SUMMARY OF PRODUCT CHARACTERISTICS

UNI-PHARMA
Pharmaceutical Laboratories S.A.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Thyrofix 25 micrograms Tablets

Thyrofix 50 micrograms Tablets

Thyrofix 75 micrograms Tablets

Thyrofix 100 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Thyrofix 25 micrograms tablet contains 25 micrograms of Levothyroxine sodium.

Each Thyrofix 50 micrograms tablet contains 50 micrograms of Levothyroxine sodium.

Each Thyrofix 75 micrograms tablet contains 75 micrograms of Levothyroxine sodium.

Each Thyrofix 100 micrograms tablet contains 100 micrograms of Levothyroxine sodium.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Thyrofix 25 microgram Tablets are white, round, biconvex tablets with a diameter of 6.5 mm and an average thickness of 3.5 mm, debossed with “25” on one side.

Thyrofix 50 microgram Tablets are white, round, biconvex tablets with a diameter of 6.5 mm and an average thickness of 3.5 mm, debossed with “50” on one side.

Thyrofix 75 microgram Tablets are white, round, biconvex tablets with a diameter of 6.5 mm and an average thickness of 3.5 mm, debossed with “75” on one side.

Thyrofix 100 microgram Tablets are white, round, biconvex tablets with a diameter of 6.5 mm and an average thickness of 3.5 mm, debossed with “100” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of benign euthyroid goitre, especially in adults where iodine is not indicated
- Prophylaxis of relapse after surgery for euthyroid goitre, depending on the post-operative hormone status
- Substitution therapy in hypothyroidism
- Suppression therapy in thyroid cancer
- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism

4.2 Posology and method of administration

In order to treat each patient according to his/her individual needs, tablets are available with levothyroxine sodium content from 25 to 100 micrograms. The dosage recommendations given are only for guidance.

The individual daily dose should be determined on the basis of laboratory tests and clinical examinations.

As a number of patients show elevated concentrations of T_4 and fT_4, basal "serum concentration of thyroid-stimulating hormone (TSH)" provides a more reliable basis for following treatment course.

Except for neonates with congenital hypothyroidism, where rapid replacement is important, thyroid hormone therapy should be started at low dose and increased gradually every 2 to 4 weeks until the full replacement dose is reached.

Paediatric patients

The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area.

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg Bodyweight 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.

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to

the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Infants should be given the total daily dose at least half an hour before the first meal of the day.

Tablets are to be disintegrated in some water (10 to 15 mL) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 to 10 mL).

Elderly

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 thyroid hormones, that is, a low initial dose (for example 12.5 microgram/day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 microgram/day fortnightly) with frequent monitoring of thyroid hormones. A dosage, lower than optimal dosage giving complete replacement therapy, consequentially not resulting in a complete correction of TSH level, might therefore need to be considered.

Experience has shown that a lower dose is sufficient in low-weight patients and in patients with a large nodular goitre.

Indication	**Recommended dose** (microgram levothyroxine sodium/day)
Treatment of benign euthyroid goitre	75 - 200
Prophylaxis of relapse after surgery for euthyroid goitre	75 - 200
Substitution therapy in hypothyroidism in adults - initial dose - maintenance dose	 25 - 50 100 - 200
Substitution therapy in neonates and infants Congenital hypothyroidism initial dose Acquired hypothyroidism initial - maintenance dose	 10-15 12.5 - 50 100 - 150 microgram/m² body surface
Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism	50 - 100
Suppression therapy in thyroid cancer	150 - 300

The daily doses can be given in a single administration.

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).

Duration of treatment is usually for life in the case of substitution in hypothyroidism and after strumectomy or thyroidectomy and for relapse prophylaxis after euthyroid goitre removal.

Concomitant therapy of hyperthyroidism after achieving euthyroid status is indicated for the period in which the anti-thyroid drug is given.

For benign euthyroid goitre, a treatment duration of 6 months up to 2 years is necessary. To prevent recurrent goitre, prophylaxis with low-dose iodine (100-200 mcg / day) is recommended. If the medical treatment was not sufficient within this time, surgery or radioiodine therapy of the goitre should be considered.

