score on one side of the tablet and **M** on the other side.
- The 125 mcg tablets are gray, capsule-shaped, scored tablets debossed with **L** to the left of the score and **10** to the right of the score on one side of the tablet and **M** on the other side.
- The 137 mcg tablets are turquoise, capsule-shaped, scored tablets debossed with **L** to the left of the score and 1**5** to the right of the score on one side of the tablet and **M** on the other side.
- The 150 mcg tablets are blue, capsule-shaped, scored tablets debossed with **L** to the left of the score and **11** to the right of the score on one side of the tablet and **M** on the other side.
- The 175 mcg tablets are lilac, capsule-shaped, scored tablets debossed with **L** to the left of the score and **12** to the right of the score on one side of the tablet and **M** on the other side.
- The 200 mcg tablets are pink, capsule-shaped, scored tablets debossed with **L** to the left of the score and **13** to the right of the score on one side of the tablet and **M** on the other side.
- The 300 mcg tablets are green, capsule-shaped, scored tablets debossed with **L** to the left of the score and **14** to the right of the score on one side of the tablet and **M** on the other side.

4 CONTRAINDICATIONS

Levothyroxine sodium tablets are 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 CardiovascularDisease

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 levothyroxine sodium tablets 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),* and *Use in Specific Populations (8.5)]*. Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive levothyroxine sodium tablets therapy. Monitor patients receiving concomitant levothyroxine sodium tablets and sympathomimetic agents for signs and symptoms of coronary insufficiency.

If cardiac symptoms develop or worsen, reduce the levothyroxine sodium tablets 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 levothyroxine sodium tablets *[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

Levothyroxine sodium tablets have a narrow therapeutic index. Over- or undertreatment with levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets *[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 levothyroxine sodium tablets that achieves the desired clinical and biochemical response to mitigate this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with levothyroxine sodium tablets therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5)*, and *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 levothyroxine sodium tablets (see Tables 2-5 below).

TABLE 2. DRUGS THAT MAY DECREASE T4 ABSORPTION (HYPOTHYROIDISM)

Potential impact: Concurrent use may reduce the efficacy of levothyroxine sodium tablets 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 levothyroxine sodium tablets at least 4 hours apart from these agents.
Orlistat	Monitor patients treated concomitantly with orlistat and levothyroxine sodium tablets for changes in thyroid function.
Bile Acid Sequestrants - Cholestyramine - Colestipol - Colesevelam	Bile acid sequestrants and ion exchange resins are known to decrease levothyroxine absorption. Administer levothyroxine sodium tablets at least 4 hours prior to these drugs or monitor TSH levels.
Ion Exchange Resins - Kayexalate - Sevelamer	
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.
Androgens / Anabolic Steroids Asparaginase	These drugs may decrease serum TBG concentration.

Glucocorticoids Slow-Release Nicotinic Acid Potential impact (below): Administration of these agents with levothyroxine sodium tablets 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 - Fenamates	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 levothyroxine sodium tablets 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 Propranolol > 160 mg/day)	In patients treated with large doses of propranolol (e.g., (> 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 ≥ 4 mg/day)	Short-term administration of large doses of (e.g., Dexamethasone 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 freeT3) in clinically euthyroid patients.

7.2 Antidiabetic Therapy

Addition of levothyroxine sodium tablets 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

Levothyroxine sodium tablets increase 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 levothyroxine sodium tablets dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

Levothyroxine sodium tablets 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 levothyroxine sodium tablets 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. Levothyroxine sodium tablets may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on levothyroxine sodium tablets may result in increased levothyroxine sodium tablets requirements.

7.6 Ketamine

Concurrent use of ketamine and levothyroxine sodium tablets may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

7.7 Sympathomimetics

Concurrent use of sympathomimetics and levothyroxine sodium tablets 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. 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets dosage adjusted during pregnancy *[see Clinical Considerations]*. There are no animal studies conducted with levothyroxine during pregnancy. Levothyroxine sodium tablets 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 levothyroxine sodium tablets requirements. Serum TSH levels should be monitored and the levothyroxine sodium tablets dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the levothyroxine sodium tablets 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 levothyroxine sodium tablets and any potential adverse effects on the breastfed infant from levothyroxine sodium tablets or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients.
Closely monitor infants during the first 2 weeks of levothyroxine sodium tablets 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

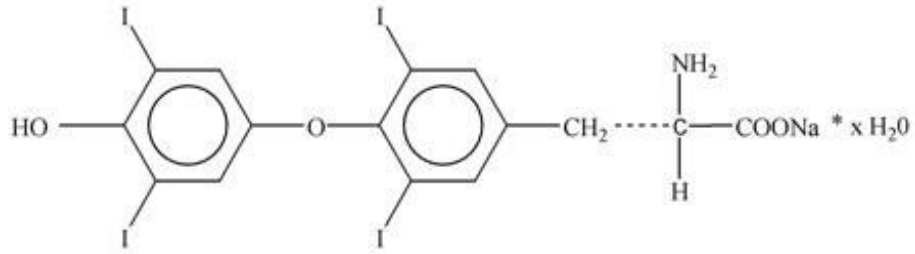
Because of the increased prevalence of cardiovascular disease among the elderly, initiate levothyroxine sodium tablets at less than the full replacement dose *[see Warnings and Precautions (5.1)*and *Dosage and Administration (2.3)]*. Atrial arrhythmias can occur in elderly patients. Atrial fibrillation 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 levothyroxine sodium tablets 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

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 a molecular formula of C15H10I4N NaO4 • H2O, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



Levothyroxine sodium 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 levothyroxine sodium tablet contains the inactive ingredients butylated hydroxyanisole, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate and sucrose. Table 6 provides a listing of the color additives by tablet strength:

TABLE 6. LEVOTHYROXINE SODIUM TABLETS COLOR ADDITIVES

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

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 levothyroxine sodium tablets dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine sodium tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%. 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 thyroxinebinding 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

5.7.1 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.

5.7.2 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.

6 TABLE 7. PHARMACOKINETIC PARAMETERS OF THYROID HORMONES IN EUTHYROID PATIENTS

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

* Includes TBG, TBPA, and TBA

† 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

Levothyroxine Sodium Tablets, USP are available containing 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg or 300 mcg of levothyroxine sodium, USP.

The 25 mcg tablets are orange, capsule-shaped, scored tablets debossed with **L** to the left of the score and **4** to the right of the score on one side of the tablet and **M** on the other side.

NDC 0378-1800-77

bottles of 90
tablets
NDC 0378-1800-10
bottles of 1000 tablets
The 50 mcg tablets are white, capsule-shaped, scored tablets debossed with **L** to the left of the score and **5** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-
1803-77
bottles of 90
tablets
NDC 0378-1803-10
bottles of 1000 tablets
The 75 mcg tablets are violet, capsule-shaped, scored tablets debossed with **L** to the left of the score and **6** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1805-77
bottles of 90 tablets
NDC 0378-1805-10
bottles of 1000 tablets
The 88 mcg tablets are olive, capsule-shaped, scored tablets debossed with **L** to the left of the score and **7** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1807-77
bottles of 90 tablets
NDC 0378-1807-10
bottles of 1000 tablets
The 100 mcg tablets are yellow, capsule-shaped, scored tablets debossed with **L** to the left of the score and **8** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1809-77
bottles of 90 tablets
NDC 0378-1809-10
bottles of 1000 tablets
The 112 mcg tablets are rose, capsule-shaped, scored tablets debossed with **L** to the left of the score and **9** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1811-77
bottles of 90 tablets
NDC 0378-1811-10
bottles of 1000 tablets
The 125 mcg tablets are gray, capsule-shaped, scored tablets debossed with **L** to the left of the score and **10** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1813-77
bottles of 90 tablets
NDC 0378-1813-10

bottles of 1000 tablets
The 137 mcg tablets are turquoise, capsule-shaped, scored tablets debossed with **L** to the left of the score and **15** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-
1823-77
bottles of 90
tablets
NDC 0378-1823-10
bottles of 1000 tablets
The 150 mcg tablets are blue, capsule-shaped, scored tablets debossed with **L** to the left of the score and **11** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1815-77
bottles of 90 tablets
NDC 0378-1815-10
bottles of 1000 tablets
The 175 mcg tablets are lilac, capsule-shaped, scored tablets debossed with **L** to the left of the score and **12** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1817-77
bottles of 90 tablets
NDC 0378-1817-10
bottles of 1000 tablets
The 200 mcg tablets are pink, capsule-shaped, scored tablets debossed with **L** to the left of the score and **13** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-
1819-77
bottles of 90
tablets
NDC 0378-1819-10
bottles of 1000 tablets
The 300 mcg tablets are green, capsule-shaped, scored tablets debossed with **L** to the left of the score and **14** to the right of the score on one side of the tablet and **M** on the other side.
NDC 0378-1821-77
bottles of 90 tablets
NDC 0378-1821-10
bottles of 1000 tablets
Storage Conditions: **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from light and moisture.**

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

PATIENT COUNSELING INFORMATION

Inform the patient of the following information to aid in the safe and effective use of *levothyroxine sodium tablets*:

Dosing and Administration:

- Instruct patients to take levothyroxine sodium tablets only as directed by their healthcare provider.
- Instruct patients to take levothyroxine sodium tablets 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 levothyroxine sodium 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 levothyroxine sodium tablets.

Important Information:

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets. 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets therapy, but this is usually temporary.

U.S. Patent No. 6,645,526
U.S. Patent No. 6,936,274
U.S. Patent No. 7,052,717
U.S. Patent No. 7,195,779

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 10/2017
LVTX:R13

PRINCIPAL DISPLAY PANEL - 25 mcg (0.025 mg)

NDC 0378-1800-77

Levothyroxine Sodium
Tablets, USP 25 mcg (0.025 mg)
Rx only 90 Tablets

Each
Tablet
contains:
Levothyro
xine
sodium,
USP 25
mcg

Dispense in a tight,
light-resistant
container as defined
in the USP using a
child-resistant
closure.
Keep container tightly closed.
Keep this and all
medication out of
the reach of
children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]

Protect from light and moisture.

Usual Dosage:
prescribing information.
U.S. Patent Nos. 6,645,526;
6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1800MM1


3 0378-1800-77 8
Each tablet contains:
Levothyroxine sodium, USP 25 mcg
[Varnish free for serialization, Lot and Exp]
NDC 0378-1800-77
Levothyroxine Sodium
Tablets, USP
25 mcg (0.025 mg)
L
Mylan®
Rx only
90 Tablets
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light and moisture.
Usual Dosage: See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
RM1800MM1
Mylan®
Mylan.com

PRINCIPAL DISPLAY PANEL - 50 mcg (0.05 mg)

NDC 0378-1803-77

Levothyroxine Sodium
Tablets, USP 50 mcg (0.5 mg)
Rx only 90 Tablets

Each
tablet
contains:
Levothyro
xine
sodium,
USP 50
mcg

Dispense in a tight,
light-resistant
container as defined
in the USP using a
child-resistant
closure.
Keep container tightly closed.
Keep this and all
medication out of the
reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]

Protect from light and moisture.

Usual Dosage:
prescribing information.
prescribing information.
U.S. Patent Nos. 6,645,526;
6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1803MM1


N 03378-1803-77 9
Each tablet contains:
Levothyroxine sodium, USP 50 mcg
[Varnish free for serialization, Lot and Exp]
NDC 0378-1803-77
Levothyroxine Sodium
Tablets, USP
50 mcg (0.05 mg)
L
S
Mylan®
Rx only
90 Tablets
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light and moisture.
Usual Dosage: See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
RM1803MM1
Mylan®
Mylan.com

PRINCIPAL DISPLAY PANEL - 75 mcg (0.075 mg)

NDC 0378-1805-77

Levothyroxine Sodium Tablets, USP
75 mcg (0.075 mg)
Rx only 90 Tablets

Each
tablet
contains:
Levothyro
xine
sodium,
USP 75
mcg

Dispense in a tight,
light-resistant
container as defined
in the USP using a
child-resistant
closure.
Keep container tightly closed.
Keep this and all
medication out of
the reach of
children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]

Protect from light and moisture.

Usual Dosage:

prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1805MM1


N 0378-1805-77 3
Each tablet contains:
Levothyroxine sodium, USP 75 mcg
[Varnish free for serialization, Lot and Exp]
NDC 0378-1805-77
Levothyroxine Sodium
Tablets, USP
75 mcg (0.075 mg)
L 6
Mylan®
Rx only
90 Tablets
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light and moisture.
Usual Dosage: See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
RM 1805MM1
Mylan®
Mylan.com

PRINCIPAL DISPLAY PANEL - 88 mcg (0.088 mg)

NDC 0378-1807-77

Levothyroxine
Sodium
Tablets, USP
88 mcg
(0.088 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 88 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Protect from light and moisture.

Usual Dosage: See accompanying
Usual Dosage: See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1807MM1

PRINCIPAL DISPLAY PANEL - 100 mcg (0.1 mg)

NDC 0378-1809-77

Levothyroxine
Sodium
Tablets, USP
100 mcg (0.1 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 100 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Protect from light and moisture.

RM1809MM1

PRINCIPAL DISPLAY PANEL - 112 mcg (0.112 mg)

NDC 0378-1811-77

Levothyroxine
Sodium
Tablets, USP
112 mcg
(0.112 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 112 mcg

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

PRINCIPAL DISPLAY PANEL - 125 mcg (0.125 mg)

NDC 0378-1813-77

Levothyroxine
Sodium
Tablets, USP
125 mcg
(0.125 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 125 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
RM1813MM1

PRINCIPAL DISPLAY PANEL - 137 mcg (0.137 mg)

NDC 0378-1823-77

Levothyroxine
Sodium
Tablets, USP
137 mcg
(0.137 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 137 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
RM1823MM1

Usual Dosage: See accompanying prescribing information.

U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com
Each tablet contains: Levothyroxine sodium, USP 137 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
RM1823MM1

PRINCIPAL DISPLAY PANEL - 150 mcg (0.15 mg)

NDC 0378-1815-77

Levothyroxine
Sodium
Tablets, USP

PRINCIPAL DISPLAY PANEL - 150 mcg (0.15 mg)

NDC 0378-1815-77

Levothyroxine
Sodium
Tablets, USP

PRINCIPAL DISPLAY PANEL - 175 mcg (0.175 mg)

NDC 0378-1817-77

Levothyroxine
Sodium
Tablets, USP
175 mcg
(0.175 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 175 mcg

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

Usual Dosage: See accompanying prescribing information.

U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM1817MM1

PRINCIPAL DISPLAY PANEL - 200 mcg (0.2 mg)

NDC 0378-1819-77

Levothyroxine
Sodium
Tablets, USP
200 mcg (0.2 mg)

Rx only 90 Tablets

Each tablet contains: Levothyroxine sodium, USP 200 mcg

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant **Usual Dosage:** See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1819MM1

PRINCIPAL DISPLAY PANEL - 300 mcg (0.3 mg)

NDC 0378-1821-77

Levothyroxine
Sodium
Tablets, USP
300 mcg (0.3 mg)
Rx only 90 Tablets
Each tablet contains: Levothyroxine sodium, USP 300 mcg
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed
Rx only 90 Tablets

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light and moisture.

