PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**SYNTHROID®**

levothyroxine sodium

Tablets, 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, Oral

USP

Thyroid Hormone
ATC Code: H03AA01

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RECENT MAJOR LABEL CHANGES

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4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	08/2021
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SYNTHROID® (levothyroxine sodium) is indicated for:

Hypothyroidism

SYNTHROID® is indicated as a replacement or supplemental therapy in patients of any age with primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism of any etiology, in any state (including pregnancy) except transient hypothyroidism during the recovery phase of subacute thyroiditis;

Pituitary Thyrotropin (Thyroid-stimulating hormone, TSH) Suppression

SYNTHROID® is indicated as an adjunct to surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

1.1 Pediatrics

Pediatrics (<18 years of age including neonates): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SYNTHROID® in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Pediatric Dosage).

1.2 Geriatrics

Geriatrics (≥65 years of age): SYNTHROID® is approved for use in the geriatric population. However, experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and dosing precautions apply (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

SYNTHROID® is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with untreated subclinical thyrotoxicosis (suppressed serum TSH with normal L-triiodothyronine/liothyronine [T_3] and L-thyroxine/levothyroxine [T_4] levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction, acute myocarditis, or acute pancarditis.

- Patients with uncorrected/untreated adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see 7 WARNINGS AND PRECAUTIONS, Immune Polyglandular Syndrome).
- Pregnant women being treated with drugs for hyperthyroidism, such as methimazole and propylthiouracil. Combination therapy of hyperthyroidism with levothryroxine and anti-thyroid agents is not indicated in pregnancy. (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Thyroid hormones, including SYNTHROID®, 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The dosage and frequency of administration of SYNTHROID® is determined by the indication, and must in every case be individualized according to patient response and laboratory findings.

Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and re-titration of the dosage, as necessary, accompanies the product switch.

Hypothyroidism:

The goal of therapy for primary hypothyroidism is to achieve and maintain a clinical and biochemical euthyroid state with consequent resolution of hypothyroid signs and symptoms. The starting dose of SYNTHROID®, the frequency of dose titration, and the optimal full replacement dose must be individualized for every patient, and will be influenced by such factors as age, weight, cardiovascular status, presence of other illness, and the severity and duration of hypothyroid symptoms.

In patients with hypothyroidism resulting from pituitary or hypothalamic disease, the possibility of secondary adrenal insufficiency should be considered, and if present, treated with glucocorticoids prior to initiation of SYNTHROID®. The adequacy of levothyroxine sodium therapy should be assessed in these patients by measuring free T4 (FT_4), which should be maintained in the upper half of the normal range, in addition to clinical assessment.

Measurement of TSH is not a reliable indicator of response to therapy for this condition.

TSH Suppression in Thyroid Cancer:

The rationale for TSH suppression therapy is that a reduction in TSH secretion may decrease the growth and function of abnormal thyroid tissue. Exogenous thyroid hormone may inhibit recurrence of tumour growth and may produce regression of metastases from well-differentiated (follicular and papillary) carcinoma of the thyroid. It is used as ancillary therapy of these conditions following surgery or radioactive iodine therapy. Medullary and anaplastic carcinoma of the thyroid is unresponsive to TSH suppression therapy.

No controlled studies have compared the various degrees of TSH suppression in the treatment of either benign or malignant thyroid nodular disease. Further, the effectiveness of TSH suppression for benign nodular disease is controversial.

The dose of SYNTHROID® used for TSH suppression should therefore be individualized by the nature of the disease, the patient being treated, and the desired clinical response, weighing the potential benefits of therapy against the risks of iatrogenic thyrotoxicosis. In general, SYNTHROID® should be given in the smallest dose that will achieve the desired clinical response.

Pediatric

Congenital or acquired hypothyroidism:

The SYNTHROID® pediatric dosage varies with age and body weight. SYNTHROID® should be given at a dose that maintains T_4 or FT_4 in the upper half of the normal range and serum TSH in the normal range (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics). Normalization of TSH may lag significantly behind T_4 in some infants. In general, despite the smaller body size of children, the dosage (on a weight basis) required to sustain full development and general thriving is higher than in adults (see Table 1 and Table 2).

4.2 Recommended Dose and Dosage Adjustment

Recommended dosage of SYNTHROID® are summarized in Table 1, with additional details provided below.

