

# NEW ZEALAND DATA SHEET

**SYNTHROID®**



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## 1. Product Name

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Synthroid, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg tablets.

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## 2. Qualitative and Quantitative Composition

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Each Synthroid tablet contains 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.

Synthroid tablets contain lactose.

For the full list of excipients, see section 6.1.

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## 3. Pharmaceutical Form

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Synthroid tablets are round, colour coded, contain a score line and are debossed with "SYNTHROID" and potency.

The colour code is as follows in table 1:

Table 1: Synthroid Tablet Visual Characteristics	
Strength (mcg)	Tablet Colour
25	Orange
50	White
75*	Violet
88*	Olive
100	Yellow
112*	Rose
125*	Brown
137*	Dark blue
150*	Blue
175*	Lilac
200*	Pink
300*	Green

\*not currently marketed.

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## 4. Clinical Particulars

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### 4.1 *Therapeutic indications*

Synthroid is indicated as replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism.

Synthroid is also indicated as a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter, and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

### 4.2 *Dose and method of administration*

#### **Dose**

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

#### ***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 levothyroxine sodium, USP, 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 levothyroxine sodium, USP. The adequacy of levothyroxine sodium therapy should be assessed in these patients by measuring FT<sub>4</sub>, 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.

The usual full replacement dose of levothyroxine sodium, USP for younger, healthy adults is approximately 1.7 mcg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T<sub>4</sub> metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day. Children generally require higher doses (see below). Women who are maintained on levothyroxine sodium, USP during pregnancy may require increased doses (see section 4.4).

Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. 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. In older patients or in younger patients with a history of cardiovascular disease, the starting dose should be 12.5 to 25 mcg once daily with adjustments of 12.5 to 25 mcg every 3 to 6 weeks until TSH is normalized and signs and symptoms resolve. 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.

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.

Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status. Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and retitration of the dosage, as necessary, accompanies the product switch.

### ***TSH suppression in thyroid cancer and thyroid nodules***

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. TSH suppression is also used in treating nontoxic solitary nodules and multinodular goiters.

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 levothyroxine sodium, USP 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, levothyroxine sodium, USP should be given in the smallest dose that will achieve the desired clinical response.

For well-differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L. Doses of levothyroxine sodium, USP greater than 2 mcg/kg/day are usually required. The efficacy of TSH suppression in reducing the size of benign thyroid nodules and in preventing nodule regrowth after surgery is controversial. Nevertheless, when treatment with levothyroxine sodium, USP is warranted, TSH is generally suppressed to a higher target range (e.g. 0.1 to 0.3 mU/L) than that employed for the treatment of thyroid cancer. Levothyroxine sodium, USP therapy may also be considered for patients with nontoxic multinodular goiter who have a TSH in the normal range, to moderately suppress TSH (e.g. 0.1 to 0.3 mU/L).

Levothyroxine sodium, USP 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.

### ***Myxedema coma***

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a medical emergency. It is characterized by hypothermia, hypotension, hypoventilation, hyponatremia, and bradycardia. In addition to restoration of normal thyroid hormone levels, therapy should be directed at the correction of electrolyte disturbances and possible infection. Because the mortality rate of patients with untreated myxedema coma is high, treatment must be started immediately, and should include appropriate supportive therapy and corticosteroids to prevent adrenal insufficiency. Possible precipitating factors should also be identified and treated.

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

## Special populations

### Paediatric

#### Congenital or acquired hypothyroidism

The levothyroxine sodium, USP paediatric dosage varies with age and body weight. Levothyroxine sodium, USP should be given at a dose that maintains T<sub>4</sub> or free T<sub>4</sub> in the upper half of the normal range and serum TSH in the normal range (see section 4.4). Normalization of TSH may lag significantly behind T<sub>4</sub> 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.