Usual Dosage: See accompanying prescribing information.
U.S. Patent Nos. 6,645,526; 6,936,274; 7,052,717; 7,195,779
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan.com

RM1821MM1

LEVOTHYROXINE SODIUM levothyroxine sodium tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1800
Route of Administration	ORAL		
Active Ingredient/Active Moiety			

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	25 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	ORANGE	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;4
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:0378-1800-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/01/2016
2	NDC:0378-1800-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1803
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	50 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)

SODIUM LAURYL SULFATE (UNII: 368GB5141J)

SUCROSE (UNII: C151H8M554)

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1803-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/28/2016	
2	NDC:0378-1803-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1805
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	75 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics

Color	PURPLE (violet)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;6
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1805-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/16/2016	
2	NDC:0378-1805-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1807
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	88 ug

Inactive Ingredients

Ingredient Name	Strength

BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)

CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)
MAGNESIUM STEARATE (UNII: 70097M6I30)
MANNITOL (UNII: 3OWL53L36A)
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)
SODIUM LAURYL SULFATE (UNII: 368GB5141J)
SUCROSE (UNII: C151H8M554)
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)

Product Characteristics

Color	GREEN (olive)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;7
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1807-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/27/2016	
2	NDC:0378-1807-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1809
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	100 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)
SODIUM LAURYL SULFATE (UNII: 368GB5141J)
SUCROSE (UNII: C151H8M554)
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)

Product Characteristics

Color	YELLOW	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;8
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1809-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/27/2016	
2	NDC:0378-1809-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1811
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	112 ug

Inactive Ingredients	
Ingredient Name	**Strength**
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
D&C RED NO. 27 (UNII: 2LRS185U6K)	
D&C RED NO. 30 (UNII: 2S42T2808B)	

Product Characteristics

Color	PINK (rose)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;9
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1811-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/27/2016	
2	NDC:0378-1811-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1813
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	125 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	GRAY	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1813-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/27/2016	

2	NDC:0378-1813-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1823
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	137 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)
SODIUM LAURYL SULFATE (UNII: 368GB5141J)
SUCROSE (UNII: C151H8M554)
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)

Product Characteristics

Color	TURQUOISE	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1823-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/16/2016	
2	NDC:0378-1823-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/26/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	12/15/2006	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1815
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	150 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	BLUE	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;11
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1815-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/27/2016	
2	NDC:0378-1815-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1817

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	175 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
D&C RED NO. 27 (UNII: 2LRS185U6K)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics

Color	PURPLE (lilac)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;12
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1817-77	90 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	04/25/2016	
2	NDC:0378-1817-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1819
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	200 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics			
Color	PINK	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;13
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1819-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	08/10/2016	
2	NDC:0378-1819-10	1000 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

6.1 levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1821
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	300 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SUCROSE (UNII: C151H8M554)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	GREEN	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	9mm
Flavor		**Imprint Code**	M;L;14
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1821-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/27/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076187	11/01/2002	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Revised: 10/2017 Mylan Pharmaceuticals Inc.

Appendix D

LEVOTHYROXINE SODIUM- LEVOTHYROXINE SODIUM TABLET LEVOTHYROXINE SODIUM- LEVOTHYROXINE SODIUM TABLET SANDOZ INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVOTHYROXINE SODIUM TABLETS safely and effectively. See full prescribing information for LEVOTHYROXINE SODIUM TABLETS.

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 levothyroxine sodium tablets should not be used for the treatment ofobesity or for weight loss.**
- **Doses beyond the range of daily hormonal requirements may produce serious or even life threateningmanifestations of toxicity (6, 10).**

INDICATIONS AND USAGE

Levothyroxine sodium tablets 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 radioiodinetherapy 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. (1)

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 affectabsorption. (2.1)

- Starting dose depends on a variety of factors, including age, body weight, cardiovascular status and concomitantmedications. 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) (2)

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) (4)

WARNINGS AND PRECAUTIONS

- *Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease:* Initiate levothyroxine sodium tablets 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 levothyroxine sodium tablets 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) (5)

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine sodium tablets 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) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA1088 or www.fda.gov/medwatch. (6)

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 levothyroxine sodium tablets. (7) (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of levothyroxine sodium tablets. (2.3, 8.1) (8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

16 HOW SUPPLIED/STORAGE AND HANDLING

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 levothyroxine sodium tablets, 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

Levothyroxine sodium tablets are indicated as a replacement therapy in primary (thyroidal), secondary (pituitary) and tertiary (hypothalamic) congenital or acquired hypothyroidism.

PITUITARY THYROTROPIN (THYROID-STIMULATING HORMONE, TSH) SUPPRESSION

Levothyroxine sodium tablets are indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.
Limitations of Use:

- Levothyroxine sodium tablets are not indicated for suppression of benign thyroid nodules and nontoxicdiffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with levothyroxine sodium tablets may induce hyperthyroidism [see Warnings and Precautions (5.4)].

- Levothyroxine sodium tablets are not indicated for treatment of hypothyroidism during the recoveryphase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Information

Take levothyroxine sodium tablets with a full glass of water as the tablet may rapidly disintegrate.
Administer levothyroxine sodium tablets as a single daily dose, on an empty stomach, one-half to one hour before breakfast.

Administer levothyroxine sodium tablets at least 4 hours before or after drugs known to interfere with levothyroxine sodium tablets absorption *[see Drug Interactions (7.1)].*
Evaluate the need for dose adjustments when regularly administering within one hour of certain foods that may affect levothyroxine sodium tablets absorption *[see Drug Interactions (7.9) and Clinical Pharmacology (12.3)].*

Administer levothyroxine sodium tablets 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 levothyroxine sodium tablets, such as soybean-based infant formula *[see Drug Interactions (7.9)].*

2.2 General Principles of Dosing

The dose of levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets in pediatric patients with hypothyroidism is based on body weight and changes with age as described in **Table 1**. Start levothyroxine sodium tablets 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. LEVOTHYROXINE SODIUM TABLETS 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: Levothyroxine sodium tablets 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 levothyroxine sodium tablets by 12.5 to 25 mcg/day and measure TSH every 4 weeks until a stable levothyroxine sodium tablets dose is reached and serum TSH is within the normal trimester-specific range. Reduce levothyroxine sodium tablets dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets at 1.0 mcg per kg body weight per day. Evaluate serum TSH every 4 weeks and adjust levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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
levothyroxine sodium tablets 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 levothyroxine sodium tablets *[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

Levothyroxine Sodium Tablets, USP are available as follows:

Tablet Strength	Tablet Color/Shape	Tablet Markings
25 mcg	Orange/Caplet	"25" and "GG/331"
50 mcg	White/ Caplet	"50" and "GG/332"
75 mcg	Violet/ Caplet	"75" and "GG/333"
88 mcg	Olive Green/ Caplet	"88" and "GG/334"
100 mcg	Yellow/ Caplet	"100" and "GG/335"
112 mcg	Rose/ Caplet	"112" and "GG/336"
125 mcg	Brown/ Caplet	"125" and "GG/337"
137 mcg	Turquoise/ Caplet	"137" and "GG/330"
150 mcg	Blue/ Caplet	"150" and "GG/338"
175 mcg	Lilac/ Caplet	"175" and "GG/339"
200 mcg	Pink/ Caplet	"200" and "GG/340"
300 mcg	Green/ Caplet	"300" and "GG/341"

4 CONTRAINDICATIONS

Levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets therapy. Monitor patients receiving concomitant levothyroxine sodium tablets and sympathomimetic agents for signs and symptoms of coronary insufficiency.

If cardiac symptoms develop or worsen, reduce the levothyroxine sodium tablets 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 levothyroxine sodium tablets *[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

Levothyroxine sodium tablets has a narrow therapeutic index. Over- or undertreatment with levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets *[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 levothyroxine sodium tablets that achieves the desired clinical and biochemical response to mitigate this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with levothyroxine sodium tablets 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 levothyroxine sodium tablets (see **Tables 2-5** below).

TABLE 2. DRUGS THAT MAY DECREASE T4 ABSORPTION (HYPOTHYROIDISM)

Potential impact: Concurrent use may reduce the efficacy of levothyroxine sodium tablets 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 levothyroxine sodium tablets at least 4 hours apart from these agents.
Orlistat	Monitor patients treated concomitantly with orlistat and levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 Estrogencontaining oral contraceptives Estrogens (oral) Heroin / Methadone 5Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.

Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.
Potential impact (below): Administration of these agents with levothyroxine sodium tablets 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 Antiinflammatory Drugs -Fenamates	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 levothyroxine sodium tablets 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 betaadrenergic antagonists may be impaired when a hypothyroid patient is converted to the euthyroid state.
Glucocorticoids (e.g., Dexamethasone ≥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 levothyroxine sodium tablets 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

Levothyroxine sodium tablets 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 levothyroxine sodium tablets dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

Levothyroxine sodium tablets 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 levothyroxine sodium tablets 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. Levothyroxine sodium tablets may accelerate the onset of action of tricyclics. Administration of sertraline in

patients stabilized on levothyroxine sodium tablets may result in increased levothyroxine sodium tablets requirements.

7.6 Ketamine

Concurrent use of ketamine and levothyroxine sodium tablets may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

7.7 Sympathomimetics

Concurrent use of sympathomimetics and levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets 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 levothyroxine sodium tablets dosage adjusted during pregnancy *[see Clinical Considerations].* There are no animal studies conducted with levothyroxine during pregnancy. Levothyroxine sodium tablets 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 levothyroxine sodium tablets requirements. Serum TSH levels should be monitored and the levothyroxine sodium tablets dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the levothyroxine sodium tablets 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.

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 levothyroxine sodium tablets and any potential adverse effects on the breastfed infant from levothyroxine sodium tablets or from the underlying maternal condition.

Pediatric Use

The initial dose of levothyroxine sodium tablets 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 levothyroxine sodium tablets 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.

6.2 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 levothyroxine sodium tablets therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these patients.
Closely monitor infants during the first 2 weeks of levothyroxine sodium tablets 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.

Geriatric Use

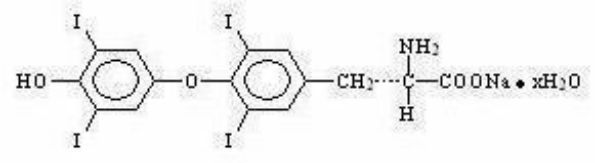
Because of the increased prevalence of cardiovascular disease among the elderly, initiate levothyroxine sodium tablets at less than the full replacement dose *[see Warnings and Precautions (5.1) and Dosage and Administration (2.3)].* Atrial arrhythmias can occur in elderly patients. Atrial fibrillation 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 levothyroxine sodium tablets 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

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 $C_{15}H_{10}I_4NNaO_4 \bullet xH_2O$ (where x = 5), molecular weight of 798.86 g/mol (anhydrous) and structural formula as shown:



Levothyroxine sodium 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 levothyroxine sodium tablet contains the inactive ingredients Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Colloidal Silicone Dioxide, NF; and Sodium Starch Glycolate, NF. Each tablet strength meets USP Dissolution Test 2. **Table 6** provides a listing of the color additives by tablet strength:

TABLE 6. LEVOTHYROXINE SODIUM TABLETS COLOR ADDITIVES

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

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 levothyroxine sodium tablets dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine sodium tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%. 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 thyroxinebinding 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

Levothyroxine Sodium Tablets, USP are supplied as follows:

Strength (mcg)	Color/Shape	Tablet Markings	NDC# for bottles of 90	NDC # for bottles of 1000
25	Orange/Caplet	"25" and "GG/331"	0781-5180-92	0781-5180-10
50	White/ Caplet	"50" and "GG/332"	0781-5181-92	0781-5181-10
75	Violet/ Caplet	"75" and "GG/333"	0781-5182-92	0781-5182-10
88	Olive Green/ Caplet	"88" and 'GG/334"	0781-5183-92	0781-5183-10
100	Yellow/ Caplet	"100" and "GG/335"	0781-5184-92	0781-5184-10

112	Rose/ Caplet	“112” and “GG/336”	0781-5185-92	0781-5185-10
125	Brown/ Caplet	“125” and “GG/337”	0781-5186-92	0781-5186-10
137	Turquoise/ Caplet	“137” and “GG/330”	0781-5191-92	0781-5191-10
150	Blue/ Caplet	“150” and “GG/338”	0781-5187-92	0781-5187-10
175	Lilac/ Caplet	“175” and “GG/339”	0781-5188-92	0781-5188-10
200	Pink/ Caplet	“200” and “GG/340”	0781-5189-92	0781-5189-10
300	Green/ Caplet	“300” and “GG/341”	0781-5190-92	0781-5190-10

STORAGE CONDITIONS

Store at 25°C (77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. Levothyroxine sodium 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 *levothyroxine sodium tablets:*

Dosing and Administration

- Instruct patients that levothyroxine sodium tablets should be taken with a full glass of water since thetablet may rapidly disintegrate.
- Instruct patients to take levothyroxine sodium tablets only as directed by their healthcare provider.
- Instruct patients to take levothyroxine sodium tablets 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 theabsorption of levothyroxine. Instruct patients not to take levothyroxine sodium tablets within 4 hours of these agents.
- Instruct patients to notify their healthcare provider if they are pregnant or breastfeeding or are thinkingof becoming pregnant while taking levothyroxine sodium tablets.

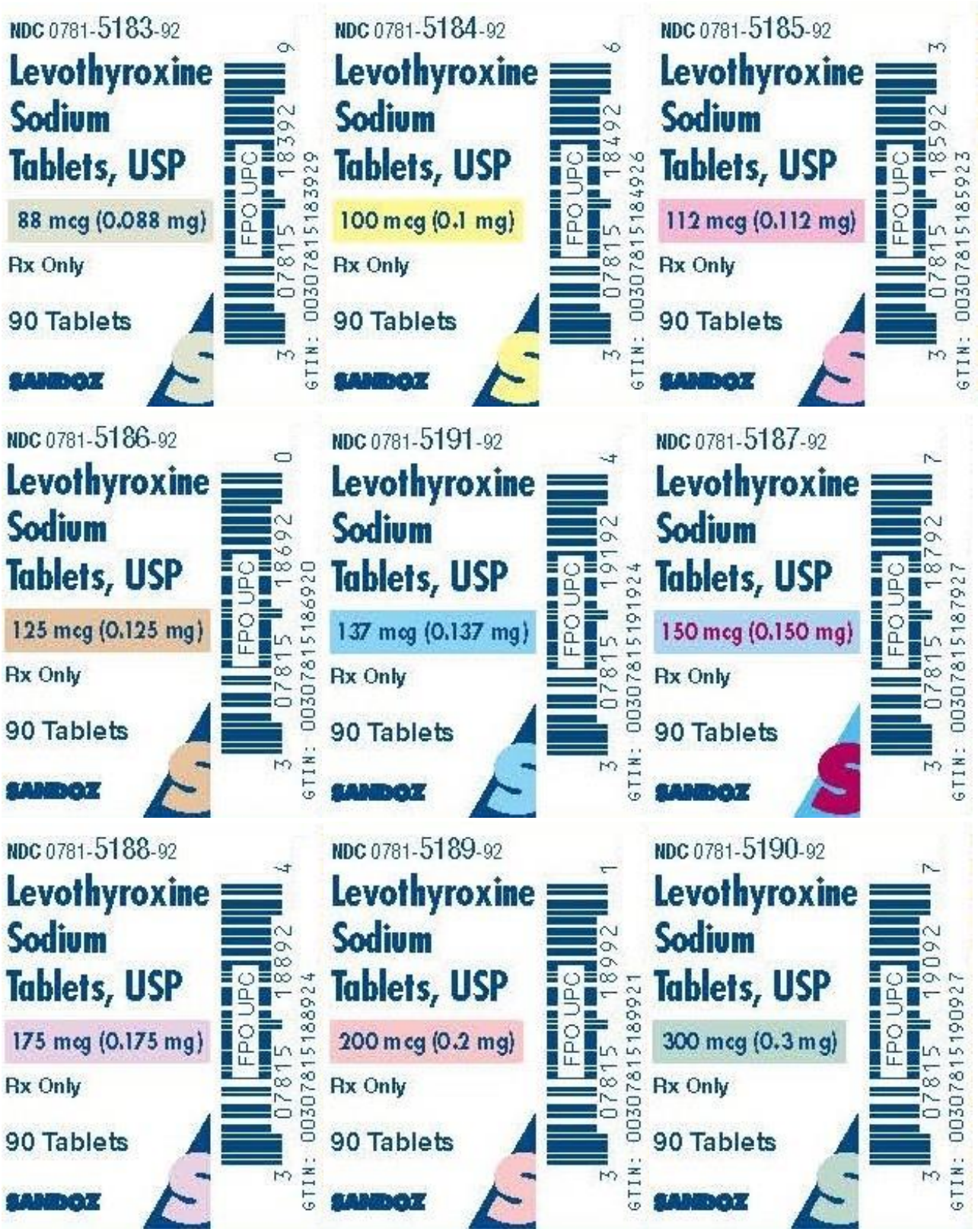
Important Information

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in levothyroxine sodium tablets is intended to replace a hormonethat is normally produced by the thyroid gland. Generally, replacement therapy is to be taken for life.
- Inform patients that levothyroxine sodium tablets should not be used as a primary or adjunctive therapyin a weight control program.

