ELTROXIN™
Levothyroxine sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION
Non-scored tablets containing 50 micrograms (0.05 mg) or 100 micrograms (0.1 mg) levothyroxine sodium, which is the monosodium salt of the levorotary isomer of levothyroxine.

PHARMACEUTICAL FORM
Tablets.

CLINICAL PARTICULARS
Indications
Hypothyroidism.

Posology and method of administration
If the dose of *ELTROXIN* is increased too rapidly, symptoms such as diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia may occur and the dosage must be reduced or withheld for a day or two, then restarted at a lower level. A pre-therapy ECG is valuable, as changes induced by hypothyroidism may be confused with ECG evidence of ischaemia.
Due to a lack of data it is not appropriate to crush levothyroxine tablets and levothyroxine tablets without a score-line must not be halved.
Levothyroxine tablets should preferably be taken on an empty stomach.

Adults: Initially 50 to 100 mcg daily, preferably taken before breakfast, and adjusted at three to four week intervals by 50 mcg until attainment of clinical and biochemical euthyroidism. This may require doses of 100 to 200 mcg daily. With patients aged over 50 years, it is not advisable to exceed 50 mcg a day initially. Where there is cardiac disease, 25 mcg daily, or 50 mcg on alternate days, is more suitable. In this condition the daily dosage may be increased by 25 mcg at intervals of approximately four weeks. In younger patients, and in the absence of heart disease, a serum levothyroxine (T4) level of about 70 to 160 nanomoles per litre, or a serum thyrotrophin level of less than 5 milli-units per litre, should be aimed at. In those aged over 50, and/or in the presence of heart disease, clinical response is probably a more acceptable criterion of dosage then serum levels. In the event that a dose of 25 mcg is required, the adult may take a 50 mcg tablet on alternative days.

Children: In congenital hypothyroidism and juvenile myxoedema, the largest dose consistent with freedom from toxic effects should be given. The dosage is guided by clinical response, growth assessment and appropriate thyroid function tests-clinically, normal pulse rate and absence of diarrhoea or constipation are the most useful indicators. Thyrotrophin levels may remain elevated during the first year of life in children with neonatal hypothyroidism due to resetting of the hypothalamic-pituitary axis.
For infants with congenital hypothyroidism, a suitable starting dose is 25 mcg *ELTROXIN* daily, with increments of 25 mcg every two to four weeks until optimal response is achieved. The same dosing regimen applies to juvenile myxoedema, except that the starting dose for children older than one year may be 2.5 to 5 mcg/kg/day. The calculated daily dose equivalent should be rounded to the nearest 25 mcg to determine the actual prescribed dose. In the event that a dose of 25 mcg is required, the child may take a 50 mcg tablet on alternative days.

In patients whose medications include levothyroxine and known interfering agents, administration should be separated by at least 4 hours (see Section 4.5).

Contra-indications
- Hypersensitivity to any component of the preparation.
- Thyrotoxicosis.
- Patients with untreated subclinical (suppressed serum TSH level with normal T3 and T4 levels) or overt thyrotoxicosis of any aetiology.
- Acute myocardial infarction, acute myocarditis and acute pancarditis
- Untreated adrenal insufficiency
- Untreated pituitary insufficiency

Special warnings and precautions for use

Laboratory monitoring
ELTROXIN has a narrow therapeutic index. Appropriate *ELTROXIN* dosage is based upon clinical assessment and laboratory monitoring of thyroid function tests. During the initial titration period, careful dosage titration and monitoring is necessary to avoid the consequences of under- or over-treatment. The symptoms of excessive *ELTROXIN* dosage are the same as many features of endogenous thyrotoxicosis.

Levothyroxine should not be used for the treatment of obesity or 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 anorectic effects.

Weight loss drugs: Orlistat may decrease levothyroxine absorption which may result in hypothyroidism. To avoid this orlistat and levothyroxine should be administered at least 4 hours apart. Regular monitoring for changes in thyroid function is required.