Therapy is usually initiated at the full replacement dose (see Table 2). Infants and neonates with very low (< 5 mcg/dL) or undetectable serum T<sub>4</sub> 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. In children with severe, longstanding hypothyroidism, levothyroxine sodium, USP 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<sub>4</sub> and TSH levels, is achieved.

Age	Daily dose (mcg) per kg of body weight *
0 - 3 months	10 - 15
3 - 6 months	8 - 10
6 - 12 months	6 - 8
1 - 5 years	5 - 6
6 - 12 years	4 - 5
> 12 years but growth and puberty incomplete	2 - 3
Growth and puberty complete	1.6

\* To be adjusted on the basis of clinical response and laboratory tests (see section 4.4).

Serum T<sub>4</sub> and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T<sub>4</sub> or FT<sub>4</sub> and TSH:

- 2 and 4 weeks after therapy initiation,
- 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 levothyroxine sodium, USP dose.

#### Missed dose

A missed dose of one tablet can be taken with the next dose. If more than 2 tablets are missed, the patient should consult with their doctor.

## Method of administration

### Paediatrics

Levothyroxine sodium, USP 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 levothyroxine sodium, USP.

Table 3 summarizes the dosage and administration of levothyroxine sodium, USP

Table 3					
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 wks	Free-T <sub>4</sub> level in upper half of normal range
Congenital/Acquired Hypothyroidism	Infants/Children	See Table 2	25 mcg/day	1-2 mos (until 1 y), 2-3 mos (until 3 y), 3-12 mos thereafter	Free-T <sub>4</sub> 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 wks	Free-T <sub>4</sub> level in upper half of normal range, normal TSH
Severe Congenital Hypothyroidism (T <sub>4</sub> < 5µg/dL)	Neonate	50 mcg/day	25 mcg/day	2-4 wks	Free-T <sub>4</sub> 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 wks	Normal TSH (age-specific reference range)
Hypothyroidism	Adults <50 yrs	1.7 mcg/kg/day	25 – 50 mcg/day	6-8 wks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 yrs	25 – 50 mcg/day	12.5 – 25 mcg/day	6-8 wks	Normal TSH (between 0.5 and 2.0 mU/L)
Hypothyroidism with Cardiac Disease	Adults <50 yrs	25 – 50 mcg/day	12.5 – 25 mcg/day	6-8 wks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 yrs	12.5 – 25 mcg/day	12.5 – 25 mcg/day	4-6 wks	Normal TSH (between 0.5 and 2.0 mU/L)

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DOSING AND ADMINISTRATION					
MEDICAL CONDITION(S)	PATIENT POPULATION	STARTING DOSE	DOSING INCREMENT	INTERVAL FOR MONITORING/ DOSING INCREMENT	THERAPEUTIC GOAL
Severe Hypothyroidism	Adults < 50 yrs	12.5 – 25 mcg/day	25 mcg/day	2-4 wks	Normal TSH (between 0.5 and 2.0 mU/L)
	Infants/Children	25 mcg/day	25 mcg/day	2-4 wks	Normal TSH (age-specific reference range)
Hypothyroidism (short period) or Recently Treated with Hyperthyroidism	Adults > 50 yrs	< 1.7 mcg/kg/day	25 – 50 mcg/day	6-8 wks	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	Each trimester and 6-8 wks postpartum	Normal TSH and FT4 in the upper third of normal range
Secondary Hypothyroidism	Not Specified	**	**	**	Free-T <sub>4</sub> level in upper third of normal range
Tertiary Hypothyroidism	Not Specified	**	**	**	Free-T <sub>4</sub> level in upper third of normal range
Subclinical Hypothyroidism	Not Specified	25 – 50 mcg/day	Adjust as necessary	6-8 wks	Normal TSH (between 0.5 and 2.0 mU)
Well-differentiated (Papillary or Follicular) Thyroid Cancers	Not Specified	> 2 mcg/kg/day	25 - 50 mcg/day	6-8 wks	TSH < 0.1 mU/L TSH <0.01 mU/L for patients with high risk tumors
Benign Nodules and Nontoxic Multinodular Goiter	Not Specified	1.7 - 2 mcg/kg/day (Suppression not <0.1 mU/L)	25 - 50 mcg/day	6-8 wks	TSH 0.1 – 0.3 mU/L for nodules and for multinodular goiter