- Instruct patients to notify their healthcare provider if they are taking any other medications, includingprescription and over-the-counter preparations.
- Instruct patients to notify their physician of any other medical conditions they may have, particularlyheart 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 levothyroxine sodium tablets. 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 levothyroxine sodium tabletsprior 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 levothyroxinesodium tablets therapy, but this is usually temporary.


NDC 0781-5183-92
Levothyroxine Sodium Tablets, USP
88 mcg (0.088 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815183929
NDC 0781-5184-92
Levothyroxine Sodium Tablets, USP
100 mcg (0.1 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815184926
NDC 0781-5185-92
Levothyroxine Sodium Tablets, USP
112 mcg (0.112 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815185923
NDC 0781-5186-92
Levothyroxine Sodium Tablets, USP
125 mcg (0.125 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815186920
NDC 0781-5191-92
Levothyroxine Sodium Tablets, USP
137 mcg (0.137 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815191924
NDC 0781-5187-92
Levothyroxine Sodium Tablets, USP
150 mcg (0.150 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815187927
NDC 0781-5188-92
Levothyroxine Sodium Tablets, USP
175 mcg (0.175 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815188924
NDC 0781-5189-92
Levothyroxine Sodium Tablets, USP
200 mcg (0.2 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815189921
NDC 0781-5190-92
Levothyroxine Sodium Tablets, USP
300 mcg (0.3 mg)
Rx Only
90 Tablets
SANDOZ
FPO UPC
GTIN: 00307815190927

LEVOTHYROXINE SODIUM
levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5183
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	88 ug

Inactive Ingredients

Ingredient Name	Strength
FD&C BLUE NO. 1--ALUMINUM LAKE (UNII: J9EQA3S2JM)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	green (olive green)	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	88;GG;334
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5183-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5183-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5184
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS

Inactive Ingredients

Ingredient Name
D&C RED NO. 30 (UNII: 2S42T2808B)
D&C RED NO. 27 (UNII: 2LRS185U6K)
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)

MAGNESIUM STEARATE (UNII: 70097M6I30)

CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)

SILICON DIOXIDE (UNII: ETJ7Z6XBU4)

SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)

Product Characteristics

Color	yellow	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	100;GG;335
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5184-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5184-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5185
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	112 ug

Inactive Ingredients

Ingredient Name	Strength
D&C RED NO. 27 ALUMINUM LAKE (UNII: ZK64F7XSTX)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	red (rose)	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	112;GG;336
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5185-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5185-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5186
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	125 ug

Inactive Ingredients

Ingredient Name	Strength
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FD&C BLUE NO. 1--ALUMINUM LAKE (UNII: J9EQA3S2JM)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	brown	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm

Flavor		**Imprint Code**	125;GG;337
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5186-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5186-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5191
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	137 ug

Inactive Ingredients	
Ingredient Name	**Strength**
FD&C BLUE NO. 1--ALUMINUM LAKE (UNII: J9EQA3S2JM)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	green (Turquoise)	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	137;GG;330
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5191-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5191-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5187
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	150 ug

Inactive Ingredients	
Ingredient Name	**Strength**
FD&C BLUE NO. 2--ALUMINUM LAKE (UNII: 4AQJ3LG584)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics			
Color	blue	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	150;GG;338
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-5187-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5187-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5188
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	175 ug

Inactive Ingredients

Ingredient Name	Strength
D&C RED NO. 27 ALUMINUM LAKE (UNII: ZK64F7XSTX)	
D&C RED NO. 30 (UNII: 2S42T2808B)	
FD&C BLUE NO. 1--ALUMINUM LAKE (UNII: J9EQA3S2JM)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	purple (lilac)	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	175;GG;339
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5188-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5188-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5189
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	200 ug

Inactive Ingredients

Ingredient Name	Strength
D&C RED NO. 27 ALUMINUM LAKE (UNII: ZK64F7XSTX)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	pink	**Score**	2 pieces

Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	200;GG;340
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5189-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5189-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5190
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	300 ug

Inactive Ingredients

Ingredient Name	Strength
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1--ALUMINUM LAKE (UNII: J9EQA3S2JM)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	green	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	300;GG;341
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5190-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5190-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5180
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	25 ug

Inactive Ingredients

Ingredient Name	Strength
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	orange	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	25;GG;331
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5180-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5180-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5181
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	50 ug

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	

CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	white	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	50;GG;332
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5181-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5181-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-5182
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4)	LEVOTHYROXINE SODIUM ANHYDROUS	75 ug

Inactive Ingredients

Ingredient Name	Strength
FD&C BLUE NO. 2--ALUMINUM LAKE (UNII: 4AQJ3LG584)	
D&C RED NO. 27 ALUMINUM LAKE (UNII: ZK64F7XSTX)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Labeler - Sandoz Inc. (110342024)

CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)

Product Characteristics

Color	purple (violet)	**Score**	2 pieces
Shape	CAPSULE	**Size**	9mm
Flavor		**Imprint Code**	75;GG;333
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-5182-92	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2012	
2	NDC:0781-5182-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	03/01/2002	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021342	03/01/2002	

Registrant - Neolpharma, Inc. (078709787)

Establishment

Name	Address	ID/FEI	Business Operations
Neolpharma, Inc		078709787	manufacture(0781-5180, 0781-5181, 0781-5182, 0781-5184, 0781-5186, 0781-5187, 0781-5183, 0781-5185, 0781-5191, 0781-5188, 0781-5189, 0781-5190) , analysis(0781-5180, 0781-5181, 0781-5182, 0781-5184, 0781-5186, 0781-5187, 0781-5183, 0781-5185, 0781-5191, 0781-5188, 0781-5189, 0781-5190) , pack(0781-5180, 0781-5181, 0781-5182, 0781-5184, 0781-5186, 0781-5187, 0781-5183, 0781-5185, 0781-5191, 0781-5188, 0781-5189, 0781-5190) , label(0781-5184, 0781-5180, 0781-5181, 0781-5182, 0781-5186, 0781-5187, 0781-5183, 0781-5185, 0781-5191, 0781-5188, 0781-5189, 0781-5190)

Establishment

Name	Address	ID/FEI	Business Operations

theon Puerto Rico, Inc.	143814544	manufacture(0781-5188, 0781-5189, 0781-5190, 0781-5183, 0781-5184, 0781-5185, 0781-5186, 07815191, 0781-5187, 0781-5180, 0781-5181, 0781-5182) , analysis(0781-5180, 0781-5181, 0781-5182, 07815183, 0781-5184, 0781-5185, 0781-5186, 0781-5187, 0781-5188, 0781-5189, 0781-5190, 0781-5191) , pack(0781-5180, 0781-5181, 0781-5182, 0781-5183, 0781-5184, 0781-5185, 0781-5186, 0781-5187, 0781-5188, 0781-5189, 0781-5190, 0781-5191) , label(0781-5180, 0781-5181, 0781-5182, 0781-5183, 0781-5184, 0781-5185, 0781-5186, 0781-5187, 0781-5188, 0781-5189, 0781-5190, 0781-5191)

Revised: 4/2019 Sandoz Inc.

APPENDIX E

CYTOMEL®

brand of ***liothyronine***

sodium tablets

DESCRIPTION

Thyroid hormone drugs are natural or synthetic preparations containing tetraiodothyronine (T_4, levothyroxine) sodium or triiodothyronine (T_3, liothyronine) sodium or both. T_4 and T_3 are produced in the human thyroid gland by the iodination and coupling of the amino acid tyrosine. T_4 contains four iodine atoms and is formed by the coupling of two molecules of diiodotyrosine (DIT). T_3 contains three atoms of iodine and is formed by the coupling of one molecule of DIT with one molecule of monoiodotyrosine (MIT). Both hormones are stored in the thyroid colloid as thyroglobulin.

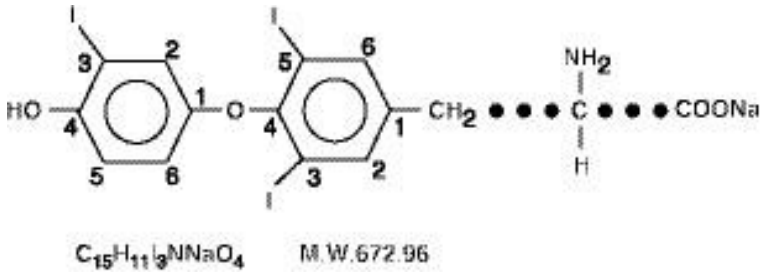
Thyroid hormone preparations belong to two categories: (1) natural hormonal preparations derived from animal thyroid, and (2) synthetic preparations. Natural preparations include desiccated thyroid and thyroglobulin. Desiccated thyroid is derived from domesticated animals that are used for food by man (either beef or hog thyroid), and thyroglobulin is derived from thyroid glands of the hog. The United States Pharmacopeia (USP) has standardized the total iodine content of natural preparations. Thyroid USP contains not less than (NLT) 0.17 percent and not more than (NMT) 0.23 percent iodine, and thyroglobulin contains not less than (NLT) 0.7 percent of organically bound iodine. Iodine content is only an indirect indicator of true hormonal biologic activity.

Cytomel (liothyronine sodium) Tablets contain liothyronine (L-triiodothyronine or L T_3), a

synthetic form of a natural thyroid hormone, and is available as the sodium salt.

The structural and empirical formulas and molecular weight of liothyronine sodium are given below.

Liothyronine Sodium



$C_{15}H_{11}I_3NNaO_4$ M.W.672.96

L-Tyrosine, O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt

Twenty-five mcg of liothyronine is equivalent to approximately 1 grain of desiccated thyroid or thyroglobulin and 0.1 mg of L-thyroxine.
Each round, white to off-white Cytomel (liothyronine sodium) tablet contains liothyronine sodium equivalent to liothyronine as follows: 5 mcg debossed JMI and D14; 25 mcg scored and debossed JMI and D16; 50 mcg scored and debossed JMI and D17. Inactive ingredients consist of calcium sulfate, gelatin, starch, stearic acid, sucrose and talc.

CLINICAL PHARMACOLOGY

The mechanisms by which thyroid hormones exert their physiologic action are not well understood. These hormones enhance oxygen consumption by most tissues of the body, increase the basal metabolic rate and the metabolism of carbohydrates, lipids and proteins. Thus, they exert a profound influence on every organ system in the body and are of particular importance in the development of the central nervous system.

PHARMACOKINETICS

Since liothyronine sodium (T_3) is not firmly bound to serum protein, it is readily available to body tissues. The onset of activity of liothyronine sodium is rapid, occurring within a few hours. Maximum pharmacologic response occurs within 2 or 3 days, providing early clinical response. The biological half-life is about 2-1/2 days.

T_3 is almost totally absorbed, 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

Liothyronine sodium has a rapid cutoff of activity which permits quick dosage adjustment and facilitates control of the effects of overdosage, should they occur.

The higher affinity of levothyroxine (T_4) for both thyroid-binding globulin and thyroid-binding prealbumin as compared to triiodothyronine (T_3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

INDICATIONS AND USAGE

Thyroid hormone drugs are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (pediatric patients, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary) or tertiary (hypothalamic) hypothyroidism (see WARNINGS).
2. As pituitary thyroid-stimulating hormone (TSH) suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter.
3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Cytomel (liothyronine sodium) Tablets can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

CONTRAINDICATIONS

Thyroid hormone preparations are generally contraindicated in patients with diagnosed but as yet uncorrected adrenal cortical insufficiency, untreated thyrotoxicosis and apparent hypersensitivity to any of their active or extraneous constituents. There is no well-documented evidence from the literature, however, of true allergic or idiosyncratic reactions to thyroid hormone.

WARNINGS

Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even lifethreatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

The use of thyroid hormones in the therapy of obesity, alone or combined with other drugs, is unjustified and has been shown to be ineffective. Neither is their use justified for the treatment of male or female infertility unless this condition is accompanied by hypothyroidism.

Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspected. These include patients with angina pectoris or the elderly, in whom there is a greater likelihood of occult cardiac disease. In these patients, liothyronine sodium therapy should be initiated with low doses, with due consideration for its relatively rapid onset of action. Starting dosage of

Cytomel (liothyronine sodium) Tablets is 5 mcg daily, and should be increased by no more than 5 mcg increments at 2-week intervals. When, in such patients, a euthyroid state can only be reached at the expense of an aggravation of the cardiovascular disease, thyroid hormone dosage should be reduced.

Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug. Myxedematous patients are very sensitive to thyroid; dosage should be started at a very low level and increased gradually.

Severe and prolonged hypothyroidism can lead to a decreased level of adrenocortical activity commensurate with the lowered metabolic state. When thyroid-replacement therapy is administered, the metabolism increases at a greater rate than adrenocortical activity. This can precipitate adrenocortical insufficiency. Therefore, in severe and prolonged hypothyroidism, supplemental adrenocortical steroids may be necessary. In rare instances the administration of thyroid hormone may precipitate a hyperthyroid state or may aggravate existing hyperthyroidism.

PRECAUTIONS

General – Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases are required.

The therapy of myxedema coma requires simultaneous administration of glucocorticoids.

Hypothyroidism decreases and hyperthyroidism increases the sensitivity to oral anticoagulants. Prothrombin time should be closely monitored in thyroid-treated patients on oral anticoagulants and dosage of the latter agents adjusted on the basis of frequent prothrombin time

determinations. In infants, excessive doses of thyroid hormone preparations may produce craniosynostosis.

Information for the Patient – Patients on thyroid hormone preparations and parents of pediatric patients on thyroid therapy should be informed that:

1. Replacement therapy is to be taken essentially for life, with the exception of cases of transient hypothyroidism, usually associated with thyroiditis, and in those patients receiving a therapeutic trial of the drug.
2. They should immediately report during the course of therapy any signs or symptoms of thyroid hormone toxicity, e.g., chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, nervousness, or any other unusual event.
3. In case of concomitant diabetes mellitus, the daily dosage of antidiabetic medication may need readjustment as thyroid hormone replacement is achieved. If thyroid medication is stopped, a downward readjustment of the dosage of insulin or oral hypoglycemic agent may be necessary to avoid hypoglycemia. At all times, close monitoring of urinary glucose levels is mandatory in such patients.
4. In case of concomitant oral anticoagulant therapy, the prothrombin time should be measured frequently to determine if the dosage of oral anticoagulants is to be readjusted.
5. Partial loss of hair may be experienced by pediatric patients in the first few months of thyroid therapy, but this is usually a transient phenomenon and later recovery is usually the rule.

Laboratory Tests – Treatment of patients with thyroid hormones requires the periodic assessment of thyroid status by means of appropriate laboratory tests besides the full clinical evaluation. The TSH suppression test can be used to test the effectiveness of any thyroid preparation, bearing in mind the relative insensitivity of the infant pituitary to the negative feedback effect of thyroid hormones. Serum T_4 levels can be used to test the effectiveness of

all thyroid medications except products containing liothyronine sodium. When the total serum T_4 is low but TSH is normal, a test specific to assess unbound (free) T_4 levels is warranted. Specific measurements of T_4 and T_3 by competitive protein binding or radioimmunoassay are not influenced by blood levels of organic or inorganic iodine and have essentially replaced older tests of thyroid hormone measurements, i.e., PBI, BEI and T_4 by column.

DRUG INTERACTIONS

OralAnticoagulants – Thyroid hormones appear to increase catabolism of vitamin K-dependent

clotting factors. If oral anticoagulants are also being given, compensatory increases in clotting factor synthesis are impaired. Patients stabilized on oral anticoagulants who are found to require thyroid replacement therapy should be watched very closely when thyroid is started. If a patient is truly hypothyroid, it is likely that a reduction in anticoagulant dosage will be required. No special precautions appear to be necessary when oral anticoagulant therapy is begun in a patient already stabilized on maintenance thyroid replacement therapy.