Table 1 - Dosing and Administration

Medical Condition(s)	Patient Population	Starting Dose	Dosing Increment	Interval For Monitoring/ Dosing Increment	Therapeutic Goal
Congenital Hypothyroidism	Neonate	10-15 mcg/kg/day	12.5 mcg/day†	4-6 weeks*	FT_4 level in upper half of normal range

Medical Condition(s)	Patient Population	Starting Dose	Dosing Increment	Interval For Monitoring/ Dosing Increment	Therapeutic Goal
Congenital/ Acquired Hypothyroidism	Infants/ Children	See Table 2	25 mcg/day	1-2 months (until 1 year), 2-3 months (until 3 years), 3-12 months thereafter*	FT_4 level in upper half of normal range, normal TSH
Congenital Hypothyroidism with risk of heart failure	Neonate	25 mcg/day	12.5 mcg/day†	4-6 weeks*	T_4 level in upper half of normal range, normal TSH
Severe Congenital Hypothyroidism (T_4 < 5 mcg/dL)	Neonate	50 mcg/day	25 mcg/day	2-4 weeks*	FT_4 level in upper half of normal range, normal TSH
Hypothyroidism with Completed Growth and Puberty	Children	1.6-1.7 mcg/kg/day	25-50 mcg/day	6-8 weeks	Normal TSH (age-specific reference range)
Hypothyroidism	Adults <50 years	1.7 mcg/kg/day	25-50 mcg/day	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 years	25-50 mcg/day	12.5†-25 mcg/day	6-8 weeks	
Hypothyroidism with Cardiac Disease	Adults <50 years	25-50 mcg/day	12.5†-25 mcg/day	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 years	12.5†-25 mcg/day	12.5†-25 mcg/day	4-6 weeks	
Severe Hypothyroidism	Adults < 50 years	12.5†-25 mcg/day	25 mcg/day	2-4 weeks	Normal TSH (between 0.5 and 2.0 mU/L)

Medical Condition(s)	Patient Population	Starting Dose	Dosing Increment	Interval For Monitoring/ Dosing Increment	Therapeutic Goal
	Infants/ Children	25 mcg/day	25 mcg/day	2-4 weeks	Normal TSH (age-specific reference range)
Hypothyroidism (short period) or Recently Treated with Hyperthyroidism	Adults > 50 years	< 1.7 mcg/kg/day	25-50 mcg/day	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
Hypothyroidism with Pregnancy	Pregnant Women	1.7 mcg/kg/day (Increased dose may be required)	25-50 mcg/day	Every 4 weeks during first half of pregnancy; at least once between week 26 and 32; approximately 6 weeks postpartum	Normal TSH (trimester-specific) and FT4 in the upper third of normal range 1st trimester: < 2.5 mU/L 2nd trimester: < 3.0 mU/L 3rd trimester: < 3.5 mU/L
Secondary Hypothyroidism	Not Specified	**	**	**	FT_4 level in upper third of normal range
Tertiary Hypothyroidism	Not Specified	**	**	**	FT_4 level in upper third of normal range
Subclinical Hypothyroidism	Not Specified	25-50 mcg/day	Adjust as necessary	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)

Medical Condition(s)	Patient Population	Starting Dose	Dosing Increment	Interval For Monitoring/ Dosing Increment	Therapeutic Goal
Well-differentiated (papillary or follicular) Thyroid Cancers	Not Specified	> 2 mcg/kg/day	25-50 mcg/day	6-8 weeks	TSH < 0.1 mU/L TSH <0.01 mU/L for patients with high risk tumors

† SYNTHROID is not available as a 12.5 mcg dosage form. A different product should be considered.

*For Congenital Hypothyroidism, the current guidelines recommend a 2 week monitoring interval at the beginning of therapy until normalization of TSH levels

**Depending on age, duration of hypothyroidism and cardiovascular risk factor

FT4: free T4

TSH: Thyroid-stimulating hormone

Adult Dosage

Hypothyroidism:

The usual full replacement dose of SYNTHROID® for younger, healthy adults is approximately 1.7 mcg/kg/day administered once daily. Therapy is usually initiated at the anticipated full replacement dose.

In older patients, the full replacement dose may be altered by decreases in T4 metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day.

For most patients older than 50 years and for patients under 50 years of age with a history of/underlying cardiac disease, an initial starting dose of 25 to 50 mcg/day of SYNTHROID® is recommended, with gradual increments in dose at six to eight week intervals, as needed. The recommended starting dose of SYNTHROID® in patients over 50 with cardiac disease is 12.5 to 25 mcg/day, with gradual dose increments at four to six week intervals. If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of levothyroxine sodium reduced. Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

Women who are maintained on SYNTHROID® during pregnancy may require increased doses (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Treatment of subclinical hypothyroidism may require lower than usual replacement doses e.g., 1.0 mcg/kg/day. Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH, and thyroid antibodies.

Few patients require doses greater than 200 mcg/day. An inadequate response to daily doses of

300 to 400 mcg/day is rare, and may suggest malabsorption, poor patient compliance, and/or drug interactions.

Clinical and laboratory evaluations should be performed at 6 to 8 week intervals (2 to 3 weeks in severely hypothyroid patients), and the dosage adjusted by 12.5 to 25 mcg increments until the serum TSH concentration is normalized and signs and symptoms resolve. Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status.

TSH Suppression in Thyroid Cancer:

For well-differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L and requires SYNTHROID® doses of greater than 2 mcg/kg/day.

SYNTHROID® should be administered with caution to patients in whom there is a suspicion of thyroid gland autonomy, in view of the fact that the effects of exogenous hormone administration will be additive to endogenous thyroid hormone production.