Special patient populations:
The initial dose and any dose increments should be carefully chosen in elderly and in patients with cardiac symptoms, diabetes mellitus or insipidus: a too high initial dose or too rapid increase may cause or aggravate symptoms of angina, arrhythmias, myocardial infarction, cardiac failure or a sudden raise in blood pressure.
Treatment with *ELTROXIN* in patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may cause reactions, including dizziness, weakness, malaise, weight loss, hypotension and adrenal crisis. It is advisable to initiate corticosteroid therapy before giving *ELTROXIN* in these cases.
Patients with myxoedema have an increased sensitivity for thyroid hormones; in these patients the starting dose should be low with slow dosing increments.
Levothyroxine absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective levothyroxine treatment with regular levothyroxine dose.
During pregnancy, serum levothyroxine levels may decrease with a concomitant increase in serum TSH level to values outside the normal range. Patients taking levothyroxine should have their TSH measured during each trimester. An elevated serum TSH level should be

corrected by an increase in the dose of levothyroxine. Since postpartum TSH serum levels are similar to preconception values, levothyroxine dosage can be reduced to the pre-pregnancy dose.
In women, long-term levothyroxine therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses of in women who are receiving suppressive doses of levothyroxine. To minimise the risk of osteoporosis, dosage of levothyroxine should be titrated to the lowest possible level.

Effects on bone mineral density:
In women, long-term levothyroxine sodium 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 levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorus, elevations in bone alkaline phosphate and suppressed serum parathyroid hormone levels, Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve and desired clinical and biochemical response.

Interferences with laboratory test
Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results. The risk of interference increases with higher doses of biotin.

When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed.

For patients taking biotin-containing products, laboratory personnel should be informed when a thyroid function test is requested. Alternative tests not susceptible to biotin interference should be used, if available (see Interactions).

Interactions

Interactions decreasing levothyroxine absorption
Cholestyramine, calcium, aluminium, magnesium, iron supplements, polystyrene sulfonates, sucralfate, lanthanum, bile acid sequestrants (e.g. colestipol), anion/cation exchange resins (e.g. kayexalate, sevelamer), and proton pump inhibitors decrease the absorption of levothyroxine. Separate the dosages of levothyroxine and the abovementioned medicines as much as possible to avoid interaction in the stomach or the small bowel.
Soy-containing compounds and high-fibre diets can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of levothyroxine may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

Interactions affecting levothyroxine
Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter *ELTROXIN* dose requirements. Enzyme inducers like rifampicin and barbiturates increase the metabolism and excretion of levothyroxine, resulting in increased levothyroxine requirements.
Medicines that (partially) inhibit the peripheral transformation of T4 to T3 - like propranolol, amiodarone, lithium, iodide, oral contrast agents, propylthiouracil and glucocorticoids- lower the T3 level and therefore also the therapeutic effect.
Treatment with tyrosine kinase inhibitors (e.g. imatinib and sunitinib) was associated with increased *ELTROXIN* dosage requirements in hypothyroid patients.

The concurrent use of sertraline can reduce serum levels of levothyroxine (with concomitant increased TSH levels).
Co-administration of oral contraceptives, as well as a number of other drugs, including oestrogen, tamoxifene, clofibrate, methadone, and 5-fluorouracil may increase serum concentration of levothyroxine-binding globulin, and therefore increase *ELTROXIN* dosage requirements.

Reports indicate that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase thyroid hormone requirements in patients receiving levothyroxine therapy. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate levothyroxine dose adjustments may be necessary when levothyroxine and statins are co-prescribed.
A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on *ELTROXIN* therapy.

Interactions affecting other drugs
Levothyroxine can increase the need for insulin or oral antidiabetics in patients with diabetes. Lowering the dose of levothyroxine can cause hypoglycemia if the insulin or oral antidiabetics dose remains unchanged.
ELTROXIN increases the effect of anticoagulants and it may be necessary to reduce the dose of anticoagulant if excessive hypoprothrombinaemia and bleeding are to be avoided.
Phenytoin levels may be increased by *ELTROXIN*.
If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.
ELTROXIN increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants. The effects of sympathomimetic agents are also enhanced.

Post-marketing cases have been reported indicating a potential interaction between protease inhibitors containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending protease inhibitors treatment.

Laboratory test interactions
A number of drugs may decrease serum concentration of levothyroxine-binding globulin, and therefore decrease *ELTROXIN* dosage requirements, including androgens and anabolic steroids.
False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy. Administration of acetylsalicylic acid together with levothyroxine results in an initial transient increase in serum free T4. Continued administration results in normal free T4 and TSH concentrations, and therefore, patients become clinically euthyroid.

Interferences with laboratory test
Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see Special warnings and precautions for use).

Pregnancy and Lactation
ELTROXIN has been taken by a large number of pregnant women and women of childbearing age without any form of definite disturbances in the reproductive process having been observed so far. Thyroid hypo- or hyperactivity in the mother may, however, unfavourably influence the fetal outcome or well being.
Levothyroxine is excreted in breast milk in low concentrations and this may be sufficient to interfere with neonatal screening for hypothroidism.