A pre-therapy ECG is valuable because ECG changes due to hypothyroidism may be confused with ECG evidence of cardiac ischemia. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors, and sometimes

angina pain where there is latent cardiac ischaemia), dosage must be reduced, or withheld, for a day or two, and then re-started at a lower level.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Levothyroxine Sodium Tablets must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.
- Combination therapy of levothyroxine and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Before starting therapy with thyroid hormones or before performing a thyroid suppression test, the following diseases or medical conditions should be excluded or treated: coronary failure, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency (hypopituitarism), adrenal insufficiency, thyroid autonomy.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. 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.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely.

Levothyroxine should not be given in a hyperthyroid metabolic state, except as supportive therapy in thyrostatic treatment of hyperthyroidism.

Once a levothyroxine treatment has been established, it is recommended to adjust the dosage following the patient's clinical response and laboratory test, in case of switching the brand.

Thyroid hormones must not be given for weight reduction. In euthyroid patients, normal doses do not cause any weight reduction. Higher doses may cause serious or even life-

threatening undesirable effects such as hypothyroidism and/or reduced control of hypothyroidism, particularly in combination with certain weight-reduction agents such as orlistat. This could be due to a decreased absorption of iodine salts and/or levothyroxine

For diabetic patients and patients under anticoagulant therapy, see section 4.5 “Interaction with other medicinal products and other forms of interaction”.

An ECG before starting treatment with levothyroxine is advised, as changes induced by hypothyroidism may be confused with evidence of ischaemia.

Parent of children receiving thyroid agent should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequent regrowth usually occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-diabetic agents:

Levothyroxine may reduce the effect of antidiabetic agents. For this reason, blood glucose levels should be checked frequently at the start of thyroid hormone therapy and the dosage of the antidiabetic agent has to be adapted, if necessary.

Coumarin derivates:

The effect of anti-coagulant therapy can be increased by concomitant treatments with levothyroxine. Therefore it is necessary for coagulation parameters to be checked regularly at the start of and during concomitant therapy. If necessary, the dosage of the anti-coagulative drug has to be adapted.

Protease inhibitors

There are reports that the therapeutic efficacy of levothyroxine may be lost if it is used at the same time as lopinavir/ritonavir. Careful monitoring of the thyroid function is therefore necessary in patients taking levothyroxine and protease inhibitors at the same time.

Bile acid sequestrants:

Ingestion of bile acid sequestrants (such as cholestyramine and colestipol) inhibits the absorption of levothyroxine sodium. Levothyroxine sodium should therefore be taken 4-5 hours before administration of such products.

Aluminium containing drugs, iron-containing drugs, calcium carbonate:

Aluminium-containing drugs (antacids, sucralfate) have been reported in the pertinent literature as potentially decreasing the effect of levothyroxine. Drugs containing levothyroxine should therefore be administered at least 2 hours prior to the administration of aluminium-containing drugs.

Same is true for iron-containing drugs and calcium carbonate.

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 unrecognized autonomy.

Sertraline, chloroquine/proguanil:

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

Enzyme inducing medicinal products:

Enzyme inducing medicinal products such as barbiturate or carbamazepine may increase hepatic clearance of levothyroxine.

Estrogens:

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

Soy-containing compounds:

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

Sevelamer:

There are reports that sevelamer may increase TSH-levels in patients co-administered sevelamer and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medications.

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.

Orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted.

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

4.6 Pregnancy and lactation

Pregnancy

The development of the child depends on the thyroid function of the mother. Thyroxine is necessary for proper brain development of the child. Therefore, during pregnancy, treatment with thyroid hormones should be given consistently. Dosage requirements may even increase during pregnancy. To date, there have been no reports of any risk following extensive use of levothyroxine during pregnancy.

Lactation

Levothyroxine Sodium Tablets can be used during lactation. Levothyroxine is secreted in low concentrations into breast milk during lactation. Even with high-dose levothyroxine therapy the concentrations achieved are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant.

Combination therapy with anti-thyroid agents

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy. Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

4.7 Effects on ability to drive and use machines

There are no available studies on the effects on the ability to drive and use machines. As levothyroxine is identical to the naturally occurring thyroid hormone, Levothyroxine is not expected to have any influence on the ability to drive and use machines.