Insulin or Oral Hypoglycemics – Initiating thyroid replacement therapy may cause increases in insulin or oral hypoglycemic requirements. The effects seen are poorly understood and depend upon a variety of factors such as dose and type of thyroid preparations and endocrine status of the patient. Patients receiving insulin or oral hypoglycemics should be closely watched during initiation of thyroid replacement therapy.

Cholestyramine – Cholestyramine binds both T_4 and T_3 in the intestine, thus impairing absorption of these thyroid hormones. *In vitro* studies indicate that the binding is not easily

removed. Therefore, 4 to 5 hours should elapse between administration of cholestyramine and thyroid hormones.

Estrogen, Oral Contraceptives – Estrogens tend to increase serum thyroxine-binding globulin (TBg). In a patient with a nonfunctioning thyroid gland who is receiving thyroid replacement therapy, free levothyroxine may be decreased when estrogens are started thus increasing thyroid requirements. However, if the patient's thyroid gland has sufficient function, the decreased free thyroxine will result in a compensatory increase in thyroxine output by the thyroid. Therefore, patients without a functioning thyroid gland who are on thyroid replacement therapy may need to increase their thyroid dose if estrogens or estrogen-containing oral contraceptives are given.

Tricyclic Antidepressants – Use of thyroid products with imipramine and other tricyclic antidepressants may increase receptor sensitivity and enhance antidepressant activity; transient cardiac arrhythmias have been observed. Thyroid hormone activity may also be enhanced.

Digitalis – Thyroid preparations may potentiate the toxic effects of digitalis. Thyroid hormonal replacement increases metabolic rate, which requires an increase in digitalis dosage.

Ketamine – When administered to patients on a thyroid preparation, this parenteral anesthetic may cause hypertension and tachycardia. Use with caution and be prepared to treat hypertension, if necessary.

Vasopressors – Thyroxine increases the adrenergic effect of catecholamines such as epinephrine and norepinephrine. Therefore, injection of these agents into patients receiving thyroid preparations increases the risk of precipitating coronary insufficiency, especially in patients with coronary artery disease. Careful observation is required.

Drug/Laboratory Test Interactions – The following drugs or moieties are known to interfere with laboratory tests performed in patients on thyroid hormone therapy: androgens, corticosteroids, estrogens, oral contraceptives containing estrogens, iodine-containing preparations and the numerous preparations containing salicylates.

1. Changes in TBg concentration should be taken into consideration in the interpretation of T_4 and T_3 values. In such cases, the unbound (free) hormone should be measured. Pregnancy, estrogens and estrogen-containing oral contraceptives increase TBg concentrations. TBg may also be increased during infectious hepatitis. Decreases in TBg concentrations are observed in nephrosis, acromegaly and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxinebinding-globulinemias have been described. The incidence of TBg deficiency approximates 1 in 9000. The binding of thyroxine by thyroxine-binding prealbumin (TBPA) is inhibited by salicylates.
2. Medicinal or dietary iodine interferes with all in vivo tests of radioiodine uptake, producing low uptakes which may not be reflective of a true decrease in hormone synthesis.
3. The persistence of clinical and laboratory evidence of hypothyroidism in spite of adequate dosage replacement indicates either poor patient compliance, poor

absorption, excessive fecal loss, or inactivity of the preparation. Intracellular resistance to thyroid hormone is quite rare.

Carcinogenesis, Mutagenesis and Impairment of Fertility – A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indications should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

Pregnancy – Category A. Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy.

Nursing Mothers – Minimal amounts of thyroid hormones are excreted in human milk. Thyroid is not associated with serious adverse reactions and does not have a known tumorigenic potential.

However, caution should be exercised when thyroid is administered to a nursing woman.

Geriatric Use – Clinical studies of liothyronine sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the

greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Use – Pregnant mothers provide little or no thyroid hormone to the fetus. The incidence of congenital hypothyroidism is relatively high (1:4000) and the hypothyroid fetus would not derive any benefit from the small amounts of hormone crossing the placental barrier. Routine determinations of serum T_4 and/or TSH is strongly advised in neonates in view of the deleterious effects of thyroid deficiency on growth and development. Treatment should be initiated immediately upon diagnosis and maintained for life, unless transient hypothyroidism is suspected, in which case, therapy may be interrupted for 2 to 8 weeks after the age of 3 years to reassess the condition. Cessation of therapy is justified in patients who have maintained a normal TSH during those 2 to 8 weeks.

ADVERSE REACTIONS

Adverse reactions, other than those indicative of hyperthyroidism because of therapeutic overdosage, either initially or during the maintenance period are rare (see OVERDOSAGE).

In rare instances, allergic skin reactions have been reported with Cytomel (liothyronine sodium) Tablets.

OVERDOSAGE

Signs and Symptoms – Headache, irritability, nervousness, sweating, arrhythmia (including tachycardia), increased bowel motility and menstrual irregularities. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may also develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Treatment Of Overdosage – Dosage should be reduced or therapy temporarily discontinued if signs and symptoms of overdosage appear. Treatment may be reinstituted at a lower dosage. In normal individuals, normal hypothalamic-pituitary-thyroid axis function is restored in 6 to 8 weeks after thyroid suppression.

Treatment of acute massive thyroid hormone overdosage is aimed at reducing gastrointestinal absorption of the drugs and counteracting central and peripheral effects, mainly those of increased sympathetic activity. Vomiting may be induced initially if further gastrointestinal absorption can reasonably be prevented and barring contraindications such as coma, convulsions, or loss of the gagging reflex. Treatment is symptomatic and supportive. Oxygen may be administered and ventilation maintained. Cardiac glycosides may be indicated if congestive heart failure develops. Measures to control fever, hypoglycemia, or fluid loss should be instituted if needed. Antiadrenergic agents, particularly propranolol, have been used advantageously in the treatment of increased sympathetic activity. Propranolol may be administered intravenously at a dosage of 1 to 3

mg over a 10-minute period or orally, 80 to 160 mg/day, especially when no contraindications exist for its use.

DOSAGE AND ADMINISTRATION

The dosage of thyroid hormones is determined by the indication and must in every case be individualized according to patient response and laboratory findings.

Cytomel (liothyronine sodium) Tablets are intended for oral administration; once-a-day dosage is recommended. Although liothyronine sodium has a rapid cutoff, its metabolic effects persist for a few days following discontinuance.

Mild Hypothyroidism: Recommended starting dosage is 25 mcg daily. Daily dosage then may be increased by up to 25 mcg every 1 or 2 weeks. Usual maintenance dose is 25 to75mcg daily.

The rapid onset and dissipation of action of liothyronine sodium (T_3), as compared with levothyroxine sodium (T_4), has led some clinicians to prefer its use in patients who might be more susceptible to the untoward effects of thyroid medication. However, the wide swings in serum T_3 levels that follow its administration and the possibility of more pronounced cardiovascular side effects tend to counterbalance the stated advantages.

Cytomel (liothyronine sodium) Tablets may be used in preference to levothyroxine (T_4) during radioisotope scanning procedures, since induction of hypothyroidism in those cases is more abrupt and can be of shorter duration. It may also be preferred when impairment of peripheral conversion of T_4 to T_3 is suspected.

Myxedema: Recommended starting dosage is 5 mcg daily. This may be increased by 5 to 10 mcg daily every 1 or 2 weeks. When 25 mcg daily is reached, dosage may be increased by 5 to 25 mcg every 1 or 2 weeks until a satisfactory therapeutic response is attained. Usual maintenance dose is 50 to 100 mcg daily.

Myxedema Coma: Myxedema coma is usually precipitated in the hypothyroid patient of long standing by intercurrent illness or drugs such as sedatives and anesthetics and should be considered a medical emergency.

An intravenous preparation of liothyronine sodium is marketed by Jones Pharma Incorporated, under the trade name Triostat® for use in myxedema coma/precoma.

Congenital Hypothyroidism: Recommended starting dosage is 5 mcg daily, with a 5 mcg increment every 3 to 4 days until the desired response is achieved. Infants a few months old may require only 20 mcg daily for maintenance. At 1 year, 50 mcg daily may be required. Above 3 years, full adult dosage may be necessary (see PRECAUTIONS, Pediatric Use).

Simple (non-toxic) Goiter: Recommended starting dosage is 5 mcg daily. This dosage may be increased by 5 to 10 mcg daily every 1 or 2 weeks. When 25 mcg daily is reached, dosage may be increased every week or two by 12.5 or 25 mcg. Usual maintenance dosage is 75 mcg daily.

In the elderly or in pediatric patients, therapy should be started with 5 mcg daily and increased only by 5 mcg increments at the recommended intervals.

When switching a patient to Cytomel (liothyronine sodium) Tablets from thyroid, Lthyroxine or thyroglobulin, discontinue the other medication, initiate Cytomel at a low dosage, and increase gradually according to the patient's response. When selecting a starting dosage, bear in mind that this drug has a rapid onset of action, and that residual effects of the other thyroid preparation may persist for the first several weeks of therapy.

Thyroid Suppression Therapy: Administration of thyroid hormone in doses higher than those produced physiologically by the gland results in suppression of the production of endogenous hormone. This is the basis for the thyroid suppression test and is used as an aid in the diagnosis of patients with signs of mild hyperthyroidism in whom baseline

laboratory tests appear normal or to demonstrate thyroid gland autonomy in patients with Graves' ophthalmopathy. ^{131}I uptake is determined before and after the administration of the exogenous hormone. A 50% or greater suppression of uptake indicates a normal thyroid-pituitary axis and thus rules out thyroid gland autonomy.

Cytomel (liothyronine sodium) Tablets are given in doses of 75 to 100 mcg/day for 7 days, and radioactive iodine uptake is determined before and after administration of the hormone. If thyroid function is under normal control, the radioiodine uptake will drop significantly after treatment. Cytomel (liothyronine sodium) Tablets should be administered cautiously to patients in whom there is a strong suspicion of thyroid gland autonomy, in view of the fact that the exogenous hormone effects will be additive to the endogenous source.

HOW SUPPLIED

Cytomel (liothyronine sodium) Tablets: 5 mcg in bottles of 100;

25 mcg in bottles of 100; and 50 mcg in bottles of 100.

5 mcg 100's: NDC 52604-3414-1

25 mcg 100's: NDC 52604-3416-1

50 mcg 100's: NDC 52604-3417-1

Store between 15° and 30°C (59° and 86°F).

DATE OF ISSUANCE November 2001

Monarch Pharmaceuticals®

Manufactured by:

Schering Canada, Inc., 3535 Trans-Canada Highway, Pointe Claire, Quebec H9R 1B4 Canada

Distributed by:

Monarch Pharmaceuticals, Inc., Bristol, TN 37620

83-481648 Rev. 11/01

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/s/

David Orloff
5/17/02 12:30:24 PM

APPENDIX F

IOTHYRONINE SODIUM- LIOTHYRONINE SODIUM TABLET MAYNE PHARMA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIOTHYRONINE SODIUM TABLETS safely and effectively. See full prescribing information for LIOTHYRONINE SODIUM TABLETS.

LIOTHYRONINE SODIUM tablets, for oral use
Initial U.S. Approval: 1956

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

See full prescribing information for complete boxed warning.

- **Thyroid hormones, including liothyronine sodium tablets, 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, 7.7, 10).**

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3)	12/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5, 2.6)	12/2018
Contraindications (4)	12/2018
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)	12/2018

INDICATIONS AND USAGE

Liothyronine sodium tablets are an L-triiodothyronine (T3) indicated for:

- Hypothyroidism: As replacement in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism (1.1)
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer (1.2)

  Thyroid Suppression Test: As a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy (1.3)

Limitations of Use:

- Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients. (1)
- Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis. (1)

DOSAGE AND ADMINISTRATION

- Administer liothyronine sodium tablets orally once daily and individual dosage according to patient response and laboratory findings (2.1)
- See full prescribing information for recommended dosage for hypothyroidism (2.2) TSH suppression in well differentiated thyroid cancer (2.3) and for thyroid suppression test (2.4)
- When switching a patient to liothyronine sodium tablets, discontinue levothyroxine therapy and initiate liothyronine sodium
- Adequacy of therapy determined with periodic monitoring of TSH and T3 levels as well as clinical status (2.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mcg, 25 mcg, 50 mcg (3)

CONTRAINDICATIONS

Uncorrected adrenal cortical insufficiency (4)

WARNINGS AND PRECAUTIONS

Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease: Initiate liothyronine sodium tablets 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 liothyronine sodium tablets 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

Most common adverse reactions for liothyronine sodium tablets are primarily those of hyperthyroidism due to therapeutic overdosage: arrhythmias, myocardial infarction, dyspnea, 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 Mayne Pharma at 1-844-825-8500 or FDA at 1-800FDA-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 liothyronine sodium tablets (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of thyroid hormone (2.2, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS 1 INDICATIONS AND USAGE

* 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 liothyronine sodium tablets, 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

1.1 Hypothyroidism

Liothyronine sodium tablets are indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

1.2 Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression

Liothyronine sodium tablets are indicated as an adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer.

1.3 Thyroid Suppression Test

Liothyronine sodium tablets are indicated as a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Limitations of Use

Limitations of Use

- Liothyronine sodium tablets are 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 liothyronine sodium tablets may induce hyperthyroidism *[see Warnings and Precautions (5.4)]*.
- Liothyronine sodium tablets are not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

6.3 2.1 General Principles of Dosing

The dose of liothyronine sodium tablets for hypothyroidism or pituitary Thyroid-Stimulating Hormone
(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 (2.2, 2.3, 2.4), 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)]*.

Administer liothyronine sodium tablets orally once daily.

2.2 Recommended Dosage for

Hypothyroidism Adults

The recommended starting dosage is 25 mcg orally once daily. Increase the dose by 25 mcg daily every 1 or 2 weeks, if needed. The usual maintenance dose is 25 mcg to 75 mcg once daily.

For elderly patients or patients with underlying cardiac disease, start with liothyronine sodium tablets 5 mcg once daily and increase by 5 mcg increments at the recommended intervals.

Serum TSH is not a reliable measure of liothyronine sodium tablets dose adequacy in patients with secondary or tertiary hypothyroidism and should not be used to monitor therapy. Use the serum T3 level to monitor adequacy of therapy in this patient population.

Pediatric Patients

The recommended starting dosage is 5 mcg once daily, with a 5 mcg increase every 3 to 4 days until the desired response is achieved. Infants a few months old may require 20 mcg

once daily for maintenance. At 1 year of age, 50 mcg once daily may be required. Above 3 years of age, the full adult dosage may be necessary *[see Use in Specific Populations (8.4)].*

Newborns (0 to 3 months) at Risk for Cardiac Failure:

Consider a lower starting dose in infants at risk for cardiac failure. Increase the dose as needed based on clinical and laboratory response.

Pediatric Patients at Risk for Hyperactivity

To minimize the risk of hyperactivity in pediatric patients, 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: Thyroid hormone 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 trimesterspecific reference range. For patients with serum TSH above the normal trimester-specific range, increase the dose of thyroid hormone and measure TSH every 4 weeks until a stable dose is reached and serum TSH is within the normal trimester-specific range. Reduce thyroid hormone dosage to prepregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure thyroid hormone dose is appropriate.

2.3 Recommended Dosage for TSH Suppression in Well-Differentiated Thyroid Cancer

The dose of liothyronine sodium tablets should target TSH levels within the desired therapeutic range.

This may require higher doses, depending on the target level for TSH suppression.

2.4 Recommended Dosage for Thyroid Suppression Test

The recommended dose is 75 mcg to 100 mcg daily for 7 days, with radioactive iodine uptake being determined before and after the 7 day administration of liothyronine sodium tablets. If thyroid function is normal, the radioiodine uptake will drop significantly after treatment. A 50% or greater suppression of uptake indicates a normal thyroid-pituitary axis.