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

### 4.3 Contraindications

Synthroid is contraindicated in:

- Patients with an apparent hypersensitivity to thyroid hormones or to any of the excipients listed in section 6.1. (Note: The 50 mcg tablet is formulated without colour additives for patients who are sensitive to dyes.) There is no well-documented evidence of true allergic or idiosyncratic reactions to thyroid hormone.
- Patients with untreated subclinical (suppressed serum TSH with normal T<sub>3</sub> and T<sub>4</sub> levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction.
- Patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis (see section 4.4).

## **4.4 Special warnings and precautions for use**

### **Serious**

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.

### **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 levothyroxine sodium, USP necessitating adjustments in dosing or monitoring of clinical or laboratory parameters to maintain therapeutic response (see section 4.5).

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.

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 T<sub>3</sub> and T<sub>4</sub> serum levels. It is therefore, recommended that patients who are switched from one levothyroxine formulation to another be retitrated to the desired thyroid function. Accuracy in retitration 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.

Lithium blocks the TSH-mediated release of T<sub>4</sub> and T<sub>3</sub>. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual levothyroxine sodium, USP dose may be required.

### **Cardiovascular**

Levothyroxine sodium, USP 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 section 4.2). 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 levothyroxine sodium, USP 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.

### **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.

### ***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 levothyroxine sodium, USP 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 section 4.3). If the serum TSH level is not suppressed, levothyroxine sodium, USP should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

## **Associated endocrine disorders**

### ***Hypothalamic/pituitary hormone deficiencies***

In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated for adrenal insufficiency.

### ***Autoimmune polyglandular syndrome***

Use of levothyroxine sodium, USP 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 section 4.2).

## **Hematologic**

T<sub>4</sub> enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both levothyroxine sodium, USP and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

## **Sexual function/reproduction**

The use of levothyroxine sodium, USP is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

## **Paediatric population**

### ***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<sub>4</sub> 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<sub>4</sub> or FT<sub>4</sub> in the upper half of the normal range and serum TSH in the normal range.

An initial starting dose of 10 to 15 mcg/kg/day (ages 0 to 3 months) will generally increase serum T<sub>4</sub> concentrations to the upper half of the normal range in less than 3 weeks. Clinical assessment of growth, development, and thyroid status should be monitored frequently. In most cases, the



levothyroxine sodium, USP dose per body weight will decrease as the patient grows through infancy and childhood (see section 4.2). Prolonged use of large doses in infants may be associated with temperament problems, which appear to be transient.

Thyroid function tests (serum total T<sub>4</sub> or FT<sub>4</sub>, and TSH) should be monitored closely and used to determine the adequacy of levothyroxine sodium therapy. Serum T<sub>4</sub> normalization is usually followed by a rapid decline in TSH. Nevertheless, TSH normalization may lag behind T<sub>4</sub> 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<sub>4</sub> or FT<sub>4</sub> levels. Increasing the levothyroxine sodium dosage to suppress TSH into the normal range may produce overtreatment, with an elevated serum T<sub>4</sub> 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 hyperthyroidism**

The initial levothyroxine sodium, USP dose varies with age and body weight, and should be adjusted to maintain serum total T<sub>4</sub> or free T<sub>4</sub> levels in the upper half of the normal range. In general, unless there are overriding clinical concerns, children should be started on a full replacement dose. Children with underlying heart disease should be started at lower dosages, with careful upward titration. Children with severe, longstanding hypothyroidism may also be started on a lower initial dose followed by an upward titration, attempting to avoid premature epiphyseal closure. The recommended dose per body weight decreases with age (see section 4.2).