Pediatric Dosage

Congenital or acquired hypothyroidism:

The initial SYNTHROID® dose varies with age and body weight, and should be adjusted to maintain serum total T_4 or FT_4 levels in the upper half of the normal range. The recommended dose per body weight decreases with age. In general, unless there are overriding clinical concerns, therapy in children is usually initiated at the full replacement dose (see Table 2). Infants and neonates with very low (< 5 mcg/dL) or undetectable serum T_4 levels should be started at higher end of the dosage range (e.g., 50 mcg daily). A lower dose (e.g., 25 mcg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached. Children with underlying heart disease should be started at lower dosages, with careful upward titration. In children with severe, longstanding hypothyroidism or pre-existing cardiac insufficiency, SYNTHROID® should be initiated gradually, with an initial 25 mcg dose for two weeks, then increasing by 25 mcg every 2 to 4 weeks until the desired dose, based on serum T_4 and TSH levels, is achieved. (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

Table 2 - Dosage Guidelines for Pediatric Hypothyroidism

Age	Daily dose (mcg) per kg of 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

Age	Daily dose (mcg) per kg of body weight *
> 12 years but growth and puberty incomplete	2 – 3 mcg/kg/day
Growth and puberty complete	1.6– 1.7 mcg/kg/day
*To be adjusted on the basis of clinical response and laboratory tests (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).	

Serum T_4 and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T_4 or FT_4 and TSH:

- 2 and 4 weeks after therapy initiation, until complete normalization of TSH,
- every 1 to 2 months during the first year of life,
- every 2 to 3 months between 1 and 3 years of age,
- every 3 to 12 months thereafter until growth is completed

Evaluation at more frequent intervals is indicated when compliance is questioned or abnormal laboratory values are obtained. Patient evaluation is also advisable approximately 2 to 4 weeks after any change in SYNTHROID® dose.

4.4 Administration

Adults

Administer SYNTHROID® as a single daily dose, preferably on an empty stomach, one-half to one-hour before breakfast. As food and drink can significantly change the absorption of levothyroxine sodium, patients should be advised to take levothyroxine sodium at the same time every day and be consistent in how they take it with regards to meals.

Administer SYNTHROID® at least 4 hours before or after drugs that are known to interfere with its absorption (see 9 DRUG INTERACTIONS).

Evaluate the need for dose adjustments when regularly administering within one hour of certain foods that may affect SYNTHROID® absorption (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).

Pediatrics

SYNTHROID® tablets may be given to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount of water (5 to 10 mL), breast milk or non-soybean based formula. The suspension can be given by spoon or dropper. **DO NOT STORE THE SUSPENSION FOR ANY PERIOD OF TIME**. The crushed tablet may also be sprinkled over a small amount of food, such as apple sauce. Foods or formula containing large amounts of soybean, fibre, or iron should not be used for administering SYNTHROID®.

4.5 Missed Dose

If a scheduled dose is missed, the dose should be taken as soon as the patient remembers it.

However, if it is almost time for the next dose, the missed dose can be skipped and the regular dosing schedule continued. Two doses should not be taken together. If more than two doses are missed, the patient should contact their healthcare professional.

5 OVERDOSAGE

Signs and Symptoms

Excessive doses of SYNTHROID® result in a hypermetabolic state indistinguishable from thyrotoxicosis of endogenous origin. Signs and symptoms of thyrotoxicosis include exophthalmic goiter, weight loss, increased appetite, palpitations, nervousness, diarrhea, abdominal cramps, sweating, tachycardia, increased pulse and blood pressure, cardiac arrhythmias, angina pectoris, tremors, insomnia, heat intolerance, fever, and menstrual irregularities. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a child ingesting 18 mg of levothyroxine. Overdose of SYNTHROID® may result in hyperthyroidism and could lead to symptoms of acute psychosis, especially in patients at risk of psychotic disorders. Symptoms are not always evident or may not appear until several days after ingestion of SYNTHROID®.

Treatment of Overdosage

SYNTHROID® should be reduced in dose or temporarily discontinued if signs and symptoms of overdosage appear.

In the treatment of acute massive SYNTHROID® overdosage, symptomatic and supportive therapy should be instituted immediately. Treatment is aimed at reducing gastrointestinal absorption and counteracting central and peripheral effects, mainly those of increased sympathetic activity. The stomach should be emptied immediately by emesis or gastric lavage if not otherwise contraindicated (e.g., by coma, convulsions or loss of gag reflex). Cholestyramine and activated charcoal have also been used to decrease levothyroxine sodium absorption. Beta-receptor antagonists, particularly propranolol, are useful in counteracting many of the effects of increased central and peripheral sympathetic activity, especially when no contraindications exist for its use. Provide respiratory support as needed; control congestive heart failure and arrhythmia, control fever, hypoglycemia, and fluid loss as necessary. Large doses of antithyroid drugs (e.g., methimazole, carbimazole, or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Cardiac glycosides may be administered if congestive heart failure develops. Glucocorticoids may be administered to inhibit the conversion of T_4 to T_3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Since T4 is extensively protein bound, very little drug will be removed by dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet, 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 of levothyroxine sodium.	Acacia, colour additives*†, confectioner's sugar, lactose, magnesium stearate, povidone, and talc.
* colour additives by tablet strength are shown in Table 4. †The 50 mcg tablet is formulated without colour additives for patients who are sensitive to dyes.		

SYNTHROID®: round, colour coded, scored tablet debossed with "SYNTHROID" on one side and potency on the other side.

Gluten-free. Each tablet contains less than 70 mg of lactose.

The strengths available, including colour additives by tablet strength, and packaging sizes are as follows (see Table 4):

Table 4 – SYNTHROID® Tablet Characteristics

Strength (mcg)	Tablet Colour	Colour Additive(s)	Pack Size
25	Orange	FD&C Yellow No. 6	Available in bottles of 90 and 1000 tablets
50	White	None	Available in bottles of 90 and 1000 tablets
75	Violet	FD&C Red No. 40 FD&C Blue No. 2	Available in bottles of 90 and 1000 tablets
88	Olive	FD&C Blue No. 1 FD&C Yellow No. 6 D&C Yellow No. 10	Available in bottles of 90 and 1000 tablets
100	Yellow	D&C Yellow No. 10 FD&C Yellow No. 6	Available in bottles of 90 and 1000 tablets

Strength (mcg)	Tablet Colour	Colour Additive(s)	Pack Size
112	Rose	D&C Red No. 27 & 30	Available in bottles of 90 and 1000 tablets
125	Brown	FD&C Yellow No. 6 FD&C Red No. 40 FD&C Blue No. 1	Available in bottles of 90 and 1000 tablets
137	Turquoise	FD&C Blue No. 1	Available in bottles of 90 and 1000 tablets
150	Blue	FD&C Blue No. 2	Available in bottles of 90 and 1000 tablets
175	Lilac	FD&C Blue No. 1 D&C Red. No. 27 & 30	Available in bottles of 90 and 1000 tablets
200	Pink	FD&C Red No. 40	Available in bottles of 90 and 1000 tablets
300	Green	D&C Yellow No. 10 FD&C Yellow No. 6 FD&C Blue No. 1	Available in bottles of 90 tablets

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

SYNTHROID® has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under- treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Many drugs interact with SYNTHROID® necessitating adjustments in dosing or monitoring of clinical or laboratory parameters to maintain therapeutic response (see 9 DRUG INTERACTIONS).

The bioavailability of levothyroxine may differ to some extent among marketed brands. Once the patient is stabilized on a particular brand of levothyroxine sodium, caution should be exercised when a change in drug product brand is implemented. If a switch to another levothyroxine-containing product is required, there is a need to undertake close clinical and biological monitoring during the transition period due to a potential risk of imbalance. In some patients, a dose adjustment could be necessary.

It has been shown that differences in formulations of levothyroxine, despite an identical content of active ingredient, may be associated with differences in fractional gastrointestinal absorption. These differences may not be observed through measurement of total T3 and T4 serum levels. It is therefore recommended that patients who are switched from one levothyroxine formulation to another be re-titrated to the desired thyroid function. Accuracy in re-titration can best be achieved by using sensitive thyrotropin assays.

Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.

Carcinogenesis and Mutagenesis

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T4 is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving SYNTHROID® for established indications should not discontinue therapy.

Cardiovascular

SYNTHROID® should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. In these patients, levothyroxine sodium therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac diseases (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics and 4 DOSAGE AND ADMINISTRATION). If cardiac symptoms develop or worsen, the levothyroxine sodium dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Over-treatment with SYNTHROID® may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias.

Patients with coronary artery disease who are receiving levothyroxine sodium therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Thyroid hormones, either alone or together 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. Patients treated concomitantly with SYNTHROID® and orlistat should be monitored for changes in thyroid function (see 9 DRUG INTERACTIONS). Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine.

Effects on Bone Mineral Density

In women, long-term levothyroxine therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in postmenopausal women on greater replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. Therefore, it is recommended that patients receiving SYNTHROID® be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease

In patients with non-toxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see 2 CONTRAINDICATIONS).

Hypothalamic/pituitary Hormone Deficiencies

In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated by adequate adrenal replacement therapy before starting the therapy with levothyroxine, to prevent acute adrenal insufficiency (see 2 CONTRAINDICATIONS).

Myxedema Coma

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a medical emergency. It is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products, such as SYNTHROID®, are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

Gastrointestinal

Thyroxine absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective thyroxine treatment with regular thyroxine dose.

Hematologic

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both SYNTHROID® and oral anticoagulants, and the dosage of

anticoagulant adjusted accordingly.

Immune

Autoimmune Polyglandular Syndrome

Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Use of SYNTHROID® in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms.

Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids (see 4 DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Treatment of patients with SYNTHROID® requires periodic assessment of thyroid status by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. Measurement of FT_4 and TSH levels, using a sensitive TSH assay, is recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.
TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and FT_4. Measurement of total serum T_4 and T_3, resin T_3 uptake, and free T_3 concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. Positive microsomal antibody presence in an euthyroid patient is a major risk factor for the development of hypothyroidism. An elevated serum TSH in the presence of a normal T_4 may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum T_4 levels.

Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring FT_4, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

Adequacy of levothyroxine sodium therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total T_4 or FT_4; these should be maintained in the upper half of the normal range. In congenital hypothyroidism, serum TSH normalization may lag behind serum T_4 normalization by 2 to 3 months or longer. Rarely, in some patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T_4 or FT_4 levels (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

Serum biotin may interfere with thyroid function immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see 9.7 Drug-Laboratory Test Interaction). The risk of interference increases with higher doses of biotin. When possible, it is recommended that patients abstain from taking biotin supplements for at least 2 days prior to specimen collection.
When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed.

Psychiatric
When initiating SYNTHROID® therapy in patients at risk of psychotic disorders, it is recommended to start at a low SYNTHROID® dose at the beginning of the therapy, and to slowly increase the dosage thereafter. Monitoring of the patient is advised. If signs of psychotic disorders occur, adjustment of the dose of levothyroxine should be considered.

Reproductive Health: Female and Male Potential

Fertility

The use of SYNTHROID® is unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

7.1 Special Populations

7.1.1 Pregnant Women

Studies in pregnant women have not shown that SYNTHROID® increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote.

Thyroid hormones cross the placental barrier to some extent. T_4 levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T_4 may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, preeclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. On the basis of current knowledge, SYNTHROID® should not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T_4 concentrations may decrease and TSH concentrations may increase to values outside normal ranges. As such, trimester-specific TSH reference values are recommended (see 4 DOSAGE & ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Table 1). Postpartum values are similar to preconception values. Elevations in TSH may occur as early as the fourth week of gestation.

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is contraindicated in pregnancy. Such combination would require higher doses of anti-thyroid

agents such as methimazole and propylthiouracil, which are known to pass the placenta and to induce hypothyroidism in the infant.

Pregnant women who are maintained on SYNTHROID® should have their TSH measured approximately every 4 weeks during the first half of pregnancy, and at least once between week 26 and 32, as levothyroxine dose adjustments are often required.

An elevated TSH should be corrected by an increase in levothyroxine sodium dose. After pregnancy, the dose can be decreased to the optimal preconception dose. A serum TSH level should be obtained approximately six weeks postpartum.

7.1.2 Breast-feeding

Minimal amounts of thyroid hormones are excreted in human milk. While caution should be exercised when SYNTHROID® is administered to a breast-feeding woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

7.1.3 Pediatrics

Pediatrics (All ages including neonates): Haemodynamic parameters should be monitored when levothyroxine therapy is initiated in very low birth weight preterm neonates as circulatory collapse may occur due to the immature adrenal function.

Congenital hypothyroidism

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

Rapid restoration of normal serum T_4 concentrations is essential to prevent deleterious neonatal thyroid hormone deficiency effects on intelligence, overall growth, and development. Treatment should be initiated immediately upon diagnosis and generally maintained for life. The therapeutic goal is to maintain serum total T_4 or FT_4 in the upper half of the normal range and serum TSH in the normal range.

Prolonged use of large doses in infants may be associated with temperament problems, which appear to be transient.

Thyroid function tests (serum total T_4 or FT_4, and TSH) should be monitored closely and used to determine the adequacy of levothyroxine sodium therapy. Serum T_4 normalization is usually followed by a rapid decline in TSH. Nevertheless, TSH normalization may lag behind T_4 normalization by 2 to 3 months or longer. The relative serum TSH elevation is more marked in the early months, but can persist to some degree throughout life. In rare patients TSH remains relatively elevated despite clinical euthyroidism and age-specific normal total T_4 or FT_4 levels. Increasing the levothyroxine sodium dosage to suppress TSH into the normal range may produce overtreatment, with an elevated serum T_4 and clinical features of hyperthyroidism including: irritability, increased appetite with diarrhea, and sleeplessness. Another risk of prolonged overtreatment in infants is premature cranial synostosis.

Acquired hypothyroidism

Treated children may resume growth at a greater than normal rate (period of transient catch-up growth). In some cases, the catch-up may be adequate to normalize growth. However, severe and prolonged hypothyroidism may reduce adult height. Excessive thyroxine replacement may initiate accelerated bone maturation, producing disproportionate skeletal age advancement and shortened adult stature.

If transient hypothyroidism is suspected hypothyroidism permanence may be assessed after the child reaches 3 years of age. Levothyroxine therapy may be interrupted for 30 days and serum T_4 and TSH measured. Low T_4 and elevated TSH confirm permanent hypothyroidism; therapy should be re-instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic thyroid function test re-evaluation may be warranted.

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

7.1.4 Geriatrics

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 4.1 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment). Atrial arrhythmias can occur in elderly patients. Atrial fibrillation is the most common of the arrhythmias observed with levothyroxine overtreatment in the elderly.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Inadequate doses of SYNTHROID® may produce or fail to resolve symptoms of hypothyroidism.