2.5 Switching from Levothyroxine to Liothyronine Sodium Tablets

Liothyronine sodium tablets has a rapid onset of action and residual effects of the other thyroid preparation may persist for the first several weeks after initiating liothyronine sodium tablets therapy. When switching a patient to liothyronine sodium tablets, discontinue levothyroxine therapy and initiate liothyronine sodium tablets at a low dosage. Gradually increase the liothyronine sodium tablets dose according to the patient's response.

2.6 Monitoring TSH and Triiodothyronine (T3) 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 liothyronine sodium tablets 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 periodically after initiation of the therapy or any change in dose. To check the immediate response to therapy before the TSH has had a chance to respond or if your patient's status needs to be assessed prior to that point, measurement of total T3 would be most appropriate. 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 pediatric patients with hypothyroidism, assess the adequacy of replacement therapy by measuring serum TSH and T3 levels. For pediatric patients three years of age and older, the recommended monitoring is every 3 to 12 months thereafter, following dose stabilization until growth and puberty are 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 TSH to decrease below 20 IU per liter after initiation of liothyronine sodium tablets therapy 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 liothyronine sodium tablets*[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.4)]*.

Secondary and Tertiary Hypothyroidism

Monitor serum T3 levels and maintain in the normal range.

3 DOSAGE FORMS AND STRENGTHS

Tablets (round, flat, white to off-white) available as follows:

- 5 mcg: debossed "5" over "220" on one side and plain on the other
- 25 mcg: debossed "25" above the score and "222" below the score on one side and plain on the other
-

50 mcg: debossed "50" above the score and "223" below the score on one side and plain on the other

4 CONTRAINDICATIONS

Liothyronine sodium tablets are 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

Overtreatment with thyroid hormone 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 liothyronine sodium tablets 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) and Use in Specific Populations (8.5)].*

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive liothyronine sodium tablets therapy. Monitor patients receiving concomitant liothyronine sodium tablets and sympathomimetic agents for signs and symptoms of coronary insufficiency. If cardiovascular symptoms develop or worsen, reduce or withhold the liothyronine sodium tablets dose 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 thyroid hormone 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 liothyronine sodium tablets*[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

Liothyronine sodium tablets has a narrow therapeutic index. Over- or undertreatment with liothyronine sodium tablets may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Titrate the dose of liothyronine sodium tablets 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 liothyronine sodium tablets and adjust the dose as necessary *[see Drug Interactions (7) and Clinical Pharmacology (12.3)].*

5.5 Worsening of Diabetic Control

Addition of thyroid hormone 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 liothyronine sodium tablets*[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 thyroid hormone 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 liothyronine sodium tablets that achieves the desired clinical and biochemical response to mitigate against this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with liothyronine sodium tablets therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5.4) and 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 and cramps

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

Endocrine: decreased bone mineral density

Reproductive: menstrual irregularities, impaired fertility

Adverse Reactions in Pediatric Patients

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in pediatric patients receiving thyroid replacement therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in pediatric patients 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.

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs can exert effects on thyroid hormone pharmacokinetics (e.g. absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to liothyronine sodium tablets (see Tables 1 – 4).

Table 1: Drugs That May Decrease T3 Absorption (Hypothyroidism)

Potential impact: Concurrent use may reduce the efficacy of liothyronine sodium tablets by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.

DRUG OR DRUG CLASS	**EFFECT**
Bile Acid Sequestrants -Colesevelam -Cholestyramine -Colestipol	Bile acid sequestrants and ion exchange resins are known to decrease thyroid hormones absorption. Administer liothyronine sodium tablets at least 4 hours prior to these drugs or monitor thyrotropin-

Ion Exchange Resins stimulating hormone
TSH) levels.
-Kayexalate
-Sevelamer

Table 2: Drugs That May Alter Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism)

DRUG OR DRUG CLASS	EFFECT
Clofibrate Estrogen-containing oral Contraception Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen Androgens / Anabolic Steroids Asparaginase	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.
Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.
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 Furosemide (>80 mg IV) Heparin Hydantoins Non-Steroidal Anti-inflammatory Drugs Phenylbutazone Fenamates	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 increased free-T4 fraction in serum. Furosemide competes for T4-binding sites on prealbumin, and albumin, so that a single high dose can acutely lower the total T4 level. Phenytoin and carbamazepine reduce serum protein binding of thyroid hormones, and total and FT4 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 3: Drugs That May Alter Hepatic Metabolism of Thyroid hormones

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of thyroid hormones, resulting in increased liothyronine sodium tablets requirements.

DRUG OR DRUG CLASS	EFFECT
Phenobarbital	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
Rifampin	Rifampin are added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of thyroid hormones.

TABLE 4: 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 ≥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 liothyronine sodium tablets 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 liothyronine sodium tablets are started, changed, or discontinued *[see Warnings and Precautions (5.5)]*.

7.3 Oral Anticoagulants

Liothyronine sodium tablets 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 liothyronine sodium tablets dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

Liothyronine sodium tablets may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may be decreased 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 liothyronine sodium tablets 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. Liothyronine sodium tablets may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on liothyronine sodium tablets may result in increased liothyronine sodium tablets requirements.

7.6 Ketamine

Concurrent use of ketamine and liothyronine sodium tablets may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

7.7 Sympathomimetics

Concurrent use of sympathomimetics and liothyronine sodium tablets 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-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogencontaining oral contraceptives, and acute intermittent porphyria increase TBG concentrations. 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 liothyronine 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 liothyronine sodium tablets dosage adjusted during pregnancy *(see Clinical Considerations)*. There are no animal studies conducted with liothyronine during pregnancy. Liothyronine sodium tablets 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 liothyronine sodium tablets requirements. Serum TSH levels should be monitored and the liothyronine sodium tablets dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the liothyronine sodium tablets dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration (2.3)].*

Data

Human Data

Liothyronine is approved for use as a replacement therapy for hypothyroidism. Data from postmarketing studies have not reported increased rates of fetal malformations, miscarriages, or other adverse maternal or fetal outcomes associated with liothyronine use in pregnant women.

8.2 Lactation

Risk Summary

Limited published studies report that liothyronine is present in human milk. However, there is insufficient information to determine the effects of liothyronine on the breastfed infant and no available information on the effects of liothyronine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for liothyronine sodium tablets and any potential adverse effects on the breastfed infant from liothyronine sodium tablets or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of liothyronine sodium tablets 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 pediatric patients in whom a diagnosis of permanent hypothyroidism has not been established, discontinue thyroid hormone for a trial period, but only after the child is at least 3 years of age. Obtain serum TSH, T4, and T3 levels at the end of the trial period, and use laboratory test results and clinical assessments to guide diagnosis and treatment, if warranted *[see Dosage and Administration (2.6)].*

Congenital Hypothyroidism [see Dosage and Administration (2.2, 2.6)]

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 thyroid hormone immediately upon diagnosis. Thyroid hormone is generally continued for life in these patients.

Closely monitor infants during the first 2 weeks of thyroid hormone 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 *[see Dosage and Administration (2.6) and Adverse Reactions (6)]*.

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 *[see Adverse Reactions (6)]*.

8.5 Geriatric Use

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

10 OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*. In addition, confusion and disorientation may occur. Cerebral embolism, seizure, shock, coma, and death have been reported. Symptoms may not necessarily be evident or may not appear until several days after ingestion.

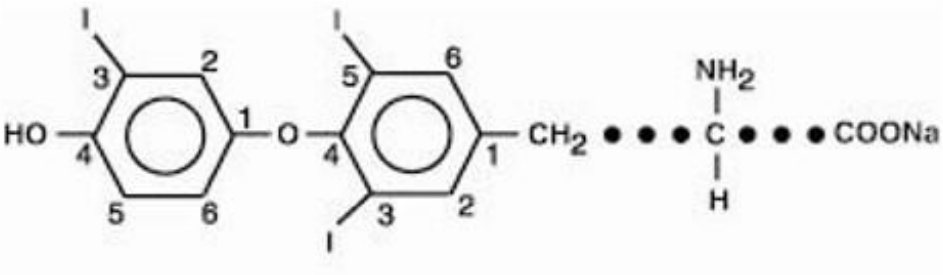
Reduce the liothyronine sodium tablets dose or temporarily discontinued if signs or symptoms of overdosage occur. Initiate appropriate supportive treatment as dictated by the patient's medical status.

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

Liothyronine sodium tablets contain the active ingredient, liothyronine (L-triiodothyronine or LT3), a synthetic form of a thyroid hormone liothyronine in sodium

salt form. It is chemically designated as LTyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt. The molecular formula, molecular weight and structural formula of liothyronine sodium are given below.



C15H11I3NNaO4 M.W.672.96

Liothyronine sodium tablets contain liothyronine sodium equivalent to liothyronine in 5 mcg, 25 mcg, and 50 mcg. Inactive ingredients consist of calcium sulfate, microcrystalline cellulose, hypromellose, talc, and colloidal silicon dioxide.

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

The onset of activity of liothyronine sodium occurs within a few hours. Maximum pharmacologic response occurs within 2 or 3 days.

12.3 Pharmacokinetics

Absorption

T3 is almost totally absorbed, 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

Distribution

Liothyronine sodium (T3) is not firmly bound to serum protein. The higher affinity of levothyroxine

(T4) for both thyroid-binding globulin and thyroid-binding prealbumin as compared to triiodothyronine (T3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

Elimination

Metabolism

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. T3 is 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. The biological half-life is about 2-1/2 days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of liothyronine sodium.

16 HOW SUPPLIED/STORAGE AND HANDLING

Liothyronine sodium tablets, USP (round, flat, white to off-white) are supplied as follows:

STRENGTH	TABLET MARKINGS	NDC – BOTTLES OF 100
5 mcg	debossed "5" over "220" on one side and plain on the other	51862-**320**-01
25 mcg	debossed "25" above the score and "222" below the score on one side and plain on the other	51862-**321**-01

50 mcg	"50" above the score and "223" below the score on one side and plain on the other	51862-**322**-01

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Dosing and Administration

- Instruct patients that liothyronine sodium tablets should only be taken as directed by their healthcare provider.
- Instruct patients to notify their healthcare provider should they become pregnant or breastfeeding or are thinking of becoming pregnant, while taking liothyronine sodium tablets.

Important Information

- Inform patients that the liothyronine in liothyronine sodium tablets are 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 liothyronine sodium tablets 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 healthcare provider of any other medical conditions, 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 taking liothyronine sodium tablets. If patents are taking anticoagulants (blood thinners), their clotting status should be checked frequently.

- Instruct patients to notify their physician or dentist if they are taking liothyronine sodium tablets 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 *[see Adverse Reactions (6)]*.

- Inform patients that partial hair loss may occur rarely during the first few months of liothyronine sodium tablets therapy; this is usually temporary *[see Adverse Reactions (6)]*.

Manufactured by:

7 MAYNE PHARMA

Greenville, NC 27834

61859
Rev 03/2019

PRINCIPAL DISPLAY PANEL - 5 mcg Tablet Bottle Label

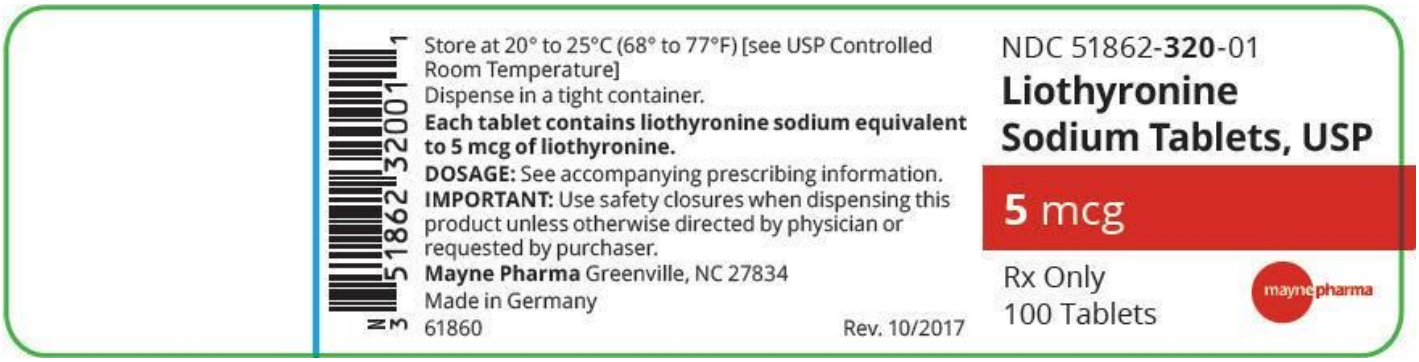
NDC 51862-**320**-01

8 LIOTHYRONINE SODIUM TABLETS, USP

5 mcg

Rx Only
100 Tablets

mayne**pharma**



PRINCIPAL DISPLAY PANEL - 25 mcg Tablet Bottle Label

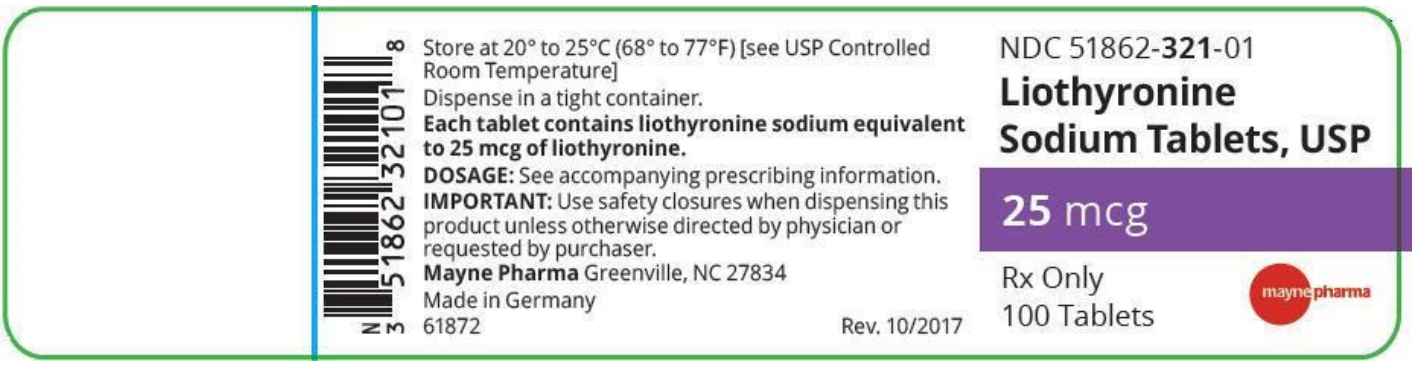
NDC 51862-**321**-01

9 LIOTHYRONINE SODIUM TABLETS, USP

25 mcg

Rx Only
100 Tablets

mayne**pharma**



PRINCIPAL DISPLAY PANEL - 50 mcg Tablet Bottle Label

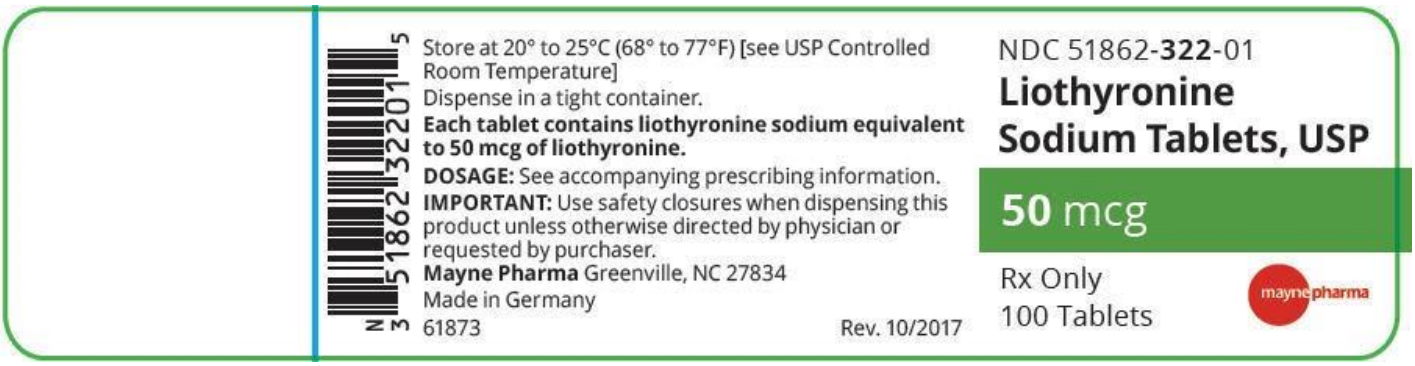
NDC 51862-**322**-01

10 LIOTHYRONINE SODIUM TABLETS, USP

50 mcg

Rx Only
100 Tablets

mayne**pharma**



LIOTHYRONINE SODIUM liothyronine sodium tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-320
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Liothyronine Sodium (UNII: GCA9VV7D2N) (liothyronine - UNII:06LU7C9H1V)	liothyronine	5 ug

