Abbott Laboratories South Africa (Pty) Ltd	**Submission Date: 17 March 2023**	**Type: Post-registration variation**
SYNTHROID 25 µg / 50 µg / 75 µg / 100 µg	**Approval Date: 17 March 2023 (Variation previously approved 22 November 2021. Editorial correction for typographical error)**	**Category: IAIN**
25 µg, 50 µg, 75 µg, 100 µg, Tablets	**Implementation: 17 March 2023**	**Code: C.I.0.2a**
Country Code: ZA	**Reg No.: 25 µg: 42/21.3/0670** **Reg No.: 50 µg: 42/21.3/0671** **Reg No.: 75 µg: 42/21.3/0672** **Reg No.: 100 µg: 42/21.3/0674**	**Sequence No.: 0005**

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

APPROVED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

SYNTHROID 25 µg tablets

SYNTHROID 50 µg tablet

SYNTHROID 75 µg tablets

SYNTHROID 100 µg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYNTHROID 25 µg: Each tablet contains 25 µg of levothyroxine sodium

SYNTHROID 50 µg: Each tablet contains 50 µg of levothyroxine sodium

SYNTHROID 75 µg: Each tablet contains 75 µg of Levothyroxine sodium

SYNTHROID 100 µg: Each tablet contains 100 µg of Levothyroxine sodium

Contains sugar (all strengths): 62,8 mg sucrose per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

SYNTHROID 25 µg: an orange, round tablet, debossed on one side with “FLINT”, the opposite side partially scored and debossed with “25”

SYNTHROID 50 µg: a white, round tablet, debossed on one side with “FLINT”, the opposite side partially scored and debossed with “50”

SYNTHROID 75 µg: a violet, round tablet, debossed on one side with “FLINT” the opposite side partially scored and debossed with “75”

SYNTHROID 100 µg: a yellow, round tablet, debossed on one side with “FLINT”, the opposite side partially scored and debossed with “100”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SYNTHROID is indicated for the following:

Hypothyroidism

As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. or

Pituitary TSH Suppression

In the treatment or prevention of various types of euthyroid goiters (see section 4.4), including thyroid nodules (see section 4.4), subacute or chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis), multinodular goiter (see section 4.4) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

4.2 Posology and method of administration

General Principles

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of SYNTHROID that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see section 4.4). Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualised and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (see section 4.4, **Laboratory Tests**).

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

Caution should be exercised when administering SYNTHROID to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see section 4.4).

Posology

Specific Patient Populations

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

1. Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (see section 4.4, Laboratory Tests)

Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of SYNTHROID is approximately 1,7 µg /kg/day (e.g.,100 to 125 µg /day for a 70 kg adult). Older patients may require less than 1 µg /kg/day. SYNTHROID doses greater than 200 µg /day are seldom required. An inadequate response to daily doses greater than or equal to 300 µg /day is rare and may indicate poor compliance, malabsorption, and/or medicine interactions.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of 25 to 50 µg /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 elderly patients with cardiac disease is 12,5 to 25 µg /day, with gradual dose increments at four to six week intervals. The SYNTHROID dose is generally adjusted in 12,5 to 25 µg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalised.

In patients with severe hypothyroidism, the recommended initial SYNTHROID dose is 12,5 to 25 µg /day with increases of 25 µg /day every two to four weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalised.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the SYNTHROID dose should be titrated until the patient is clinically euthyroid and the serum free- levothyroxine (T_4) level is restored to the upper half of the normal range.

2. Paediatric Dosage – Congenital or Acquired Hypothyroidism (see section 4.4)

General Principles

In general, SYNTHROID therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development. Undertreatment and overtreatment should be avoided (see section 4.4, *Paediatric Use*).

To ensure maximum absorption, it is recommended that SYNTHROID be taken one-half to one-hour before breakfast. However, if the child's diet/sleep/activity schedule is such that it cannot be taken this way, consistency becomes the key. If SYNTHROID is administered with food, take it every day with food, consistently. If administration changes from taking it on an empty stomach, then around six to eight weeks after you start taking it with food, another TSH test should be done to ensure the child is receiving the proper amount of SYNTHROID.

3. Newborns

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

The recommended starting dose of **SYNTHROID** in newborn infants is **10 to 15 µg /kg/day.** A lower starting dose (e.g., 25 µg /day) should be considered in infants at risk for cardiac failure, and the dose should be increased in four to six weeks as needed based on clinical and laboratory response to treatment. In infants with very low (less than 5 µg /dL) or undetectable serum levothyroxine (T_4) concentrations, the recommended initial starting dose is **50 µg /day** of **SYNTHROID**.