Adverse reactions associated with SYNTHROID® are primarily those of thyrotoxicosis due to therapeutic overdosage (see 7 WARNINGS AND PRECAUTIONS and 5 OVERDOSAGE). Adverse reactions observed with levothyroxine use include the following:

Cardiac disorders:	palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, cardiac failure, angina, myocardial infarction and cardiac arrest
Gastrointestinal System:	diarrhea, vomiting and abdominal cramps

General:	fatigue, heat intolerance, fever and excessive sweating
Immune system disorders:	Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.
Investigations:	decreased bone mineral density, elevations in liver function tests
Metabolism and nutrition disorders:	increased appetite, weight loss
Musculoskeletal and connective tissue:	tremors, muscle weakness, slipped capital femoral epiphysis in children, excessive dose may result in craniosynostosis and premature closure of the epiphyses in children (with resultant compromised adult height)
Nervous System:	headache, pseudotumor cerebri, seizures
Psychiatric disorders:	hyperactivity, nervousness, anxiety, irritability, emotional lability and insomnia
Reproductive System:	menstrual irregularities, impaired fertility
Respiratory System:	dyspnea
Skin and subcutaneous tissue disorders:	alopecia (generally transient)
Vascular disorders:	flushing

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The magnitude and relative clinical importance of the effects noted below are likely to be patient-specific and may vary by such factors as age, gender, race, intercurrent illnesses, dose of either agent, additional concomitant medications, and timing of drug administration. Any agent that alters thyroid hormone synthesis, secretion, distribution, effect on target tissues, metabolism, or elimination may alter the optimal therapeutic dose of SYNTHROID®.

9.3 Drug-Behavioural Interactions

This information is not available for this drug product.

9.4 Drug-Drug Interactions

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to SYNTHROID®. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and actions of other drugs. A listing of drug-thyroidal axis interactions is contained in Table 5.

The list of drug-thyroidal axis interactions in Table 5 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery or previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 - Established or Potential Drug-Drug Interactions (Drug-Thyroidal Axis Interactions)

Proper/Common name	Effect
Drugs that may reduce TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine/Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: • dopamine (greater than or equal to 1 mcg/kg/min); • glucocorticoids (hydrocortisone greater than or equal to 100 mg/day or equivalent); • octreotide (greater than 100 mcg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Thioamides	Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. The fetus, neonate, elderly and euthyroid patients with

Proper/Common name	Effect
- Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides Tolbutamide	underlying thyroid disease (e.g., Hashimotos's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. Lithium blocks the TSH-mediated release of T_4 and T_3. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual SYNTHROID® dose may be required.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T_4 absorption, which may result in hypothyroidism	
Anion/ Cation Exchange Resins -Sevelamer -Sodium Polystyrene Sulfonate Antacids - Aluminum & Magnesium Hydroxides -Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Ferrous Sulfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least four (4) hours apart from these agents. Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function. Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine.

Proper/Common name	Effect
Lanthanum carbonate Orlistat Sucralfate	
Drugs that may alter T4 and T3 serum transport - but FT4 concentration remains normal; and therefore, the patient remains euthyroid	
Clofibrate Estrogen-containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Increase serum thyroxin-binding globulin (TBG) Concentration
Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	Decrease serum TBG Concentration
Drugs that may cause protein-binding site replacement	
Furosemide (greater than 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone - Salicylates (greater than 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in Serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum saliyclate concentrations, although total T_4 levels may decrease by as much as 30%.
Drugs that may alter T_4 and T_3 metabolism	
Drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoins Phenobarbital	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and

Proper/Common name	Effect
Rifampin Ritonavir	carbamazepine reduce serum protein binding of levothyroxine, and total and FT_4 may be reduced by 20 to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Post marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine, resulting in TSH increased levels and hypothyroidism. TSH should be monitored in patients treated concomitantly with ritonavir and levothyroxine for at least the first month after starting and/or ending ritonavir treatment, and levothyroxine dose should be adjusted as needed.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists (e.g., propanolol greater than 160 mg/day) Glucocorticoids (e.g., dexamethasone greater than or equal to 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propanolol (greater than 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the levothyroxine sodium dose is increased. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.

Proper/Common name	Effect
Antidepressants - Tricyclics (e.g., amitriptyline) - Tetracyclics (e.g., maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., sertraline)	Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state, necessitating an increase in the dose of digitalis glycosides. Therapeutic effect of digitalis glycosides may be reduced by SYNTHROID®.
Cytokines - Interferon-alpha - Interleukin-2	Therapy with interferon-alpha has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-beta and -gamma have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.

Proper/Common name	Effect
Methylxanthine Bronchodilators (e.g., theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic agents	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Tyrosine Kinase Inhibitors	Plasma concentration of levothyroxine (thyroxine) possibly reduced by Tyrosine Kinase Inhibitors (e.g. imatinib, sunitinib).
Proton Pump Inhibitors	Plasma concentration of levothyroxine (thyroxine) possibly reduced by Proton Pump Inhibitors. Monitoring of TSH plasma level is recommended.
Chloral Hydrate Ciprofloxacin Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.
FT4: free T4 TSH: Thyroid-stimulating hormone	

9.5 Drug-Food Interactions

Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, calcium and calcium-fortified orange juice, and dietary fibre may bind and decrease the absorption of

levothyroxine sodium from the gastrointestinal tract.

9.6 Drug-Herb Interactions

St. John's Wort may increase hepatic metabolism of levothyroxine, which may result in hypothyroidism.

9.7 Drug-Laboratory Test Interactions

A number of drugs or moieties are known to alter serum levels of TSH, T_4 and T_3 and may thereby influence the interpretation of laboratory tests of thyroid function (see 9 DRUG INTERACTIONS).
Changes in thyroxine-binding globulin (TBG) concentration should be taken into consideration when interpreting T4 and T3 values. Drugs such as estrogens and estrogen-containing oral contraceptives increase serum TBG concentrations. TBG concentrations may also be increased during pregnancy, in infectious hepatitis and acute intermittent porphyria. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypothyroxine-binding-globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the protein binding of T_4. In such cases, the unbound (free) hormone should be measured and/or determination of the free T_4 index (FT_4I) should be done.

Serum biotin may interfere with thyroid function immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).
When available, alternative tests not susceptible to biotin interference should be used for patients taking biotin-containing products.
Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose suggests either poor patient compliance, impaired absorption, drug interactions, or decreased potency of the preparation due to improper storage.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The synthesis and secretion of the major thyroid hormones, T_3 and T_4, from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulating hormone, TSH), which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T_3 and T_4 are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid

individuals results in suppression of endogenous thyroid hormone secretion.

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_3 and T_4 are transported into cells by passive and active mechanisms. T_3 in cell cytoplasm and T_3 generated from T_4 within the cell diffuse into the nucleus and bind to thyroid receptor proteins, which appear to be primarily attached to DNA. Receptor binding leads to activation or repression of DNA transcription, thereby altering the amounts of mRNA and resultant proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

Thyroid hormones enhance oxygen consumption of most body tissues and increase the basal metabolic rate and metabolism of carbohydrates, lipids, and proteins. Thus, they exert a profound influence on every organ system and are of particular importance in the development of the central nervous system. Thyroid hormones also appear to have direct effects on tissues, such as increased myocardial contractility and decreased systemic vascular resistance.

The physiologic effects of thyroid hormones are produced primarily by T_3, a large portion of which (approximately 80%) is derived from the deiodination of T_4 in peripheral tissues. About 70 to 90 percent of peripheral T_3 is produced by monodeiodination of T_4 at the 5 position (outer ring). Peripheral monodeiodination of T_4 at the 5 position (inner ring) results in the formation of reverse triiodothyronine (rT_3), which is calorigenically inactive.

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

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of Hashimoto's thyroiditis and as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see 1 INDICATIONS, 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

10.3 Pharmacokinetics

Absorption

Few clinical studies have evaluated the kinetics of orally administered thyroid hormone. In animals, the most active sites of absorption appear to be the proximal and mid-jejunum. T_4 is not absorbed from the stomach and little, if any, drug is absorbed from the duodenum. There seems to be no absorption of T_4 from the distal colon in animals. A number of human studies have confirmed the importance of an intact jejunum and ileum for T_4 absorption and have shown some absorption from the duodenum. Studies involving radioiodinated T_4 fecal tracer excretion methods, equilibration, and AUC methods have shown that absorption varies from 48 to 80 percent of the administered dose. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as celiac disease (i.e., sprue, gluten-sensitive enteropathy). Absorption may also decrease with age. The degree of T_4 absorption is dependent on the product formulation as well as on the character of the intestinal contents, the intestinal flora, including plasma protein and soluble dietary factors, which bind thyroid

hormone, making it unavailable for diffusion. Decreased absorption may result from administration of infant soybean formula, ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate, or bile acid sequestrants. T_4 absorption following intramuscular administration is variable. The relative bioavailability of SYNTHROID® tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%.

Distribution:

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated. More than 99% of circulating hormones is bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA). T_4 is more extensively and firmly bound to serum proteins than is T_3. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for T_4 partly explains the higher serum levels, slower metabolic clearance, and longer serum elimination half-life of this hormone.

Certain drugs and physiologic conditions can alter the binding of thyroid hormones to serum proteins and/or the concentrations of the serum proteins available for thyroid hormone binding. These effects must be considered when interpreting the results of thyroid function tests (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 9 DRUG INTERACTIONS).

Metabolism:

The liver is the major site of degradation for both hormones. T_3 and T_4 are conjugated with glucuronic and sulfuric acids and excreted in the bile. There is an enterohepatic circulation of thyroid hormones, as they are liberated by hydrolysis in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated as free compounds in the feces. In man, approximately 20 to 40 percent of T_4 is eliminated in the stool. About 70 percent of the T_4 secreted daily is deiodinated to yield equal amounts of T_3 and rT_3. Subsequent deiodination of T_3 and rT3 yields multiple forms of diiodothyronine. A number of other minor T_4 metabolites have also been identified. Although some of these metabolites have biologic activity, their overall contribution to the therapeutic effect of T_4 is minimal.