Inactive Ingredients

Ingredient Name	Strength
calcium sulfate, unspecified form (UNII: WAT0DDB505)	
microcrystalline cellulose (UNII: OP1R32D61U)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
talc (UNII: 7SEV7J4R1U)	
silicon dioxide (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	5;220
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-320-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/01/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA090097	01/01/2018	

LIOTHYRONINE SODIUM

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-321
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Liothyronine Sodium (UNII: GCA9VV7D2N) (liothyronine - UNII:06LU7C9H1V)	liothyronine	25 ug

Inactive Ingredients

Ingredient Name	Strength
calcium sulfate, unspecified form (UNII: WAT0DDB505)	
microcrystalline cellulose (UNII: OP1R32D61U)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
talc (UNII: 7SEV7J4R1U)	
silicon dioxide (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	25;222
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-321-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/01/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090097	01/01/2018	

LIOTHYRONINE SODIUM

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-322
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Liothyronine Sodium (UNII: GCA9VV7D2N) (liothyronine - UNII:06LU7C9H1V)	liothyronine	50 ug

Inactive Ingredients

Ingredient Name	Strength
calcium sulfate, unspecified form (UNII: WAT0DDB505)	
microcrystalline cellulose (UNII: OP1R32D61U)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
talc (UNII: 7SEV7J4R1U)	
silicon dioxide (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	50;223
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-322-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/01/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090097	01/01/2018	

Labeler - Mayne Pharma (867220261)

Establishment

Name	Address	ID/FEI	Business Operations
Mayne Pharma Inc.		867220261	ANALYSIS(51862-320, 51862-321, 51862-322) , MANUFACTURE(51862-320, 51862-321, 51862-322) , PACK(51862-320, 51862-321, 51862-322) , LABEL(51862-320, 51862-321, 51862-322)

Revised: 4/2019 Mayne Pharma

APPENDIX G

CYTOMEL- LIOTHYRONINE SODIUM TABLET PFIZER LABORATORIES DIV PFIZER INC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CYTOMEL safely and effectively. See full prescribing information for CYTOMEL.

CYTOMEL® (liothyronine sodium) tablets, for oral use
Initial U.S. Approval: 1956

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

See full prescribing information for complete boxed warning.

- **Thyroid hormones, including CYTOMEL, 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, 7.7, 10).**

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3)	12/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5, 2.6)	12/2018
Contraindications (4)	12/2018
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)	12/2018

INDICATIONS AND USAGE

CYTOMEL is an L-triiodothyronine (T3) indicated for:

- Hypothyroidism: As replacement in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism (1.1)
- Pituitary Thyroid-Stimulating Hormone (TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer (1.2)
- Thyroid Suppression Test: As a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy (1.3)

Limitations of Use:

- Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients. (1)

- Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis. (1)

DOSAGE AND ADMINISTRATION

- Administer CYTOMEL orally once daily and individual dosage according to patient response and laboratory findings (2.1)
- See full prescribing information for recommended dosage for hypothyroidism (2.2) TSH suppression in welldifferentiated thyroid cancer (2.3) and for thyroid suppression test (2.4)
- When switching a patient to CYTOMEL, discontinue levothyroxine therapy and initiate CYTOMEL at a low dosage. Gradually increase the dose according to the patient's response (2.5)
- Adequacy of therapy determined with periodic monitoring of TSH and T3 levels as well as clinical status (2.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mcg, 25 mcg, 50 mcg (3)

CONTRAINDICATIONS

Uncorrected adrenal cortical insufficiency (4)

WARNINGS AND PRECAUTIONS

- Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease: Initiate CYTOMEL 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 CYTOMEL 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

Most common adverse reactions for CYTOMEL are primarily those of hyperthyroidism due to therapeutic overdosage: arrhythmias, myocardial infarction, dyspnea, 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 Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA1088 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 CYTOMEL (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of thyroid hormone (2.2, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2019

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS 1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS 4 CONTRAINDICATIONS 5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS 7 DRUG INTERACTIONS

* 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 CYTOMEL, 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

1.1 Hypothyroidism

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

1.2 Pituitary Thyroid-Stimulating Hormone(TSH) Suppression

CYTOMEL is indicated as an adjunct to surgery and radioiodine therapy in the management of welldifferentiated thyroid cancer.

1.3 Thyroid Suppression Test

CYTOMEL is indicated as a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

~~Limitations of Use~~

- CYTOMEL 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 CYTOMEL may induce hyperthyroidism *[see Warnings and Precautions (5.4)]*.
- CYTOMEL is not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

2.1 General Principles of Dosing

The dose of CYTOMEL 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 (2.2, 2.3, 2.4), 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)]*.

Administer CYTOMEL tablets orally once daily.

2.2 Recommended Dosage for Hypothyroidism

Adults

The recommended starting dosage is 25 mcg orally once daily. Increase the dose by 25 mcg daily every 1 or 2 weeks, if needed. The usual maintenance dose is 25 mcg to 75 mcg once daily.

For elderly patients or patients with underlying cardiac disease, start with CYTOMEL 5 mcg once daily and increase by 5 mcg increments at the recommended intervals.

Serum TSH is not a reliable measure of CYTOMEL dose adequacy in patients with secondary or tertiary hypothyroidism and should not be used to monitor therapy. Use the serum T3 level to monitor adequacy of therapy in this patient population.

Pediatric Patients

The recommended starting dosage is 5 mcg once daily, with a 5 mcg increase every 3 to 4 days until the desired response is achieved. Infants a few months old may require 20 mcg once daily for maintenance. At 1 year of age, 50 mcg once daily may be required. Above 3 years of age, the full adult dosage may be necessary *[see Use in Specific Populations (8.4)].*

Newborns (0 to 3 months) at Risk for Cardiac Failure:

Consider a lower starting dose in infants at risk for cardiac failure. Increase the dose as needed based on clinical and laboratory response.

Pediatric Patients at Risk for Hyperactivity:

To minimize the risk of hyperactivity in pediatric patients, 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: Thyroid hormone 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 trimesterspecific reference range. For patients with serum TSH above the normal trimester-specific range, increase the dose of thyroid hormone and measure TSH every 4 weeks until a stable dose is reached and serum TSH is within the normal trimester-specific range. Reduce thyroid hormone dosage to prepregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure thyroid hormone dose is appropriate.

2.3 Recommended Dosage for TSH Suppression in Well-Differentiated Thyroid Cancer

The dose of CYTOMEL should target TSH levels within the desired therapeutic range. This may require higher doses, depending on the target level for TSH suppression.

2.4 Recommended Dosage for Thyroid Suppression Test

The recommended dose is 75 mcg to 100 mcg daily for 7 days, with radioactive iodine uptake being determined before and after the 7 day administration of CYTOMEL. If thyroid function is normal, the radioiodine uptake will drop significantly after treatment. A 50% or greater suppression of uptake indicates a normal thyroid-pituitary axis.

2.5 Switching from Levothyroxine to CYTOMEL

CYTOMEL has a rapid onset of action and residual effects of the other thyroid preparation may persist for the first several weeks after initiating CYTOMEL therapy. When switching a patient to CYTOMEL, discontinue levothyroxine therapy and initiate CYTOMEL at a low dosage. Gradually increase the CYTOMEL dose according to the patient's response.

2.6 Monitoring TSH and Triiodothyronine (T3) 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 CYTOMEL 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 periodically after initiation of the therapy or any change in dose. To check the immediate response to therapy before the TSH has had a

chance to respond or if your patient's status needs to be assessed prior to that point, measurement of total T3 would be most appropriate. 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 pediatric patients with hypothyroidism, assess the adequacy of replacement therapy by measuring serum TSH and T3 levels. For pediatric patients three years of age and older, the recommended monitoring is every 3 to 12 months thereafter, following dose stabilization until growth and puberty are 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 TSH to decrease below 20 IU per liter after initiation of CYTOMEL therapy 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 CYTOMEL *[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.4)]*.

Secondary and Tertiary Hypothyroidism

Monitor serum T3 levels and maintain in the normal range.

3 DOSAGE FORMS AND STRENGTHS

Tablets (round, white to off-white) available as follows:

- 5 mcg: debossed with KPI on one side and 115 on the other side
- 25 mcg: scored on one side and debossed with KPI and 116 on the other side
- 50 mcg: scored on one side and debossed with KPI and 117 on the other side

4 CONTRAINDICATIONS

CYTOMEL 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

Overtreatment with thyroid hormone 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 CYTOMEL 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) and Use in Specific Populations (8.5)].*

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive CYTOMEL therapy. Monitor patients receiving concomitant CYTOMEL and sympathomimetic agents for signs and symptoms of coronary insufficiency. If cardiovascular symptoms develop or worsen, reduce or withhold the CYTOMEL dose 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 thyroid hormone 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 CYTOMEL *[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

CYTOMEL has a narrow therapeutic index. Over- or undertreatment with CYTOMEL may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Titrate the dose of CYTOMEL 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 CYTOMEL and adjust the dose as necessary *[see Drug Interactions (7) and Clinical Pharmacology (12.3)].*

5.5 Worsening of Diabetic Control

Addition of thyroid hormone 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 CYTOMEL *[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 thyroid hormone 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 CYTOMEL that achieves the desired clinical and biochemical response to mitigate against this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with CYTOMEL therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5.4) and 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 and cramps

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

Endocrine: decreased bone mineral density

Reproductive: menstrual irregularities, impaired fertility

Adverse Reactions in Pediatric Patients

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in pediatric patients receiving thyroid replacement therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in pediatric patients 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.

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs can exert effects on thyroid hormone pharmacokinetics (e.g. absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to CYTOMEL (see Tables 1 – 4).

TABLE 1: DRUGS THAT MAY DECREASE T3 ABSORPTION (HYPOTHYROIDISM)

Potential impact: Concurrent use may reduce the efficacy of CYTOMEL by binding and **delaying or preventing absorption, potentially resulting in hypothyroidism.**

Drug or Drug Class	Effect
Bile Acid Sequestrants **-Colesevelam** **-Cholestyramine** **-Colestipol**	**Bile acid sequestrants and ion exchange resins are known to decrease thyroid hormones absorption. Administer CYTOMEL at least 4 hours prior to these drugs or monitor TSH levels.**
Ion Exchange Resins **-Kayexalate** **-Sevelamer**	

Table 2: Drugs That May Alter Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism)

DRUG OR DRUG CLASS	Effect
Clofibrate Estrogencontaining oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration.
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.

Salicylates inhibit binding of T4 and T3 to TBG and transthyretin. An Salicylates (>2 initial increase in serum FT4 is followed by return of FT4 to normal g/day) levels with sustained therapeutic serum salicylate concentrations, although total T4 levels may decrease by as much as 30%.

Other drugs:

These drugs may cause protein binding site displacement. Furosemide Carbamazepine has been shown to inhibit the protein binding of T4 to TBG and Furosemide (>80 albumin, causing an increased free-T4 fraction in serum. Furosemide mg IV) competes for T4-binding sites on TBG, prealbumin, and albumin, so Heparin that a single high dose can acutely lower the total T4 level. Phenytoin Hydantoins Nonand carbamazepine reduce serum protein binding of thyroid hormones, Steroidal Antiand total and FT4 may be reduced by 20% to 40%, but most patients inflammatory have normal serum TSH levels and are clinically euthyroid. Closely Drugs monitor thyroid hormone parameters.

- Fenamates

Table 3: Drugs That May Alter Hepatic Metabolism of Thyroid Hormones

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of thyroid hormones, resulting in increased CYTOMEL requirements.

DRUG OR DRUG CLASS	Effect
Phenobarbital	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 Phenobarbital serum levels. Changes in thyroid status may occur if barbiturates are
Rifampin	added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of thyroid hormones.

TABLE 4: 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	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 >160 mg/day) euthyroid state
Glucocorticoids	Short-term administration of large doses of glucocorticoids may decrease serum T3 concentrations by 30% with minimal change in (e.g., serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG ≥4 mg/day) 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 CYTOMEL 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 CYTOMEL is started, changed, or discontinued *[see Warnings and Precautions (5.5)]*.

7.3 Oral Anticoagulants

CYTOMEL 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 CYTOMEL dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

CYTOMEL may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may be decreased 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 CYTOMEL 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. CYTOMEL may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on CYTOMEL may result in increased CYTOMEL requirements.

7.6 Ketamine

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

7.7 Sympathomimetics

Concurrent use of sympathomimetics and CYTOMEL 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-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogencontaining oral contraceptives, and acute intermittent porphyria increase TBG concentrations. 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.

11 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Experience with liothyronine 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 CYTOMEL dosage adjusted during pregnancy *(see Clinical Considerations)*. There are no animal studies conducted with liothyronine during pregnancy. CYTOMEL 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 CYTOMEL requirements. Serum TSH levels should be monitored and the CYTOMEL dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the CYTOMEL dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration (2.3)].*

Data

Human Data

Liothyronine is approved for use as a replacement therapy for hypothyroidism. Data from postmarketing studies have not reported increased rates of fetal malformations, miscarriages, or other adverse maternal or fetal outcomes associated with liothyronine use in pregnant women.

8.2 Lactation

Risk Summary

Limited published studies report that liothyronine is present in human milk. However, there is insufficient information to determine the effects of liothyronine on the breastfed infant and no available information on the effects of liothyronine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYTOMEL and any potential adverse effects on the breastfed infant from CYTOMEL or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of CYTOMEL 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 pediatric patients in whom a diagnosis of permanent hypothyroidism has not been established, discontinue thyroid hormone for a trial period, but only after the child is at least 3 years of age. Obtain serum TSH, T4, and T3 levels at the end of the trial period, and use laboratory test results and clinical assessments to guide diagnosis and treatment, if warranted *[see Dosage and Administration (2.6)].*

Congenital Hypothyroidism [see Dosage and Administration (2.2, 2.6)]

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 thyroid hormone immediately upon diagnosis. Thyroid hormone is generally continued for life in these patients.

Closely monitor infants during the first 2 weeks of thyroid hormone 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 *[see Dosage and Administration (2.6) and Adverse Reactions (6)]*.

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 *[see Adverse Reactions (6)]*.

8.5 Geriatric Use

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

10 OVERDOSAGE

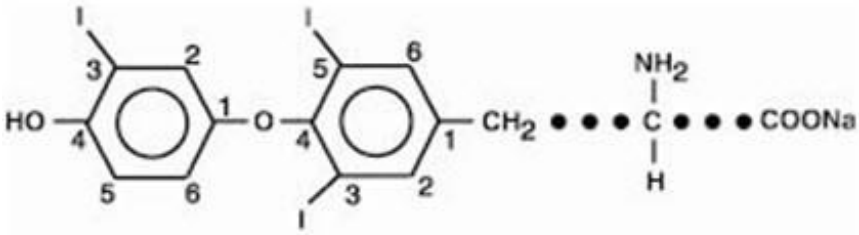
The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*. In addition, confusion and disorientation may occur. Cerebral embolism, seizure, shock, coma, and death have been reported. Symptoms may not necessarily be evident or may not appear until several days after ingestion.

Reduce the CYTOMEL dose or temporarily discontinued 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

CYTOMEL tablets contain the active ingredient, liothyronine (L-triiodothyronine or LT3), a synthetic form of a thyroid hormone liothyronine in sodium salt form. It is chemically designated as L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt. The molecular formula, molecular weight and structural formula of liothyronine sodium are given below.



$C_{15}H_{11}I_3NNaO_4$ M.W.672.96

CYTOMEL tablets contain liothyronine sodium equivalent to liothyronine in 5 mcg, 25 mcg, and 50 mcg. Inactive ingredients consist of calcium sulfate, corn starch, gelatin, stearic acid, sucrose and talc.

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

The onset of activity of liothyronine sodium occurs within a few hours. Maximum pharmacologic response occurs within 2 or 3 days.

12.3 Pharmacokinetics

Absorption

T3 is almost totally absorbed, 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

Distribution

Liothyronine sodium (T3) is not firmly bound to serum protein. The higher affinity of levothyroxine
(T4) for both thyroid-binding globulin and thyroid-binding prealbumin as compared to triiodothyronine (T3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

Elimination

Metabolism

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. T3 is 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. The biological half-life is about 2–1/2 days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of liothyronine sodium.

16 HOW SUPPLIED/STORAGE AND HANDLING

CYTOMEL tablets (round, white to off-white) are supplied as follows:

Strength	Tablet Markings	NDC – bottles of 100
5 mcg	Debossed with KPI on one side and 115 on the other side	60793-115-01
25 mcg	Scored on one side and debossed with KPI and 116 on the other side	60793-116-01
50 mcg	Scored on one side and debossed with KPI and 117 on the other side	60793-117-01

Store between 15°C and 30°C (59°F and 86°F).

17 PATIENT COUNSELING INFORMATION

Dosing and Administration

- Instruct patients that CYTOMEL should only be taken as directed by their healthcare
- provider. Instruct patients to notify their healthcare provider should they become pregnant or breastfeeding or are thinking of becoming pregnant, while taking CYTOMEL.

Important Information

- Inform patients that the liothyronine in CYTOMEL 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 CYTOMEL 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 healthcare provider of any other medical conditions, 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 taking CYTOMEL. If patents are taking anticoagulants (blood thinners), their clotting status should be checked frequently.

- Instruct patients to notify their physician or dentist if they are taking CYTOMEL 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 *[see Adverse Reactions (6)]*.
- Inform patients that partial hair loss may occur rarely during the first few months of CYTOMEL therapy; this is usually temporary *[see Adverse Reactions (6)]*.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

Distributed by

Pfizer Inc
New York, NY 10017

LAB-0683-5.0

PRINCIPAL DISPLAY PANEL - 5 MCG TABLET BOTTLE LABEL

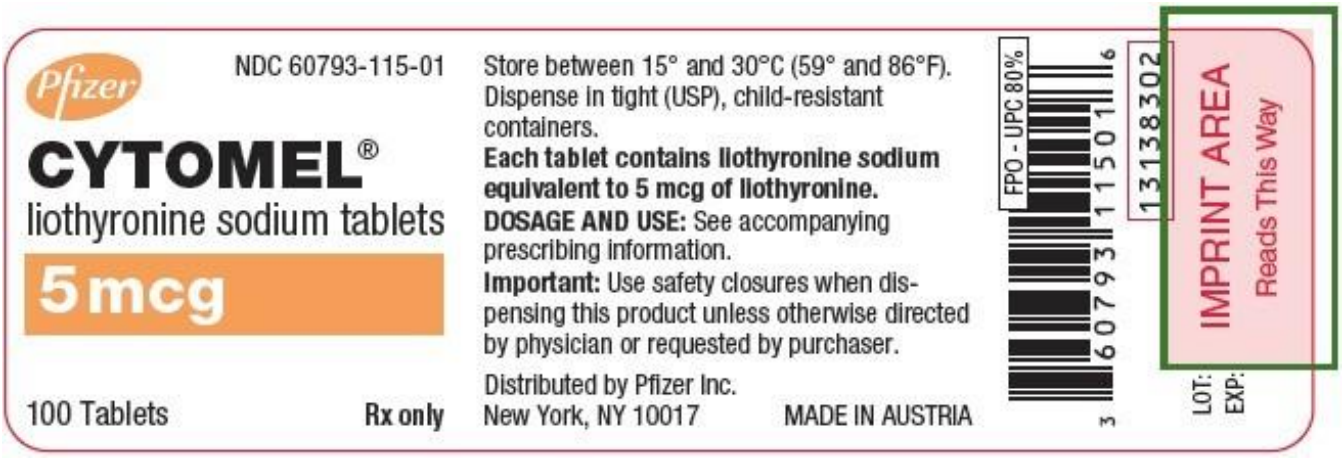
NDC 60793-115-01

Pfizer

CYTOMEL®
liothyronine sodium tablets

5 mcg

100 Tablets **RX only**



PRINCIPAL DISPLAY PANEL - 25 MCG TABLET BOTTLE LABEL

NDC 60793-116-01

Pfizer

CYTOMEL®
liothyronine sodium tablets

25 mcg

100 Tablets **RX only**

RX ONLY

PRINCIPAL DISPLAY PANEL - 50 MCG TABLET BOTTLE LABEL

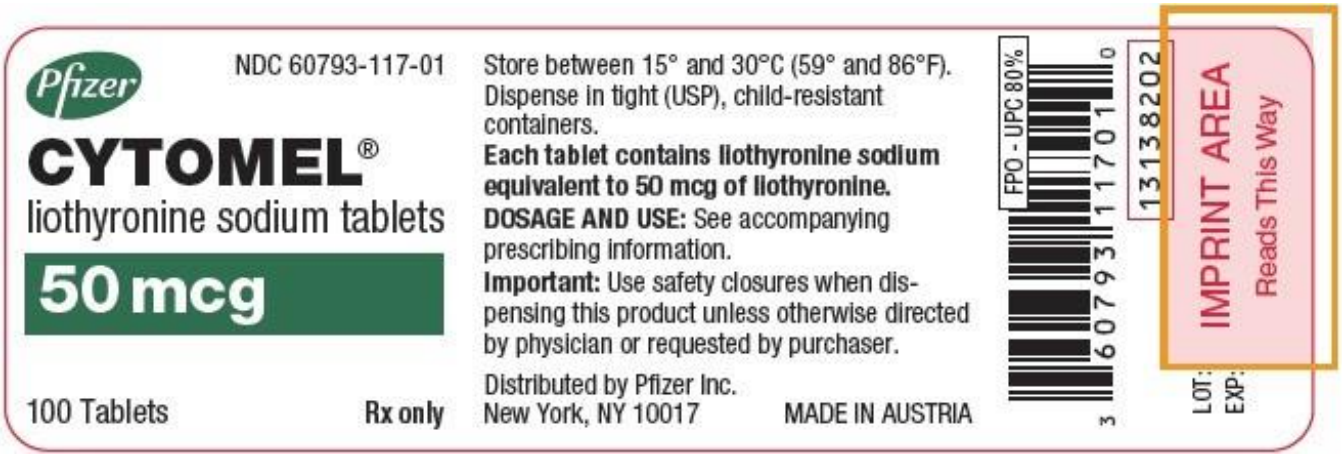
NDC 60793-117-01

Pfizer

CYTOMEL®
liothyronine sodium tablets

50 mcg**5 mcg**

100 Tablets **RX only**



CYTOMEL liothyronine sodium tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60793-115
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	5 ug

Product Characteristics			
Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	6mm

Flavor		**Imprint Code**	KPI;115
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60793-115-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/1956	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA010379	05/08/1956	

CYTOMEL

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60793-116
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	25 ug

Product Characteristics

Color	WHITE (white to off-white)	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	KPI;116

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60793-116-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/1956	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA010379	05/08/1956	

CYTOMEL

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:60793-117
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	50 ug

Product Characteristics

Color	WHITE (white to off-white)	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	KPI;117
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:60793-117-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/08/1956	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA010379	05/08/1956	

Labeler - Pfizer Laboratories Div Pfizer Inc (134489525)

Establishment

Name	Address	ID/FEI	Business Operations
Peptido GmbH		327335410	API MANUFACTURE(60793-115)

APPENDIX H

LIOTHYRONINE SODIUM- LIOTHYRONINE SODIUM TABLET
SIGMAPHARM LABORATORIES, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIOTHYRONINE SODIUM TABLETS, USP safely and effectively. See full prescribing information for LIOTHYRONINE SODIUM TABLETS, USP.

LIOTHYRONINE SODIUM TABLETS, USP, for oral use

Initial U.S. Approval: 1956

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

See full prescribing information for complete boxed warning.

- **Thyroid hormones, including liothyronine sodium 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, 7.7, 10)**

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3)	12/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5, 2.6)	12/2018
Contraindications (4)	12/2018
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)	12/2018

INDICATIONS AND USAGE

Liothyronine sodium is an L-triiodothyronine (T3) indicated for:

- Hypothyroidism: As replacement in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism (1.1)

Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer (1.2)

Thyroid Suppression Test: As a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy (1.3)

Limitations of Use:

- Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients. (1)
- Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis. (1)

DOSAGE AND ADMINISTRATION

- Administer Liothyronine Sodium Tablets, USP orally once daily and individual dosage according to patient response and laboratory findings (2.1)
- See full prescribing information for recommended dosage for hypothyroidism (2.2) TSH suppression in welldifferentiated thyroid cancer (2.3) and for thyroid suppression test (2.4)

  When switching a patient to Liothyronine Sodium Tablets, USP discontinue levothyroxine therapy and initiate

  Liothyronine Sodium Tablets, USP at a low dosage. Gradually increase the dose according to the patient's response (2.5)
- Adequacy of therapy determined with periodic monitoring of TSH and T3 levels as well as clinical status (2.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mcg, 25 mcg, 50 mcg (3)

CONTRAINDICATIONS

Uncorrected adrenal cortical insufficiency (4)

WARNINGS AND PRECAUTIONS

- Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease: Initiate Liothyronine Sodium Tablets, USP 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 liothyronine sodium 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

Most common adverse reactions for Liothyronine Sodium Tablets, USP are primarily those of hyperthyroidism due to therapeutic overdosage: arrhythmias, myocardial infarction, dyspnea, 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 Sigmapharm Laboratories, LLC, Pharmacovigilance at 1-855-332-0731 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

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 liothyronine sodium (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of thyroid hormone (2.2, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2019

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FULL PRESCRIBING INFORMATION

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

- **Thyroid hormones, including liothyronine sodium, 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

1.1 Hypothyroidism

Liothyronine Sodium Tablets, USP are indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

1.2 Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression

Liothyronine Sodium Tablets, USP are indicated as an adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer.

1.3 Thyroid Suppression Test

Liothyronine Sodium Tablets, USP are indicated as a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Limitations of Use

- Liothyronine Sodium Tablets, USP are 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 Liothyronine Sodium Tablets, USP may induce hyperthyroidism *[see Warnings and Precautions (5.4)].*
- Liothyronine Sodium Tablets, USP are not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

2 DOSAGE AND ADMINISTRATION

2.1 General Principles of Dosing

The dose of Liothyronine Sodium Tablets, USP for hypothyroidism or pituitary Thyroid-Stimulating Hormone (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 (2.2, 2.3, 2.4), 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)].*

Administer Liothyronine Sodium Tablets, USP orally once daily.

2.2 Recommended Dosage for Hypothyroidism

Adults

The recommended starting dosage is 25 mcg orally once daily. Increase the dose by 25 mcg daily every 1 or 2 weeks, if needed. The usual maintenance dose is 25 mcg to 75 mcg once daily.

For elderly patients or patients with underlying cardiac disease, start with Liothyronine Sodium Tablets, USP 5 mcg once daily and increase by 5 mcg increments at the recommended intervals.

Serum TSH is not a reliable measure of liothyronine sodium dose adequacy in patients with secondary or tertiary hypothyroidism and should not be used to monitor therapy. Use the serum T3 level to monitor adequacy of therapy in this patient population.

Pediatric Patients

The recommended starting dosage is 5 mcg once daily, with a 5 mcg increase every 3 to 4 days until the desired response is achieved. Infants a few months old may require 20 mcg once daily for maintenance. At 1 year of age, 50 mcg once daily may be required. Above 3 years of age, the full adult dosage may be necessary *[see Use in Specific Populations (8.4)].*

Newborns (0 to 3 months) at Risk for Cardiac Failure:
Consider a lower starting dose in infants at risk for cardiac failure. Increase the dose as needed based on clinical and laboratory response.

Pediatric Patients at Risk for Hyperactivity:
To minimize the risk of hyperactivity in pediatric patients, 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

Pregnancy

Pre-existing Hypothyroidism: Thyroid hormone 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 trimesterspecific range, increase the dose of thyroid hormone and measure TSH every 4 weeks until a stable dose is reached and serum TSH is within the normal trimester-specific range. Reduce thyroid hormone dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure thyroid hormone dose is appropriate.

2.3 Recommended Dosage for TSH Suppression in Well-Differentiated Thyroid Cancer

The dose of Liothyronine Sodium Tablets, USP should target TSH levels within the desired therapeutic range. This may require higher doses, depending on the target level for TSH suppression.

2.4 Recommended Dosage for Thyroid Suppression Test

The recommended dose is 75 mcg to 100 mcg daily for 7 days, with radioactive iodine uptake being determined before and after the 7 day administration of Liothyronine Sodium Tablets, USP. If thyroid function is normal, the radioiodine uptake will drop significantly after treatment. A 50% or greater suppression of uptake indicates a normal thyroid-pituitary axis.

2.5 Switching from Levothyroxine to Liothyronine Sodium Tablets, USP

Liothyronine sodium has a rapid onset of action and residual effects of the other thyroid preparation may persist for the first several weeks after initiating liothyronine sodium therapy. When switching a patient to Liothyronine Sodium Tablets, USP, discontinue levothyroxine therapy and initiate Liothyronine Sodium Tablets, USP at a low dosage. Gradually increase the liothyronine sodium dose according to the patient's response.

2.6 Monitoring TSH and Triiodothyronine (T3) 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 Liothyronine Sodium Tablets, USP 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 periodically after initiation of the therapy or any change in dose. To check the immediate response to therapy before the TSH has had a chance to respond or if your patient's status needs to be assessed prior to that point, measurement of total T3 would be most appropriate. 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 pediatric patients with hypothyroidism, assess the adequacy of replacement therapy by measuring serum TSH and T3 levels. For pediatric patients three years of age and older, the recommended monitoring is every 3 to 12 months thereafter, following dose stabilization until growth and puberty are 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 TSH to decrease below 20 IU per liter after initiation of liothyronine sodium therapy 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 Liothyronine Sodium Tablets, USP *[see Warnings and Precautions (5.1) andUse in Specific Populations (8.4)].*

Secondary and Tertiary Hypothyroidism

Monitor serum T3 levels and maintain in the normal range.

3 DOSAGE FORMS AND STRENGTHS

Tablets (white to off-white, round, SC) available as follows:

- 5 mcg: debossed "∑" on one side and "18" on the other side
- 25 mcg: debossed "∑19" on one side and "BISECTED" on the other side
- 50 mcg: debossed "∑20" on one side and "BISECTED" on the other side

4 CONTRAINDICATIONS

Liothyronine Sodium Tablets, USP are 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

Overtreatment with thyroid hormone 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 liothyronine sodium 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) and Use in Specific Populations (8.5)].*

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive liothyronine sodium therapy. Monitor patients receiving concomitant Liothyronine Sodium Tablets, USP and sympathomimetic agents for signs and symptoms of coronary insufficiency. If cardiovascular symptoms develop

or worsen, reduce or withhold the liothyronine sodium dose 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 thyroid hormone 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 Liothyronine Sodium Tablets, USP *[see Contraindications (4)].*

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

Liothyronine sodium has a narrow therapeutic index. Over- or undertreatment with liothyronine sodium may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Titrate the dose of Liothyronine Sodium Tablets, USP 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 Liothyronine Sodium Tablets, USP and adjust the dose as necessary *[see Drug Interactions (7) and Clinical Pharmacology (12.3)].*

5.5 Worsening of Diabetic Control

Addition of thyroid hormone 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 Liothyronine Sodium Tablets, USP *[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 thyroid hormone 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 Liothyronine Sodium Tablets, USP that achieves the desired clinical and biochemical response to mitigate against this risk.