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<sub>4</sub> and TSH measured. Low T<sub>4</sub> and elevated TSH confirm permanent hypothyroidism; therapy should be re-instituted. If T<sub>4</sub> 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 reevaluation 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 levothyroxine sodium, USP 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, levothyroxine sodium, USP treatment should be discontinued for another 30-day trial period followed by repeat serum T<sub>4</sub> and TSH testing.

### **Use in the elderly**

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see sections 4.2 and 4.4).

### **Patient monitoring**

Treatment of patients with levothyroxine sodium, USP 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. A measurement of free T<sub>4</sub> 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 free T<sub>4</sub>. Measurement of total serum T<sub>4</sub> and T<sub>3</sub>, resin T<sub>3</sub> uptake, and free T<sub>3</sub> 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<sub>4</sub> 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<sub>4</sub> levels. Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T<sub>4</sub>, which should be maintained in the upper half of the normal range. Adequacy of levothyroxine sodium therapy for congenital and acquired paediatric hypothyroidism should be assessed by measuring serum total T<sub>4</sub> or free T<sub>4</sub>; these should be maintained in the upper half of the normal range.

### **Interference with laboratory tests**

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

In congenital hypothyroidism, serum TSH normalization may lag behind serum T<sub>4</sub> normalization by 2 to 3 months or longer. In rare patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T<sub>4</sub> or free T<sub>4</sub> levels. (See section 4.4).

A number of drugs or moieties are known to alter serum levels of TSH, T<sub>4</sub> and T<sub>3</sub> and may thereby influence the interpretation of laboratory tests of thyroid function (see section 4.5).

1. 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 hypo-thyroxine-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<sub>4</sub>. In such cases, the unbound (free) hormone should be measured and /or determination of the free -T<sub>4</sub> index (FT4I) should be done.
2. 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.

### **4.5 Interaction with other medicines and other forms of interaction**

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 agents, 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.

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to levothyroxine sodium, USP. 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 4.

The list of drug-thyroidal axis interactions in Table 4 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.

## Anticoagulants

Levothyroxine levels 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 dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see Table 4).

## Digitalis glycosides

The therapeutic effects of digitalis glycosides may be reduced by levothyroxine sodium, USP. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see Table 4).

<b>Table 4 Drug-Thyroidal Axis Interactions</b>	
<b>Drug or Drug Class</b>	<b>Effect</b>
<b>Drugs that may reduce TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur</b>	
Dopamine/Dopamine Agonists Glucocorticoids Ocreotide	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); Ocreotide (greater than 100 mcg/day).
<b>Drug or Drug Class</b>	<b>Effect</b>
<b>Drugs that alter thyroid hormone secretion</b>	
<b>Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism</b>	
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Thioamides - Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T <sub>4</sub> and T <sub>3</sub> levels and increase TSH, although all values remain within normal limits in most patients.
<b>Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism</b>	
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.

**Table 4  
Drug-Thyroidal Axis Interactions**

<b>Drugs that may decrease T<sub>4</sub> absorption, which may result in hypothyroidism</b>	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Kayexalate Ferrous Sulfate Orlistat Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least four (4) hours apart from these agents. Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function.
<b>Drug or Drug Class</b>	<b>Effect</b>
<b>Drugs that may alter T<sub>4</sub> and T<sub>3</sub> serum transport - but FT<sub>4</sub> concentration remains normal; and therefore, the patient remains euthyroid</b>	
<b>Drugs that may increase serum TBG Concentration</b>	<b>Drugs that may decrease serum TBG Concentration</b>
Clofibrate Estrogen-containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
<b>Drugs that may cause protein-binding site replacement</b>	
Furosemide (greater than 80 mg IV) Heparin Hydantoin 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 <sub>4</sub> . Continued administration results in a decrease in Serum T <sub>4</sub> and normal FT <sub>4</sub> and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T <sub>4</sub> and T <sub>3</sub> to TBG and transthyretin. An initial increase in serum FT <sub>4</sub> is followed by return of FT <sub>4</sub> to normal levels with sustained therapeutic serum salicylate concentrations, although total-T <sub>4</sub> levels may decrease by as much as 30%.
<b>Drugs that may alter T<sub>4</sub> and T<sub>3</sub> metabolism</b>	
<b>Drugs that may increase hepatic metabolism, which may result in hypothyroidism</b>	
Carbamazepine Hydantoin Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T <sub>4</sub> may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.