4. Infants and Children

SYNTHROID therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see **Table 3).** However, in children with chronic or severe hypothyroidism, an initial dose of 25 µg /day of SYNTHROID is recommended with increments of 25 µg every two to four weeks until the desired effect is achieved. Hyperactivity in an older child can be minimised if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached.

Table 3: SYNTHROID Dosing Guidelines for Paediatric Hypothyroidism

Age	**Daily Dose Per Kg Body Weight[a]**
0 to 3 months	**10 to 15 µg/kg/day**
3 to 6 months	**8 to 10 µg/kg/day**
6 to 12 months	**6 to 8 µg/kg/day**
1 to 5 years	**5 to 6 µg/kg/day**

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

6 to 12 years	**4 to 5 µg/kg/day**
Greater than 12 years, but growth and puberty incomplete	**2 to 3 µg/kg/day**
Growth and puberty complete	**1,7 µg/kg/day**
[a] The dose should be adjusted based on clinical response and laboratory parameters (see section 4.4, Laboratory Tests and *Paediatric Use).*	

Pregnancy

Pregnancy may increase SYNTHROID requirements (see section 4.6).

TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules

The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of SYNTHROID used for TSH suppression should be individualised based on the specific disease and the patient being treated. In the treatment of well-differentiated (papillary and follicular) thyroid cancer, SYNTHROID is used as an adjunct to surgery and radioiodine therapy.

Generally, TSH is suppressed to less than 0,1 mU/L, and this usually requires a SYNTHROID dose of greater than 2 µg /kg/day. However, in patients with high-risk tumors, the target level for TSH suppression may be less than 0,01 mU/L. In the treatment of benign nodules and nontoxic

multinodular goiter, TSH is generally suppressed to a higher target (e.g., 0,1 to either 0,5 or 1,0 mU/L) than that used for the treatment of thyroid cancer.

SYNTHROID is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (see sections 4.3 and 4.4).

Myxedema Coma

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

Method of administration

SYNTHROID is administered as a single daily dose, preferably one-half to one-hour before breakfast. SYNTHROID should be taken at least four (4) hours apart from medicines that are known to interfere with its absorption (see section 4.5).

SYNTHROID may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5 to 10 mL or one to two teaspoons) of potable water, breast milk or non-soybean based formula. This suspension can be administered by spoon or by dropper. DO NOT STORE THE SUSPENSION.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Foods or formula containing large amounts of soybean fibre or iron should not be used for administering SYNTHROID (see section 4.5, **Medicine-Food Interactions**). The crushed tablet may also be sprinkled over a small amount of food, such as cooked cereal or apple sauce.

4.3 Contraindications

- Untreated subclinical (suppressed serum TSH level with normal T_3 and levothyroxine (T_4) levels) or overt thyrotoxicosis of any aetiology and in patients with acute myocardial infarction.
- Uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see section 4.4).
- Hypersensitivity to levothyroxine sodium or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

WARNING: THYROID HORMONES, INCLUDING SYNTHROID, EITHER ALONE OR WITH OTHER THERAPEUTIC MEDICINES, 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.
SYNTHROID should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism. In patients with nontoxic diffuse goiter or nodular thyroid

disease, particularly the elderly or those with underlying cardiovascular disease, SYNTHROID 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, SYNTHROID 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.

General

SYNTHROID has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration and response monitoring 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 medicines interact with **SYNTHROID** necessitating adjustments in dosing to maintain therapeutic response (see section 4.5**).**

Effects on Bone Mineral Density

In women, long-term **SYNTHROID** therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of **SYNTHROID.** The increased bone resorption may be associated with increased serum levels and urinary excretion

of calcium and phosphorus, 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 underlying Cardiovascular Disease

Exercise caution when administering SYNTHROID to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, SYNTHROID therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see sections 4.2 and Geriatric Use). If cardiac symptoms develop or worsen, the SYNTHROID 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 dysrhythmias, particularly in patients with cardiovascular disease and in elderly patients. Patients with coronary artery disease who are receiving SYNTHROID therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac dysrhythmias may be greater in those treated with SYNTHROID. Concomitant administration of SYNTHROID and sympathomimetic medicines to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Exercise caution when administering **SYNTHROID** to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see section 4.4). If the serum TSH is already suppressed, **SYNTHROID** should not be administered (see section 4.3).