Effects on Ability to Drive and Use Machines
From the pharmacokinetic and pharmacodynamic properties of levothyroxine, treatment with *ELTROXIN* would not be expected to interfere with ability to drive or operate machinery.

Undesirable effects
The following effects are indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days:

The frequency classification for these adverse reactions is not known due to a lack of robust clinical trial data to accurately determine frequency estimates.

System organ class		**Side effects**
Cardiac disorders	Not known	Anginal pain, cardiac arrhythmias, palpitations, tachycardia, increased blood pressure, heart failure, myocardial infarction
Endocrine disorders	Not known	Hyperthyroidism
Gastrointestinal disorders	Not known	Abdominal cramps, nausea, vomiting, diarrhoea
General disorders and administration site conditions	Not known	Fatigue, heat intolerance, fever
Immune system disorders	Not known	Hypersensitivity reactions such as skin rash, pruritus, anaphylactic reactions.
Metabolism and nutrition disorders	Not known	Increased appetite, abnormal loss of weight
Musculoskeletal and connective tissue disorders	Not known	Muscle spasms, muscular weakness. Excessive dose may result in epiphyses premature fusion in children with compromised adult height. Excessive dose may result in craniosynostosis in infants
Investigation	Not known	Bone density decreased
Nervous system disorders	Not known	Headache, tremor, seizure. Rare cases of pseudotumor cerebri (benign intracranial hypertension) have been reported especially in children.
Psychiatric disorders	Not known	Anxiety, emotional lability, nervousness, excitability, insomnia, restlessness.
Reproductive system and breast disorders	Not known	Menstrual irregularity, impaired fertility
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Skin and subcutaneous tissue disorders	Not known	Sweating, alopecia
Vascular disorders	Not known	Flushing

Overdose

Symptoms and Signs
In addition to exaggeration of side effects the following symptoms may for example be seen: agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions. The appearance of clinical hyper-thyroidism may be delayed for up to five days. Thyrotoxic crisis has been occasionally reported following massive or chronic intoxication, leading to cardiac arrhythmias, heart failure and coma.

Treatment
The goal of therapy is restoration of clinical and biochemical euthyroid state by omitting or reducing the *ELTROXIN* dosage, and other measures as needed depending on clinical status.

Treatment is symptomatic, and tachycardia has been controlled in adults by 40 mg doses of propranolol given every six hours and other symptoms by diazepam and/or chlorpromazine as appropriate. Further management should be as clinically indicated or as recommended by the national poison centre, where available.

PHARMACOLOGICAL PROPERTIES

Clinical Pharmacology

Levothyroxine sodium is the monosodium salt of the levorotary isomer of levothyroxine.

Pharmacodynamics

ATC code
Pharmacotherapeutic group - Thyroid hormone ATC code: H03AA01

Levothyroxine (T4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone tri iodothyronine (T3) in peripheral tissues. The precise signals controlling the conversion of T4 to T3 within the cell are not known. The thyroid hormones are required for normal growth and development, particularly of the nervous system. They increase the resting or basal metabolic rate of the whole organism and have stimulatory effects on the heart, skeletal muscle, liver and kidney. Thyroid hormones enhance lipolysis and the utilization of carbohydrate.
100 micrograms levothyroxine is equivalent in activity to 20 to 30 micrograms liothyronine/tri iodothyronine or 60 mg thyroid BP and/or local pharmacopoeia specification.

Pharmacokinetics

Absorption
Following oral administration, the absorption of levothyroxine is incomplete and variable, especially when taken with food. The amount absorbed increases during fasting conditions.

Distribution
Levothyroxine is nearly totally bound to serum protein.

Metabolism
The main pathway for the metabolism of levothyroxine (T4) is its conversion, by de iodination, to the active metabolite tri iodothyronine (T3). Further de-iodination of T4 and T3 leads to production of inactive products.

Elimination
Levothyroxine is eliminated slowly from the body with a half-life of approximately seven days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients.
In man, approximately 20 to 40% of levothyroxine is eliminated in the faeces and approximately 30 to 55% of a dose of levothyroxine is excreted in the urine.

Special Patient Populations:
Renal disease and hepatic disease does not appear to have any significant effect on the disposition of levothyroxine.

PHARMACEUTICAL PARTICULARS

List of Excipients
Microcrystalline cellulose
Pregelatinised starch
Talc
Colloidal anhydrous silica
Magnesium stearate

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Do not store at temperatures exceeding 25°C.
Store in the original container, protected from light.
Keep the container tightly closed.

Instructions for Use/Handling
None.

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