**Table 4  
Drug-Thyroidal Axis Interactions**

<b>Drugs that may decrease T<sub>4</sub> 5'-deiodinase activity</b>	
<p>Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol greater than 160 mg/day) Glucocorticoids - (e.g., Dexamethasone greater than or equal to 4 mg/day) Propylthiouracil (PTU)</p>	<p>Administration of these enzyme inhibitors decreases the peripheral conversion of T<sub>4</sub> to T<sub>3</sub>, leading to decreased T<sub>3</sub> levels. However, serum T<sub>4</sub> levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (greater than 160 mg/day), T<sub>3</sub> and T<sub>4</sub> 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<sub>3</sub> concentrations by 30% with minimal change in serum T<sub>4</sub> levels. However, long-term glucocorticoid therapy may result in slightly decreased T<sub>3</sub> and T<sub>4</sub> levels due to decreased TBG production (see above).</p>
<b>Drug or Drug Class</b>	<b>Effect</b>
<b>Miscellaneous</b>	
<p>Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives</p>	<p>Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.</p>
<p>Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)</p>	<p>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.</p>
<p>Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin</p>	<p>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.</p>
<p>Cardiac glycosides</p>	<p>Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.</p>
<p>Cytokines - Interferon-alpha - Interleukin-2</p>	<p>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.</p>
<p>Growth Hormones - Somatrem - Somatropin</p>	<p>Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.</p>
<p>Ketamine</p>	<p>Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.</p>

<b>Table 4 Drug-Thyroidal Axis Interactions</b>	
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 <sup>123</sup> I, <sup>131</sup> I, and <sup>99m</sup> 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.
Drug or Drug Class	Effect
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

### Interactions with food

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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Studies in pregnant women have not shown that levothyroxine sodium, USP 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<sub>4</sub> 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<sub>4</sub> 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, levothyroxine sodium, USP should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T<sub>4</sub> concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as the fourth week gestation.

Pregnant women who are maintained on levothyroxine sodium, USP should have their TSH measured periodically. 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 six to eight weeks postpartum.

### **Breast-feeding**

Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when levothyroxine sodium, USP is administered to a nursing woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

### **Fertility**

No data available.

## **4.7 Effects on ability to drive and use machines**

Not relevant.

## **4.8 Undesirable effects**

Adverse reactions other than those indicative of thyrotoxicosis as a result of therapeutic overdosage, either initially or during the maintenance periods, are rare (see section 4.9). Seizures have been reported rarely with the institution of levothyroxine sodium therapy. Pseudotumor cerebri and slipped capital femoral epiphysis have also been reported in children receiving levothyroxine therapy. Over treatment in children may result in craniosynostosis and premature closure of the epiphyses with resultant compromised adult height.

Inadequate doses of Synthroid may produce or fail to resolve symptoms of hypothyroidism. Hair loss may occur during the initial months of therapy, but is generally transient. The incidence of continued hair loss is unknown.

Adverse reactions associated with levothyroxine sodium, USP are primarily those of hyperthyroidism due to therapeutic overdosage (see sections 4.4 and 4.9). They include the following:

<b>General:</b>	fatigue, increased appetite, weight loss, heat intolerance, fever, and excessive sweating;
<b>Cardiovascular system:</b>	palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction and cardiac arrest;
<b>Central nervous system:</b>	headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, psychotic depression and insomnia;
<b>Dermatologic:</b>	hair loss, flushing;
<b>Endocrine system:</b>	decreased bone mineral density;
<b>Gastrointestinal system:</b>	diarrhea, vomiting, abdominal cramps, and elevations in liver function tests;
<b>Musculoskeletal system:</b>	tremors, muscle weakness;
<b>Reproductive system:</b>	menstrual irregularities, impaired fertility;
<b>Respiratory system:</b>	dyspnea.