Associated Endocrine Disorders

Hypothalamic/pituitary Hormone Deficiencies - In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see *Autoimmune Polyglandular Syndrome*) for adrenal insufficiency.

Autoimmune Polyglandular Syndrome – Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anaemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with **SYNTHROID.** Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with **SYNTHROID** (see section 4.5).

Other Associated Medical Conditions

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

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.

Laboratory Tests

General

The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity less than or equal to 0,1 mIU/L or third generation assay sensitivity less than or equal to 0,01 mIU/L) and measurement of free levothyroxine (T_4).

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see section 4.5).
Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of SYNTHROID may be evidence of inadequate oral absorption, poor compliance, medicine interactions, or decreased levothyroxine (T4) potency of the medicine.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during SYNTHROID dose titration depends on the clinical situation but it is generally recommended at

six to eight week intervals until normalization. For patients who have recently initiated SYNTHROID therapy and whose serum TSH has normalised or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8 to 12 weeks.

When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6 to 12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving SYNTHROID (see section 4.2).

Paediatrics

In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free levothyroxine (T_4). During the first three years of life, the serum total- or free- levothyroxine (T_4) should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalise the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalise due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum levothyroxine (T_4) to increase into the upper half of the normal range within two weeks of initiation of SYNTHROID therapy and/or of the serum TSH to decrease below 20 mU/L within four weeks should alert the physician to the possibility that the child is not receiving adequate therapy.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of SYNTHROID.

The recommended frequency of monitoring of TSH and total or free levothyroxine (T_4) in children is as follows: at two and four weeks after the initiation of treatment; every one to two months during the first year of life; every two to three months between one and three years of age; and every 3 to 12 months thereafter until growth is completed.

More frequent intervals of monitoring may be necessary if poor compliance is suspected or abnormal values are obtained. It is recommended that TSH and levothyroxine (T_4) levels, and a physical examination, if indicated, be performed two weeks after any change in **SYNTHROID** dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see section 4.2*).*

Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism

Adequacy of therapy should be assessed by measuring serum free- levothyroxine (T_4) levels, which should be maintained in the upper half of the normal range in these patients.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of **SYNTHROID.** The synthetic levothyroxine (T_4) in **SYNTHROID** is identical to that produced naturally by the human thyroid gland.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Paediatric Use

General

The goal of treatment in paediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development. The initial dose of SYNTHROID varies with age and body weight (see section 4.2, Table 3).

Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see **Laboratory Tests**).

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

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

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 levothyroxine (T_4) and TSH testing.

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

Congenital Hypothyroidism (see **Laboratory Tests** and section 4.2)

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

During the first two (2) weeks of SYNTHROID therapy, infants should be closely monitored for cardiac overload, dysrhythmias, and aspiration from avid suckling.

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Paediatric Patients

The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature. Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalise adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalise adult height.

Geriatric Use

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

Sucrose

SYNTHROID contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take SYNTHROID.

4.5 Interaction with other medicines and other forms of interaction

Medicine Interactions

Many medicines 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 medicines. A listing of medicine - thyroidal axis interactions is contained in Table 2.

The list of medicine-thyroidal axis interactions in Table 2 may not be comprehensive due to the introduction of new medicines that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (e.g., the professional information of newly approved medicines, medical literature) for additional information if a medicine-medicine interaction with SYNTHROID is suspected.

Table 2: Medicine Thyroidal Axis Interactions	
Medicine or Medicine Class	**Effect**
Medicines that may reduce TSH secretion -the reduction is not sustained; therefore, hypothyroidism does not occur	

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Dopamine/Dopamine Agonists Glucocorticoids Octreotide	Use of these medicines may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (greater than or equal to 1 µg /kg/min); Glucocorticoids (hydrocortisone greater than or equal to 100 mg/day or equivalent); Octreotide (greater than 100 µg /day).
Medicines that alter thyroid hormone secretion	
Medicines that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast medicines) Lithium Thioamides - Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides	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 foetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Graves' disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic medicines and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast medicines. Long-term aminoglutethimide therapy may minimally decrease levothyroxine (T_4) and T_3 levels and increase TSH, although all values remain within normal limits in most patients.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Tolbutamide	
Medicines that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing radiographic contrast medicines)	Iodide and medicines that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Graves' disease previously treated with antithyroid medicines 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.
Medicines that may decrease levothyroxine (T_4) absorption, which may result in hypothyroidism	
Antacids – Aluminium & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Colesevelam - Cholestyramine - Colestipol	Concurrent use may reduce the efficacy of **SYNTHROID** 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 SYNTHROID at least four (4) hours apart from these medicines.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Phosphate Binders - Calcium Carbonate - Ferrous Sulfate - Sevelamer - Lanthanum Cation Exchange Resins - Kayexalate Proton Pump Inhibitors Sucralfate Orlistat	Gastric acidity is an essential requirement for adequate absorption of levothyroxine. Sucralfate, antacids and proton pump inhibitors may cause hypochlorhydria, affect intragastric pH, and reduce levothyroxine absorption. Monitor patients treated concomitantly with sucralfate, antacids, proton pump inhibitors or orlistat and SYNTHROID for changes in thyroid function.
Medicines that may alter levothyroxine (T_4) and T_3 serum transport -but FT_4 concentration remains normal; and therefore, the patient remains euthyroid	
Medicines that may increase serum TBG concentration	**Medicines that may decrease serum TBG concentration**
Clofibrate	Androgens / Anabolic Steroids Asparaginase

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Oestrogen-containing oral contraceptives Oestrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	Glucocorticoids Slow-Release Nicotinic Acid
Medicines that may cause protein-binding site displacement	
Furosemide (greater than 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-Inflammatory Medicines - Fenamates - Phenylbutazone - Salicylates (greater than 2 g/day)	Administration of these medicines with SYNTHROID results in an initial transient increase in FT4. Continued administration results in a decrease in serum levothyroxine (T_4) and normal FT4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of levothyroxine (T_4) and T_3 to TBG and transthyretin. An initial increase in serum FT4 is followed by return of FT4 to normal levels with sustained therapeutic serum salicylate concentrations, although total- levothyroxine (T_4) levels may decrease by as much as 30 %.
Medicines that may alter levothyroxine (T_4) and T_3 metabolism	
Medicines that may increase hepatic metabolism, which may result in hypothyroidism	

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Carbamazepine Hydantoins Phenobarbital	Stimulation of hepatic microsomal medicine-metabolizing enzyme activity may cause increased hepatic degradation of SYNTHROID, resulting in increased SYNTHROID requirement. Phenytoin and
Rifampicin	carbamazepine reduce serum protein binding of SYNTHROID, and total- and free- levothyroxine (T_4) may be reduced by 20 % to 40 %, but most patients have normal serum TSH levels and are clinically euthyroid. Phenobarbital has been shown to reduce the response to thyroxine. Phenobarbital increases L-thyroxine metabolism by inducing uridine 5'-diphospho-glucuronosyltransferase (UGT) and leads to a lower T_4 serum levels. Changes in thyroid status may occur if barbiturates are added or withdrawn from patients being treated for hypothyroidism. Rifampin has been shown to accelerate the metabolism of levothyroxine.
Medicines that may decrease levothyroxine (T_4) 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonist – (e.g., Propranolol greater than 160 mg/day) Glucocorticoids – (e.g.	Administration of these enzyme inhibitors decreases the peripheral conversion of levothyroxine (T_4) to T_3, leading to decreased T_3 levels. However, serum levothyroxine (T_4) levels are usually normal but may occasionally be slightly increased. In patient treated with large doses pf propranolol (greater than 160 mg/day), T_3 and levothyroxine (T_4) levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Dexamethasone greater than or equal to 4 mg/day)	of particular beta-adrenergic antagonist may be impaired when the hypothyroid patient is converted to euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentration by 30 % with minimal change in serum (T_4) levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and levothyroxine (T_4) levels due to decreased TBG production (see above).
Propylthiouracil (PTU)	
Miscellaneous	
Anticoagulants (oral) – Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these medicines impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking SYNTHROID and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g. Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin	Concurrent use of tri/tetracyclic antidepressants and SYNTHROID may increase the therapeutic and toxic effects of both medicine, 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 SYNTHROID

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Reuptake Inhibitors (SSRIs; e.g., Sertraline)	may result in increased SYNTHROID requirements.
Antidiabetic medicines - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin	Addition of SYNTHROID to antidiabetic or insulin therapy may result in increased antidiabetic medicine or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac Glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-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.

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Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic medicines	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 medicines are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside	These medicines have been associated with thyroid hormone and/or TSH level alterations by various mechanisms

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Para-aminosalicylate Sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	

Antidiabetic Therapy –

Addition of SYNTHROID therapy in patients with diabetes mellitus may worsen glycaemic control and result in increased antidiabetic medicine or insulin requirements. Carefully monitor glycaemic control, especially when thyroid therapy is started, changed, or discontinued (see section 4.4).

Oral Anticoagulants –

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

Digitalis Glycosides –

The therapeutic effects of digitalis glycosides may be reduced by SYNTHROID. Serum digitalis

glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see Table 2).

Antidepressant Therapy –

Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and SYNTHROID may increase the therapeutic and toxic effects of both medicines, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac dysrhythmias and central nervous system (CNS) stimulation. SYNTHROID may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilised on SYNTHROID may result in increased SYNTHROID requirements.

Ketamine –

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

Sympathomimetics –

Concurrent use of sympathomimetics and SYNTHROID may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic medicines are administered to patients with coronary artery disease.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Tyrosine-Kinase Inhibitors –

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

Medicine-Food Interactions

Consumption of certain foods may affect SYNTHROID 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 SYNTHROID from the GI tract.

Medicine-Laboratory Test Interactions

Changes in TBG concentration must be considered when interpreting levothyroxine (T_4) and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free levothyroxine (T_4) index (FT4I). Pregnancy, infectious hepatitis, oestrogens, oestrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also Table 2). Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum levothyroxine (T_4) levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as four weeks gestation, pregnant women taking SYNTHROID should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of SYNTHROID. Since postpartum TSH levels are similar to preconception values, the SYNTHROID dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained six to eight weeks postpartum.

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

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Lactation

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

4.7 Effects on ability to drive and use machines

SYNTHROID is unlikely to affect your ability to drive and use machinery (see section 4.8). Caution is advised before driving a vehicle or operating machinery until the effects of SYNTHROID are known.

4.8 Undesirable effects

Adverse reactions associated with **SYNTHROID** therapy are primarily those of hyperthyroidism due to therapeutic overdosage (see section 4.4 and section 4.9). They include the following:

Metabolism and nutrition disorders:

Frequency not known: Increased appetite

Psychiatric disorders:

Frequency not known: Nervousness, anxiety, irritability, emotional lability, insomnia

Nervous system disorders:

Frequency not known: Headache; hyperactivity; tremors

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Cardiac disorders:

Frequency not known: Palpitations, tachycardia, dysrhythmias, increased pulse and blood pressure, heart failure, angina pectoris, myocardial infarction, cardiac arrest

Vascular disorders:

Frequency not known: Flushing

Respiratory, thoracic and mediastinal disorders:

Frequency not known: Dyspnoea

Gastrointestinal disorders:

Frequency not known: Diarrhoea, vomiting, abdominal cramps

Hepatobiliary disorders:

Frequency not known: Elevations in liver function tests

Skin and subcutaneous tissue disorders:

Frequency not known: Excessive sweating; hair loss

Musculoskeletal and connective tissue disorders:

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Frequency not known: Muscle weakness

Reproductive system and breast disorders:

Frequency not known: Menstrual irregularities; impaired fertility

General disorders and administration site conditions:

Frequency not known: Fatigue; heat intolerance; fever

Investigations:

Frequency not known: Decreased bone mineral density; weight loss

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving **SYNTHROID** therapy. Over-treatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height. Seizures have been reported rarely with the institution of **SYNTHROID** therapy.

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

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI

symptoms (abdominal pain, nausea, vomiting and diarrhoea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to **SYNTHROID** itself is not known to occur.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of SYNTHROID is important. It allows continued monitoring of the benefit/risk balance of SYNTHROID. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The signs and symptoms of overdosage are those of hyperthyroidism (sections 4.4 and 4.8). 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 SYNTHROID. Symptoms may not necessarily be 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 or symptoms of overdosage occur.

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Acute Massive Overdosage

This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. Activated charcoal or cholestyramine may also be used to decrease absorption. Central and peripheral increased sympathetic activity may be treated by administering beta-receptor antagonists, e.g. propranolol, provided there are no medical contraindications to their use.

Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hypoglycaemia, and fluid loss as necessary. Large doses of antithyroid medicines (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. Glucocorticoids may be given to inhibit the conversion of levothyroxine (T_4) to T_3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because levothyroxine (T_4) is highly protein bound, very little medicine will be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A .21.3 Thyroid preparations

Pharmacotherapeutic group: Thyroid hormones

ATC code: H03AA01

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

Mechanism of action

SYNTHROID contains synthetic levothyroxine sodium (T_4).

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), by the thyroid gland. Circulating serum T_3 and levothyroxine (T_4) levels exert a feedback effect on both TRH and TSH secretion. When serum T_3 and levothyroxine (T_4) levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_3 and levothyroxine (T_4) diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic

effects of thyroid hormones are essential to normal growth and development. The physiological actions of thyroid hormones are produced predominantly by T_3, the majority of which (approximately 80 %) is derived from levothyroxine (T_4) by deiodination in peripheral tissues.

Pharmacodynamics

Oral levothyroxine sodium is a synthetic T_4 hormone that exerts the same physiologic effect as endogenous T_4, thereby maintaining normal T_4 levels when a deficiency is present.

5.2 Pharmacokinetic properties

Absorption

Absorption of orally administered levothyroxine (T_4) from the gastrointestinal (GI) tract ranges from 40 % to 80 %. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine (T_4) in SYNTHROID tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93 %. Levothyroxine (T_4) absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fibre decreases bioavailability of levothyroxine (T_4). Absorption may also decrease with age. In addition, many medicines and foods affect levothyroxine (T_4) absorption (see section 4.5**, Medicine Interactions and Medicine-Food Interactions**).

Distribution

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Circulating thyroid hormones are greater than 99 % bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for levothyroxine (T_4) partially explains the higher serum levels, slower metabolic clearance, and longer half-life of levothyroxine (T_4) compared to T_3. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many medicines and physiologic conditions affect the binding of thyroid hormones to serum proteins (see section 4.5**, Medicine Interactions and Medicine-Food Interactions**). Thyroid hormones do not readily cross the placental barrier (see section 4.6).

Metabolism

Levothyroxine (T_4) is slowly eliminated (see **Table 1).** The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T_3 is derived from peripheral levothyroxine (T_4) by monodeiodination. The liver is the major site of degradation for both levothyroxine (T_4) and T_3 with levothyroxine (T_4) deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80 % of the daily dose of levothyroxine (T_4) is deiodinated to yield equal amounts of T_3 and reverse T_3 (r T_3). T_3 and r T_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolised via conjugation with glucuronides and sulphates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination

Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the faeces. Approximately 20 % of levothyroxine (T_4) is eliminated in the stool. Urinary excretion of levothyroxine (T_4) decreases with age.

Table 1: Pharmacokinetic Parameters of SYNTHROID

Hormone	Ratio in Thyroglobulin	Biologic Potency	$T_{1/2}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	10 to 20	1	6 to 7[1]	99,96
Liothyronine (T_3)	1	4	≤ 2	99,5

[1] Three to four days in hyperthyroidism, nine to ten days in hypothyroidism.

[2] Includes TBG, TBPA, and TBA

6. PHARMACEUTICAL PARTICULARS

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

6.1 List of excipients

Acacia

Colourants

Lactose monohydrate

Magnesium stearate (E572)

Povidone K30

Talc (E553b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Abbott Laboratories South Africa (Pty) Ltd	**Submission Date: 17 March 2023**	**Type: Post-registration variation**
SYNTHROID 25 µg / 50 µg / 75 µg / 100 µg	**Approval Date: 17 March 2023 (Variation previously approved 22 November 2021. Editorial correction for typographical error)**	**Category: IAIN**
25 µg, 50 µg, 75 µg, 100 µg, Tablets	**Implementation: 17 March 2023**	**Code: C.I.0.2a**
Country Code: ZA	**Reg No.: 25 µg: 42/21.3/0670** **Reg No.: 50 µg: 42/21.3/0671** **Reg No.: 75 µg: 42/21.3/0672** **Reg No.: 100 µg: 42/21.3/0674**	**Sequence No.: 0005**

1.3.1.1 APPROVED CLEAN PROFESSIONAL INFORMATION

PVC/Aluminium/OPA blister strips placed in an outer carton containing 30, 90 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories South Africa (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof

1709

8. REGISTRATION NUMBERS

SYNTHROID 25 µg – 42/21.3/0670

SYNTHROID 50 µg – 42/21.3/0671

SYNTHROID 75 µg – 42/21.3/0672

SYNTHROID 100 µg – 42/21.3/0674

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 April 2011

Abbott Laboratories South Africa (Pty) Ltd	**Submission Date: 17 March 2023**	**Type: Post-registration variation**
SYNTHROID 25 µg / 50 µg / 75 µg / 100 µg	**Approval Date: 17 March 2023 (Variation previously approved 22 November 2021. Editorial correction for typographical error)**	**Category: IAIN**
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10. DATE OF REVISION OF THE TEXT

17 March 2023