Elimination:

Thyroid hormones are primarily eliminated by the kidneys. T_4 is eliminated slowly from the body (see Table 6), with a half-life of 6 to 7 days. T_3 has a half-life of 1 to 2 days.

Table 6 - Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	t½ (days)	Protein Binding (%)[2]
Levothyroxine, T_4	10 to 20	1	6 to 7[1]	99.96

Hormone	Ratio in Thyroglobulin	Biologic Potency	t½ (days)	Protein Binding (%)[2]
Liothyronine, T_3	1	4	≤ 2	99.5
1 Three to four days in hyperthyroidism, nine to ten days in hypothyroidism 2 Includes TBG (thyroxine-binding globulin), TBPA (thyroxine-binding prealbumin), and TBA (thyroxine-binding albumin)				

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 to 25°C). Protect from light and moisture.

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

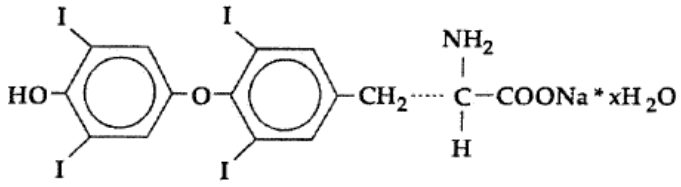
Drug Substance

Proper name: Levothyroxine sodium

Chemical name: L-3,3',5,5'-tetraiodothyronine sodium salt

Molecular formula and molecular mass: $C_{15}H_{10}I_4N\,NaO_4 \bullet H_2O$, 798.86 g/mol (anhydrous)

Structural formula:



Physicochemical properties: Levothyroxine sodium occurs as a light yellow to buff-coloured, odourless, tasteless, hygroscopic powder. Levothyroxine sodium is very slightly soluble in water and slightly soluble in alcohol.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials in specific indication

Author/ Manuscript Title	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Kabadi UM., 1994/ "Optimal L-thyroxine dose in primary hypothyroidism" .	Longitudinal	25-200 mcg/day Oral dosage form	186	NR (25-84 years)	152 M/34 F

Author/ Manuscript Title	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Kabadi UM., 1989/ "Optimal L-thyroxine dose in hypothyroidism".	Longitudinal	50-200 mcg/day Oral dosage form	156*	NR (25-84 years)	133 M/23 F
Kabadi UM, Jackson T., 1995/ "TSH predictor in hypothyroidism".	Longitudinal	25-225 mcg/day Oral dosage form	192	NR (25-84 years)	171 M/21 F
Hennessey J, et al., 1985/ "Equivalency of two L thyroxine preparations".	Crossover	50-200 mcg/day Oral dosage form	34	NR	NR
Fish LH, et al., 1987/ "Replacement dose in hypothyroidism".	Longitudinal	25-150 mcg/day Oral dosage form	19	NR	NR
Ain KG, et al., 1996/ "Effects of restrictive formulary".	Longitudinal	Restricted arm (n=87): 1.9 ± 0.1 mcg/kg/day Non-restricted arm (n=148): 2.0 ± 0.1 mcg/kg/day Oral dosage form	241	Restricted arm: (n=89): 39.3 ± 2.4 year (range NR) Non-restricted arm (n=152): 44.2 ± 1.3 year (range NR)	74 M/167 F

Author/ Manuscript Title	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Ain KG, et al., 1993/ "TFTs affected by time of blood sampling".	Longitudinal	150-200 mcg/day Oral dosage form	51	NR	NR
Liu X-Q, et al., 1998/ "Effects of L-thyroxine on serum lipoproteins".	Longitudinal	183 (mean) Oral dosage form	10	45.7 ±10.6 year (range NR)	2 M/8 F
* This is considered to be an earlier publication of the same patient population presented in Kabadi, 1994. The 156 patients described are not added into the total number of patients. NR: not reported					

The published studies presented in this section support the effectiveness of SYNTHROID® (levothyroxine sodium tablets, USP) in the treatment of hypothyroidism. They are considered to have at least some of the characteristics of adequate and well-controlled as defined under ICH Good Clinical Practice. The controlled clinical studies are primarily: 1) studies that investigated the biochemical response to SYNTHROID® of patients with hypothyroidism and the correlation of the optimal clinical dose with the pathology of hypothyroidism, 2) conventional studies of untreated hypothyroid patients or those switched from another brand of the same active drug, and 3) studies that analyze the dose-response characteristics in hypothyroid patients replaced with SYNTHROID® or patients receiving SYNTHROID® for suppression of TSH. In all cases, objective biochemical endpoints (e.g., TSH, T_4, etc.), which minimize the potential for influence of chance or bias on results, were used to assess the effectiveness of SYNTHROID® as replacement or suppressive therapy.

14.2 Study Results

The results of the studies demonstrate that with careful dose titration to an objective, biochemical endpoint, SYNTHROID® is effective both for initial and maintenance therapy of hypothyroid adults. On the whole, the average L-thyroxine replacement doses reported in these studies are in close agreement with each other and average replacement doses reported in the literature and recommended by thyroid experts. See 14.1 Trial Design and Study Demographics.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

This information is not available for this drug product.