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

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.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 Overdose**

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. Symptoms are not always evident or may not appear until several days after ingestion of levothyroxine sodium, USP.

Levothyroxine sodium, USP should be reduced in dose or temporarily discontinued if signs and symptoms of overdosage appear.

In the treatment of acute massive levothyroxine sodium, USP 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<sub>4</sub> to T<sub>3</sub>. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Since T<sub>4</sub> is extensively protein bound, very little drug will be removed by dialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## **5. Pharmacological Properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Thyroid preparations, ATC code: H03AA01.

#### **Mechanism of action**

The synthesis and secretion of the major thyroid hormones, L-thyroxine (T<sub>4</sub>) and L-triiodothyronine (T<sub>3</sub>), 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.  $T_4$  and  $T_3$  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 various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see sections 4.1, 4.2 and 4.4).

## **5.2 Pharmacokinetic properties**

### **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 sprue. 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 levothyroxine sodium, USP 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 section 4.4 and 4.5).

## Biotransformation

The liver is the major site of degradation for both hormones.  $T_4$  and  $T_3$  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  $rT_3$  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 5), with a half-life of 6 to 7 days.  $T_3$  has a half-life of 1 to 2 days.

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%) <sup>2</sup>
Levothyroxine, $T_4$	10 to 20	14	6 to 7 <sup>1</sup>	99.96
Liothyronine $T_3$	1		$\leq 2$	99.5

<sup>1</sup> Three to four days in hyperthyroidism, nine to ten days in hypothyroidism  
<sup>2</sup> Includes TBG, TBPA, and TBA

## 5.3 Preclinical safety data

### Carcinogenesis, mutagenesis and impairment on fertility

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic  $T_4$  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 levothyroxine sodium, USP for established indications should not discontinue therapy.

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## 6. Pharmaceutical Particulars

### 6.1 List of excipients

Synthroid tablets also contain acacia, lactose monohydrate, magnesium stearate, povidone, purified talc and sucrose.

In addition to the excipients listed above, the follow excipients are unique to each strength:

25 mcg: Sunset yellow aluminium lake

75 mcg: Allura red AC, indigo carmine

88 mcg: D&C olive lake blend, quinolone yellow

100 mcg: Quinoline yellow, sunset yellow aluminium lake

112 mcg: D&C red lake blend #9570

125 mcg: Brown lake blend

137 mcg: Brilliant blue FCF

150 mcg: Indigo carmine

175 mcg: Brilliant blue FCF, D&C red lake blend #9570

200 mcg: Allura red AC

300 mcg: Brilliant blue FCF, sunset yellow aluminium lake, quinolone yellow

Synthroid tablets are gluten free.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

Shelf life is dependent on the packaging of the Synthroid tablets.

Currently marketed pack size of 90: 15 months.

## **6.4 Special precautions for storage**

Store at or below 25°C. Synthroid tablets should be protected from light and moisture.

If crushing the Synthroid tablet and suspending it in water for ease of swallowing, do not store the suspension for any period of time (see section 4.2).

## **6.5 Nature and contents of container**

Pack sizes of 90, 100 or 1000 in a HDPE bottle with a PP CRC and dessicant.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

Not applicable.

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# **7. Medicines Schedule**

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Prescription Medicine

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## **8. Sponsor Details**

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Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792.

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## **9. Date of First Approval**

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01 April 2010

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## **10. Date of Revision of the Text**

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17 July 2017            Revised to SmPC format, sponsor change and updates to sections 3 and 4.1.