4.8 Undesirable effects

During the treatment with levothyroxine sodium one does not expect side effects if the substance is used according to prescription and if clinical and laboratory parameters are monitored. Where the individual tolerance limit for levothyroxine sodium is exceeded or after overdose it is possible for the following clinical symptoms typical of hyperthyroidism to occur, especially if the dose is increased too quickly at the start of treatment:

Cardiac disorders

Tachycardia, palpitations, cardiac arrhythmias, anginal conditions

Psychiatric disorders

Restlessness, insomnia

Nervous system disorders

Pseudotumor cerebri, tremor, cephalalgia,

Musculoskeletal and connective tissues disorders

Muscular weakness

Craniostenosis in infants and premature closure to epiphysis in children

Reproductive system and breast disorders

Disorders of menstruation

Gastrointestinal disorders

Cramps, vomiting, diarrhoea

General disorders and administration site conditions

Fever, weight loss

Skin and subcutaneous tissues disorders

Flushing, hyperhidrosis

In such cases the daily dose should be reduced or the medication withdrawn for several days. Therapy may be carefully resumed once the adverse reactions have disappeared.

In case of hypersensitivity to any ingredients allergic reactions particularly of the skin and the respiratory tract may occur.

4.9 Overdose

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.

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

After suicide attempt doses of 10 mg of levothyroxine were tolerated without complications. Several cases of sudden cardiac death have been reported in patients with long years of levothyroxine abuse.

Symptoms consisting of intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia can be relieved by beta-blockers. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC-Code: H03A A01

The synthetic levothyroxine contained in Levothyroxine Sodium Tablets is identical in effect with the naturally occurring major hormone secreted by the thyroid. It is converted to T3 in peripheral organs and, like the endogenous hormone, develops its specific effects at the T3

receptors. The body is not able to differentiate between endogenous and exogenous levothyroxine.

5.2 Pharmacokinetic properties

Orally given levothyroxine is absorbed almost exclusively in the upper small intestine. Depending on the galenical formulation absorption amounts up to 80 %. Tmax is approximately 5 to 6 hours.

Levothyroxine exhibits an extremely high binding to specific transport proteins of about 99.97 %. This protein hormone binding is not covalent and so the bound hormone in plasma is in continuous and very rapid exchange with the fraction of the free hormone. The volume of distribution amounts to about 10-12 l.

Due to its high protein binding levothyroxine undergoes neither haemodialysis nor haemoperfusion.

The half-life of levothyroxine is on average 7 days. In hyperthyroidism it is shorter (3-4 days). In hypothyroidism it is longer (approx. 9-10 days). The liver contains 1/3 of the entire extra-thyroidal levothyroxine, which is rapidly exchangeable with the levothyroxine in serum. Thyroid hormones are metabolized mainly in the liver, kidneys, brain and muscles. The metabolites are excreted with urine and faeces. The overall metabolic clearance for levothyroxine is about 1.2 l plasma/day.

5.3 Preclinical safety data

Acute toxicity:
The acute toxicity of levothyroxine is very low.

Chronic toxicity:
Chronic toxicity studies have been carried out in various animal species (rat, dog). At high doses, signs of hepatopathy, the increased occurrence of spontaneous nephrosis and changes in organ weight were seen in rats.

Reproduction toxicity:
Reproduction toxicity studies have not been carried out in animals.

Mutagenicity:
No data are available on the mutagenic potential of levothyroxine. But to date, no suspicious findings or evidence have been reported to suggest that thyroid hormones might damage offspring by altering the genome.

Carcinogenicity:
No chronic studies with levothyroxine have been carried out in animals.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose Powdered
Sodium Croscarmellose (E 468)
Silica, colloidal anhydrous
Microcrystalline Cellulose
Magnesium Stearate (E 470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package, in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packaged in transparent PVC/PVDC/Aluminum blisters. The blisters are further packaged in cardboard boxes. Each cardboard box contains 30, 50 or 100 tablets, presented in multiple blisters of 15 or 25 tablets, along with a Patient Information Leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

14th km Athens-Lamia National Road,

GR-145 64 Kifissia

Greece

8 MARKETING AUTHORISATION NUMBER(S)

25 microgram:
50 microgram:
75 microgram:
100 microgram:

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT