APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Euthyrox 25 µg Tablets

Euthyrox 50 µg Tablets

Euthyrox 75 µg Tablets

Euthyrox 100 µg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Euthyrox 25 µg tablet contains 25 µg levothyroxine sodium.

Each Euthyrox 50 µg tablet contains 50 µg levothyroxine sodium.

Each Euthyrox 75 µg tablet contains 75 µg levothyroxine sodium.

Each Euthyrox 100 µg tablet contains 100 µg levothyroxine sodium.

The formulation contains sugar (mannitol).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

EUTHYROX 25 µg tablets: off-white, round, flat on both sides, with a beveled edge, a dividing score on both sides of tablet, embossed with “EM 25” on one side

EUTHYROX 50 µg tablets: off-white, round, flat on both sides, with a beveled edge, a dividing score on both sides of tablet, embossed with “EM 50” on one side

EUTHYROX 75 µg tablets: off-white, round, flat on both sides, with a beveled edge, a dividing score on both sides of tablet, embossed with “EM 75” on one side

Euthyrox 100 µg tablets: off-white, round, flat on both sides, with a beveled edge, a dividing score on both sides of tablet, embossed with “EM 100” on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EUTHYROX is used in the treatment of hypothyroidism.

4.2 Posology and method of administration

The dose of EUTHYROX for the treatment of hypothyroidism should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

Adults

Initially 50 to 100 micrograms daily, preferably taken before breakfast, and adjusted at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained.
This may require doses of 200 to 300 micrograms daily. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), the dosage must be reduced or withheld for a day or two, then begin again at a lower level.

An initial dose of 25 microgram is appropriate when there is cardiac failure or coronary artery insufficiency. In this condition the daily dose may be increased by 25 microgram at intervals of four weeks, as needed.

Paediatric population

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg body weight per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

Juvenile myxoedema

The starting dose for children older than one year may be 2,5 micrograms to 5 micrograms / kg / day.

Special populations

In elderly patients, in patients with coronary heart disease, and in patients with severe or long- existing hypothyroidism, special caution is required when initiating therapy with EUTHYROX, that is, a low initial dose (for example 12.5 µg / day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 µg / day fortnightly) with frequent monitoring of thyroid hormones. A maintenance dose lower than that required for complete correction of TSH levels may be considered.

Method of administration

The daily dose can be given in a single administration in the morning.
Ingestion: as a single daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with a little liquid (for example, half a glass of water).

Infants receive the entire dose at once at least 30 minutes before the first meal of the day. Tablets are suspended in some water and the resultant suspension is administered with some more liquid. The suspension must be prepared freshly prior to each administration.

4.3 Contraindications

Hypersensitivity to levothyroxine or to any of the excipients listed in section 6.1.
Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
Treatment must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.

4.4 Special warnings and precautions for use

Thyroid hormones should not be given for weight reduction. In euthyroid patients, treatment with levothyroxine does not cause weight reduction.

Substantial doses may cause serious or even life-threatening undesirable effects. Levothyroxine in high doses should not be combined with certain substances for weight reduction, i.e. sympathomimetics (see section 4.9).

Before starting therapy with EUTHYROX the following diseases should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency, thyroid autonomy.
In case of adrenocortical dysfunction, this should be treated before starting the therapy with levothyroxine by adequate replacement treatment to prevent acute adrenal insufficiency (see section 4.3).

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

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac dysrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases.

In the case of secondary hypothyroidism the cause must be determined before replacement therapy is given and if necessary, replacement treatment of a compensated adrenal insufficiency must be commenced.

Where thyroid autonomy is suspected, a TRH test should be carried out or a suppression scintigram obtained before treatment.

Haemodynamic parameters should be monitored when EUTHYROX therapy is initiated in very low birth weight preterm neonates as circulatory collapse may occur due to the immature adrenal function.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, supraphysiological serum levels of EUTHYROX should be avoided, and, therefore, thyroid function should be checked regularly.

Levothyroxine should not be used in hyperthyroid metabolic states.

Patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may react unfavourably to EUTHYROX treatment and it is advisable to initiate corticosteroid therapy before giving EUTHYROX in these cases. Special care is needed when there are symptoms of myocardial insufficiency or electrocardiogram evidence of myocardial infarction.

If a switch to another levothyroxine-containing product is required, there is a need to undertake a close monitoring including a clinical and biological monitoring during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment could be necessary.

Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered (see section 4.5). Patients taking levothyroxine should be advised to consult a doctor before starting or stopping or changing treatment with orlistat, as orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted. Further, it is recommended to monitor the patient by checking the hormone levels in the serum.

EUTHYROX contains mannitol and may have a laxative effect.

4.5 interaction with other medicinal products and other forms of interaction

As thyroid status influences metabolic activity and most body systems, treatment with EUTHYROX may affect other disease states and their treatment.

Protease inhibitors:

Protease inhibitors may influence the effect of EUTHYROX. Close monitoring of thyroid hormone parameters is recommended. If necessary, the EUTHYROX dose has to be adjusted.

Phenytoin:

Phenytoin may influence the effect of levothyroxine by displacing levothyroxine from plasma proteins resulting in an elevated fT4 and fT3 fraction. On the other hand phenytoin increases the hepatic metabolisation of levothyroxine. Close monitoring of thyroid hormone parameters is recommended.

Influence of EUTHYROX on other medicines:

Antidiabetic medicines

EUTHYROX may reduce the effects of medicines which lower the blood sugar. For this reason, blood glucose levels should be checked frequently during thyroid hormone therapy and the dosage of the antidiabetic medicines adapted, if necessary.

Anticoagulant medicines /Coumarin derivatives

EUTHYROX displaces anticoagulant medicines from plasma protein, thereby enhancing the effects of these medicines. Patients on anticoagulant therapy therefore require careful monitoring when treatment with EUTHYROX is initiated or altered as the anticoagulant dose may need to be adjusted.

The following medicinal products intensify the effect of EUTHYROX:

Salicylates, furosemide, clofibrate

Salicylates, furosemide in high doses (250mg), clofibrate and other substances with a high affinity for plasma protein can displace levothyroxine sodium from plasma proteins, resulting in an elevated free-thyroxine (T4) fraction.

The following medicinal products may reduce the effect of EUTHYROX:

Proton pump inhibitors (PPIs)

Co-administration with PPIs may cause a decrease in the absorption of the thyroid hormones, due to the increase of the intragastric pH caused by PPIs.

Regular monitoring of thyroid function and clinical monitoring is recommended, with a possible increase in the dose of thyroid hormones.

Orlistat

Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of iodine salts and/or levothyroxine.

Sevelamer

Sevelamer may decrease EUTHYROX absorption. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the EUTHYROX dose has to be adjusted.

Tyrosine-kinase inhibitors

Tyrosine-kinase inhibitors (e.g., imatinib, sunitinib) may decrease the efficacy of EUTHYROX. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the EUTHYROX dose has to be adjusted.

Colestyramine, Colestipol

Ingestion of ion exchange resins such as colestyramine inhibits the absorption of levothyroxine sodium by binding to it in the gastro-intestinal tract. EUTHYROX should therefore be taken 4-5 hours before administration of colestyramine. The same is true for colestipol.

Aluminium-containing medicines, iron-containing medicines, calcium carbonate

Aluminium-containing medicines (antacids, sucralfate), iron-containing medicines and calcium carbonate have been reported to potentially decrease the effect of levothyroxine by reducing absorption of EUTHYROX from the GIT. EUTHYROX should therefore be administered at least 2 hour prior to the administration of these medicines.

Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone and iodine-containing contrast media

These substances inhibit the peripheral conversion of T4 to T3. Due to its high iodine content, amiodarone can trigger hyperthyroidism as well as hypothyroidism. Particular caution is advised in the case of nodular goitre with possibly unrecognised autonomy.

Setraline, chloroquine / proguanil

These substances decrease the efficacy of EUTHYROX and increase serum TSH level.

Barbiturates

Barbiturates and other medicines possessing hepatic enzyme inducing properties can increase hepatic clearance of EUTHYROX.

Oestrogens

Women using oestrogen-containing contraceptives or postmenopausal women under hormone replacement therapy may have an increased need for levothyroxine.

Interaction with food

Soy containing compounds can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of EUTHYROX may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with thyroid hormones should be given consistently during pregnancy and breastfeeding.

Dosage requirements may increase during pregnancy.

Since elevations in serum TSH may occur as early as 4 weeks of gestation, pregnant women taking levothyroxine should have their TSH measured during each trimester, in order to confirm that the maternal serum TSH values lie within the trimester-specific pregnancy reference range. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine. Since postpartum TSH levels are similar to preconception values, the levothyroxine dosage should return to the pre-pregnancy dose immediately after delivery.

A serum TSH level should be obtained 6–8 weeks postpartum.

Experience has shown that there is no evidence of EUTHYROX induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose levels. Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on foetal and postnatal development.

Breastfeeding

Levothyroxine is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant. However, thyroid function in mothers and infants should be monitored.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, since levothyroxine is identical to the naturally occurring thyroid hormone, it is not expected that EUTHYROX has any influence on the ability to drive and use machines, if used as recommended.

4.8 Undesirable Effects

Undesirable effects are generally associated with excessive dosage or if the dose is increased too quickly at the start of treatment and correspond to symptoms of hyperthyroidism. These symptoms usually disappear after dosage-reduction or temporary withdrawal of treatment. Therapy may be carefully resumed once the symptoms have disappeared.

In case of hypersensitivity to any ingredients of Euthyrox allergic reactions particularly of the skin (rash, urticaria) and the respiratory tract may occur.
Cases of angioedema have been reported.

The following symptoms have been reported, predominantly with excessive dosages and frequencies are unknown:

Endocrine disorders:

Heat intolerance, sweating, flushing, fever, weight loss

Psychiatric disorders:

Nervousness, excitability, insomnia, restlessness

Nervous system disorders:

Headache, tremors, pseudotumor cerebri

Cardiac disorders:

Tachycardia, palpitations, cardiac dysrhythmias, anginal pain

Gastrointestinal disorders:

Diarrhoea and vomiting

Skin and subcutaneous tissue disorders:

Hyperhidrosis, alopecia, rash, pruritus

Musculoskeletal and connective tissue disorders:

Muscle weakness and cramps

Reproductive system and breast disorders:

Menstrual irregularities

In the case of hypersensitivity, allergic reactions may occur.

Peadiatric population:

Excessive dose may result in heat intolerance, transient hair loss, benign intracranial hypertension, craniosynotosis in infants and premature closure of epiphyses in children.

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. 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 Overdosage

An elevated T3 level is a reliable indicator of overdose, more than elevated T4 or fT4 levels.

After overdose the symptoms of a sharp increase in the metabolic rate occur (see section 4.8).

Depending on the extent of the overdose it is recommended that treatment with the tablets is interrupted and that tests are carried out.

Symptoms consisting of intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia can be relieved by betablockers. After extreme doses plasmapheresis may be of help.

In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded.

Overdose of levothyroxine may result in symptoms of hyperthyroidism and could lead to acute psychosis, especially in patients at risk of psychotic disorders.

Several cases of sudden cardiac death have been reported in patients with long years of levothyroxine abuse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC-code: H03A A01

Levothyroxine sodium is a synthetic levothyroxine which is identical in effect to the naturally occurring major hormone secreted by the thyroid. It is converted to tri- iodothyronine (T3) in peripheral organs.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, levothyroxine is variably absorbed, with 50 - 80 % of the dose absorbed in the small intestine. Fasting increases absorption and tmax is reached in approximately 5 to 6 hours.

Distribution

Once in circulation, levothyroxine is extensively protein bound, principally to thyroxine-binding globulin (TBG), but also to a lesser extent to thyroxine-binding pre-albumin (TBPA), or to albumin. Due to its high protein binding, levothyroxine does not undergo haemodialysis or haemoperfusion.

Onset of action is seen after 3-5 days. The half-life is on average 7 days. In hyperthyroidism, it is shorter (3-4 days) and in hypothyroidism, it is longer (approximately 9-10 days).

Biotransformation

Levothyroxine is primarily metabolised in the liver, kidneys, brain and muscle. It is metabolised in the liver and kidney to tri-iodothyronine, and, about 40 % to inactive reverse tri-iodothyronine (reverse T3), both of which undergo further deiodination to inactive metabolites.

Elimination

The metabolites are excreted with urine and faeces. Overall metabolic clearance for levothyroxine is about 1.2 ℓ plasma/day.

5.3 Preclinical safety data:

Acute toxicity:

Levothyroxine has a very slight acute toxicity.

Chronic toxicity:

The chronic toxicity of levothyroxine was studied in various animal species (rat, dog). At high doses, signs of hepatopathy, increased occurrence of spontaneous nephroses as well as changes in organ weights were observed in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, citric acid anhydrous, croscarmellose sodium, gelatine, magnesium stearate, mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C

Protect from light.

Store blisters in outer carton at all times.

Keep out of reach of children.

6.5 Nature and contents of container

Euthyrox tablets are available in blisters of aluminium forming foil and aluminium cover foil in packs of 30’s.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive, Longmeadow Business Estate South, Modderfontein 1645, South Africa

NAME AND BUSINESS ADDRESS OF MANUFACTURER

Merck Healthcare KGaA

250 Frankfurterstrasse, 64293 Darmstadt, Germany

8. REGISTRATION NUMBER(S)

Euthyrox 25 µg tablets: A39/21.3/0401

Euthyrox 50 µg tablets: A39/21.3/0402

Euthyrox 75 µg tablets: 52/21.3/0440

Euthyrox 100 µg tablets: A39/21.3/0403

9. DATE OF FIRST AUTHORISATION

17 April 2009

10. DATE OF REVISION OF THE TEXT

23/07/2024

Country	Registration number		Schedule
Botswana	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 75 µg: Euthyrox 100 µg:	BOT1302362 BOT1302363 BOT2304118 BOT1302364	S2
Namibia	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 75 µg: Euthyrox 100 µg:	11/21.3/0135 11/21.3/0136 19/21.3/0047 11/21.3/0137	NS2
Kenya	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 100 µg:	H2015/CTD1525/425 H2015/CTD1525/426 H2015/CTD1525/427	POM
Tanzania	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 75 µg: Euthyrox 100 µg:	TZ13H215 TZ13H213 TZ18H0196 TZ13H214	POM
Uganda	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 75 µg: Euthyrox 100 µg:	NDA/MAL/HDP/0830 NDA/MAL/HDP/2199 NDA/MAL/HDP/6482 NDA/MAL/HDP/0832	POM
Zambia	Euthyrox 25 µg: Euthyrox 50 µg: Euthyrox 100 µg:	363/007 363/008 363/009	POM