6 ADVERSE REACTIONS

Adverse reactions associated with liothyronine sodium therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5.4) and 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 and cramps
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
Endocrine: decreased bone mineral density
Reproductive: menstrual irregularities, impaired fertility

Adverse Reactions in Pediatric Patients

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in pediatric patients receiving thyroid replacement therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in pediatric patients 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.

To report **SUSPECTED ADVERSE REACTIONS**, contact Sigmapharm Laboratories, LLC, Pharmacovigilance at 1-855-332-0731 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics

Many drugs can exert effects on thyroid hormone pharmacokinetics (e.g. absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to liothyronine sodium (see Tables 1 - 4).

TABLE 1: DRUGS THAT MAY DECREASE T3 ABSORPTION (HYPOTHYROIDISM)

Potential impact: Concurrent use may reduce the efficacy of liothyronine sodium by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.	
Drug or Drug Class	**Effect**
Bile Acid Sequestrants -Colesevelam -Cholestyramine -Colestipol Ion Exchange Resins -Kayexalate -Sevelamer	Bile acid sequestrants and ion exchange resins are known to decrease thyroid hormones absorption. Administer Liothyronine Sodium to these drugs or monitor TSH levels.

Table 2: Drugs That May Alter Triiodothyronine (T3) Serum Transport Without Affecting Free Thyroxine (FT4) Concentration (Euthyroidism)

Drug or Drug Class	**Effect**
Clofibrate Estrogencontaining oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	These drugs may increase serum thyroxine-binding globulin (TBG) concentration
Androgens / Anabolic Steroids Asparaginase Glucocorticoids	These drugs may decrease serum TBG concentration

Slow-Release Nicotinic Acid	
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 Antiinflammatory Drugs - Fenamates H	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 increased 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 thyroid hormones, and total and FT4 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 3: Drugs That May Alter Hepatic Metabolism of Thyroid hormones

Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of thyroid hormones, resulting in increased liothyronine sodium 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 thyroid hormones

Table 4: 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 ≥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 liothyronine sodium 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 Liothyronine Sodium Tablets, USP are started, changed, or discontinued *[see Warnings and Precautions (5.5)].*

7.3 Oral Anticoagulants

Liothyronine sodium 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 liothyronine sodium dose is increased. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

7.4 Digitalis Glycosides

Liothyronine sodium may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may be decreased 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 liothyronine sodium 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. Liothyronine sodium may accelerate the onset of action of tricyclics.

Administration of sertraline in patients stabilized on liothyronine sodium may result in increased liothyronine sodium requirements.

7.6 Ketamine

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

7.7 Sympathomimetics

Concurrent use of sympathomimetics and liothyronine sodium 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-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. 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 liothyronine 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 liothyronine sodium dosage adjusted during pregnancy (see *Clinical Considerations).* There are no animal studies conducted with liothyronine during pregnancy. Liothyronine Sodium Tablets, USP 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 liothyronine sodium requirements. Serum TSH levels should be monitored and the liothyronine sodium dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the liothyronine sodium dosage should return to the pre-pregnancy dose immediately after delivery *[see Dosage and Administration (2.3)]* .

Data

Human Data

Liothyronine is approved for use as a replacement therapy for hypothyroidism. Data from postmarketing studies have not reported increased rates of fetal malformations, miscarriages, or other adverse maternal or fetal outcomes associated with liothyronine use in pregnant women.

8.2 Lactation

Risk Summary

Limited published studies report that liothyronine is present in human milk. However, there is insufficient information to determine the effects of liothyronine on the breastfed infant and no available information on the effects of liothyronine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for liothyronine sodium and any potential adverse effects on the breastfed infant from liothyronine sodium or from the underlying maternal condition.

8.4 Pediatric Use

The initial dose of Liothyronine Sodium Tablets, USP 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 pediatric patients in whom a diagnosis of permanent hypothyroidism has not been established, discontinue thyroid hormone for a trial period, but only after the child is at least 3 years of age. Obtain serum TSH, T4, and T3 levels at the end of the trial period, and use laboratory test results and clinical assessments to guide diagnosis and treatment, if warranted *[see Dosage and Administration (2.6)].*

Congenital Hypothyroidism *[see Dosage and Administration (2.2, 2.6)]*
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 thyroid hormone immediately upon diagnosis. Thyroid hormone is generally continued for life in these patients. Closely monitor infants during the first 2 weeks of thyroid hormone 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 *[see Dosage and Administration (2.6) and Adverse Reactions (6)].*

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 *[see Adverse Reactions (6)].*

8.5 Geriatric Use

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

10 OVERDOSAGE

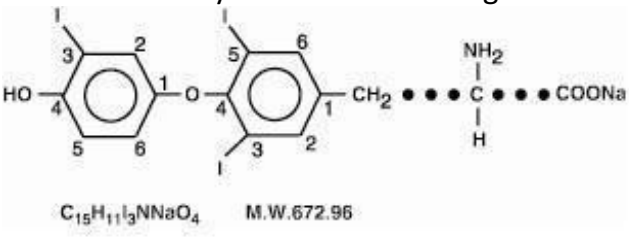
The signs and symptoms of overdosage are those of hyperthyroidism *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]* . In addition, confusion and disorientation may occur.
Cerebral embolism, seizure, shock, coma, and death have been reported. Symptoms may not necessarily be evident or may not appear until several days after ingestion.

Reduce the liothyronine sodium dose or temporarily discontinued 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

Liothyronine Sodium Tablets, USP contain the active ingredient, liothyronine (L-triiodothyronine or LT3), a synthetic form of a thyroid hormone liothyronine in sodium salt form. It is chemically designated as L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt. The molecular formula, molecular weight and structural formula of liothyronine sodium are given below.



Liothyronine Sodium Tablets, USP contain liothyronine sodium equivalent to liothyronine in 5 mcg,
25 mcg, and 50 mcg. Inactive ingredients consist of calcium sulfate dihydrate, corn starch, gelatin, magnesium stearate and mannitol.

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

The onset of activity of liothyronine sodium occurs within a few hours. Maximum pharmacologic response occurs within 2 or 3 days.

12.3 Pharmacokinetics

Absorption

T3 is almost totally absorbed, 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

Distribution

Liothyronine sodium (T3) is not firmly bound to serum protein. The higher affinity of levothyroxine
(T4) for both thyroid-binding globulin and thyroid-binding prealbumin as compared to triiodothyronine (T3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

Elimination

Metabolism

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. T3 is 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. The biological half-life is about 2-1/2 days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of liothyronine sodium.

16 HOW SUPPLIED/STORAGE AND HANDLING

Liothyronine Sodium Tablets, USP (white to off-white, round, SC) are supplied as follows:

Strength	Tablet Markings	NDC
5 mcg	debossed "Σ" on one side and "18" on the other side	30 count - 42794-018-08 60 count - 42794-018-10 90 count - 42794-018-12 100 count - 42794-018-02 1000 count - 42794-018-06
25 mcg	debossed "Σ19" on one side and "BISECTED" on the other side	30 count - 42794-019-08 60 count - 42794-019-10 90 count - 42794-019-12 100 count - 42794-019-02 1000 count - 42794-019-06
50 mcg	debossed "Σ20" on one side and "BISECTED" on the other side	30 count - 42794-020-08 60 count - 42794-020-10 90 count - 42794-020-12 100 count - 42794-020-02 1000 count - 42794-020-06

Store between 15°C and 30°C (59°F and 86°F).

17 PATIENT COUNSELING INFORMATION

Dosing and Administration

- Instruct patients that Liothyronine Sodium Tablets, USP should only be taken as directed by their healthcare provider.
- Instruct patients to notify their healthcare provider should they become pregnant or breastfeeding or are thinking of becoming pregnant, while taking Liothyronine Sodium Tablets, USP.

11.1 Important Information

- Inform patients that the liothyronine in Liothyronine Sodium Tablets, USP are 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 Liothyronine Sodium Tablets, USP 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 healthcare provider of any other medical conditions, 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 taking Liothyronine Sodium Tablets, USP. If patients are taking anticoagulants (blood thinners), their clotting status should be checked frequently.
- Instruct patients to notify their physician or dentist if they are taking Liothyronine Sodium Tablets, USP prior to any surgery.

11.2 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 *[see Adverse Reactions (6)]* .
- Inform patients that partial hair loss may occur rarely during the first few months of liothyronine sodium therapy; this is usually temporary *[see Adverse Reactions (6)]* .

Manufactured by:
Sigmapharm Laboratories, LLC
Bensalem, PA 19020

OS020-06 REV.0119

12 LIOTHYRONINE SODIUM TABLETS, USP 5 MCG- 90 TABLETS CONTAINER LABEL

13 LIOTHYRONINE SODIUM TABLETS, USP 5 MCG CONTAINER LABEL

Sigmapharm Laboratories, LLC

NDC 42794-018-12

Liothyronine Sodium Tablets, USP

5 mcg

90 Tablets

Rx Only

14 LIOTHYRONINE SODIUM TABLETS, USP 25 MCG- 90 TABLETS CONTAINER LABEL

15 LIOTHYRONINE SODIUM TABLETS, USP 25 MCG CONTAINER LABEL

Sigmapharm Laboratories, LLC

NDC 42794-019-12

Liothyronine Sodium Tablets, USP

25 mcg

90 Tablets

Rx Only

16 LIOTHYRONINE SODIUM TABLETS, USP 50 MCG- 90 TABLETS CONTAINER LABEL

17 LIOTHYRONINE SODIUM TABLETS, USP 50 MCG CONTAINER LABEL

Sigmapharm Laboratories, LLC

NDC 42794-020-12

Liothyronine Sodium Tablets, USP

50 mcg

90 Tablets

Rx Only

LIOTHYRONINE SODIUM liothyronine sodium tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42794-018
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	5 ug

Inactive Ingredients

Ingredient Name	Strength
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	

Product Characteristics

Color	white (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	18
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42794-018-02	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2012	
2	NDC:42794-018-12	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/01/2018	
3	NDC:42794-018-06	1000 in 1 BOTTLE; Type 0: Not a Combination Produc t	12/03/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200295	12/03/2012	

LIOTHYRONINE SODIUM

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42794-019
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	25 ug

Inactive Ingredients

Ingredient Name	Strength
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	

Product Characteristics

Color	white (white to off-white)	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	19
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42794-019-02	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2012	
2	NDC:42794-019-06	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2012	
3	NDC:42794-019-12	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/01/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200295	12/03/2012	

LIOTHYRONINE SODIUM

liothyronine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42794-020
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LIOTHYRONINE SODIUM (UNII: GCA9VV7D2N) (LIOTHYRONINE - UNII:06LU7C9H1V)	LIOTHYRONINE	50 ug

Product Characteristics

Color	white (white to off-white)	**Score**	2 pieces
Shape	ROUND	**Size**	8mm

Flavor		**Imprint Code**	20
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42794-020-02	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2012	
2	NDC:42794-020-12	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/01/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200295	12/03/2012	

Labeler - SIGMAPHARM LABORATORIES, LLC (556234636)

Registrant - SIGMAPHARM LABORATORIES, LLC (556234636)

Establishment

Name	Address	ID/FEI	Business Operations
SIGMAPHARM LABORATORIES, LLC		556234636	manufacture(42794-018, 42794-019, 42794-020) , analysis(42794-018, 42794019, 42794-020)

Appendix I

Quality of Life Questionnaire for Patients with Thyroid Disease

-ThyPRO39us-

This questionnaire is about how your thyroid disease has affected your life.

Please answer each question by marking ☒ by the answer that best fits you. If you are unsure about how you want to answer, please give the best answer you can.

The first section of the questionnaire is about symptoms, tiredness, memory, mood, and health.

Please base your **answers on how you have been feeling <u>in general</u>** during the past 4 weeks.

1. *The first questions are about symptoms*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
1a	- had the sensation of fullness in the neck?	☐	☐	☐	☐	☐
1c	- felt pressure in your throat?	☐	☐	☐	☐	☐
1h	- felt discomfort swallowing?	☐	☐	☐	☐	☐
1l	- had trembling hands?	☐	☐	☐	☐	☐
1m	- had a tendency to sweat a lot?	☐	☐	☐	☐	☐
1n	- experienced palpitations (rapid heart beat)?	☐	☐	☐	☐	☐
1q	- been sensitive to cold?	☐	☐	☐	☐	☐
1t	- had an upset stomach?	☐	☐	☐	☐	☐
1w	- had the sensation of dryness or "grittiness" in the eyes?	☐	☐	☐	☐	☐
1x	- had impaired vision?	☐	☐	☐	☐	☐
1bb	- been very sensitive to light?	☐	☐	☐	☐	☐
1cc	- had swollen hands or feet?	☐	☐	☐	☐	☐
1dd	- had dry skin?	☐	☐	☐	☐	☐
1ee	- had itchy skin?	☐	☐	☐	☐	☐

2. *The following questions are about tiredness*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
2a	- been tired?	☐	☐	☐	☐	☐
2c	- had difficulty getting motivated to do anything at all?	☐	☐	☐	☐	☐

3. *The following question is about your vitality*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
3b	- felt energetic?	☐	☐	☐	☐	☐

4. *The following questions are about memory and concentration*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
4a	- had difficulty remembering?	☐	☐	☐	☐	☐
4b	- had slow or unclear thinking?	☐	☐	☐	☐	☐
4f	- had difficulty concentrating?	☐	☐	☐	☐	☐

5. *The following questions are about nervousness and tension*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
5b	- felt afraid or anxious?	☐	☐	☐	☐	☐
5c	- felt tense?	☐	☐	☐	☐	☐
5e	- felt uneasy?	☐	☐	☐	☐	☐

6. *The following questions are about psychological well-being*

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
6a	- felt sad?	☐	☐	☐	☐	☐
6e	- felt unhappy?	☐	☐	☐	☐	☐

	During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
6g	- had self-confidence?	☐	☐	☐	☐	☐

7. ***The following questions are about having difficulty coping or having mood swings***

During the past 4 weeks have you	Not at all	A little	Some	Quite a bit	Very much
7c - noticed you easily felt stressed?	☐	☐	☐	☐	☐
7d - had mood swings?	☐	☐	☐	☐	☐

	Not at all	A little	Some	Quite a bit	Com-pletely
7h - felt in control of your life?	☐	☐	☐	☐	☐

The remainder of the questionnaire is about **how your thyroid disease may have affected various aspects of your life**

8. *The following questions are about your relationships with other people*

During the past 4 weeks, <u>has your thyroid disease caused</u> you to	Not at all	A little	Some	Quite a bit	Very much
8a - have difficulty being together with other people (for example, spouse, children, boy/girlfriend, friends, or others)?	☐	☐	☐	☐	☐
8b - feel you were a burden to other people?	☐	☐	☐	☐	☐
8c - have conflicts with other people?	☐	☐	☐	☐	☐

9. *The following questions are about your daily activities*

During the past 4 weeks, <u>has your thyroid disease caused</u> you to	Not at all	A little	Some	Quite a bit	Very much
9a - have difficulty managing your daily life?	☐	☐	☐	☐	☐
9c - not be able to participate in life around you?	☐	☐	☐	☐	☐
9e - feel as if everything takes longer to do?	☐	☐	☐	☐	☐

11. ***Thyroid diseases (or their treatment) may affect your <u>appearance</u>. (For example, by causing swelling of the neck, swollen face, hands, or feet, or changes in weight or to the eyes.)***

During the past 4 weeks,	Not at all	A little	Some	Quite a bit	Very much
11a - has your thyroid disease <u>affected your appearance</u> (for example, swelling of the neck, eye changes, weight changes)?	☐	☐	☐	☐	☐
11d - have you been bothered by other people looking at you?	☐	☐	☐	☐	☐
11e - has your thyroid disease influenced which clothes you wear?	☐	☐	☐	☐	☐

12. ***The final question is about to what extent your thyroid disease has affected you overall during the past 4 weeks***

During the past 4 weeks,	Not at all	A little	Some	Quite a bit	Very much
12 - has your thyroid disease had a negative effect on your quality of life?	☐	☐	☐	☐	☐

Please go back and check that you have answered all the questions.

Thank you very much for your help answering this questionnaire!