Oroxine

Levothyroxine Sodium

NAME OF THE MEDICINAL PRODUCT
OROXINE Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Tablets containing anhydrous levothyroxine sodium, which is the monosodium salt of the levorotary isomer of thyroxine.

50 or 100 microgram non-scored tablets.

PHARMACEUTICAL FORM

OROXINE Tablets 50mcg: White to off-white, round, bi-convex tablets imprinted GS 11E on one face and 50 on the other.

OROXINE Tablets 100mcg: White to off-white, round, bi-convex tablets imprinted GS 21C on one face and 100 on the other.

CLINICAL PARTICULARS
Therapeutic Indications
Hypothyroidism.

Posology and Method of Administration

Posology

General

If the dose of levothyroxine is increased too rapidly, symptoms such as diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischemia 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 ischemia.

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.
Missed Dosage

If a scheduled daily dose is missed, the dose should be taken as soon as the patient remembers, unless it is almost time for the patient's next dose. Two doses should not be taken together.

Interactions

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

Populations

Adults

Initially 50 to 100 micrograms daily, and adjusted at 4 to 6 week intervals by 50 micrograms until attainment of clinical and biochemical euthyroidism. This may require doses of 100 to 200 micrograms daily.

With patients aged over 50 years, it is not advisable to exceed 50 micrograms a day initially. Where there is cardiac disease, 50 micrograms on alternate days is more suitable. In this condition the daily dosage may be increased by 50 micrograms on alternate days, at intervals of approximately 4 weeks.

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 50 micrograms levothyroxine sodium on alternate days, with increments of 50 micrograms on alternate days at intervals of every 2 to 4 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 micrograms/kg/day. The calculated daily dose equivalent should be rounded to the nearest 25 micrograms to determine the actual prescribed dose.

Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in Pharmaceutical Particulars
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- Untreated adrenal insufficiency
- Thyrotoxicosis
- Acute myocardial infarction, acute myocarditis and acute pancarditis

- During pregnancy, combination of levothyroxine and antithyroid agents for the treatment of hyperthyroidism is contraindicated (See *Fertility, Pregnancy and Lactation*).

Special Warnings and Precautions for Use

Laboratory Monitoring

Levothyroxine has a narrow therapeutic index. Appropriate levothyroxine 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 levothyroxine 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.

If a switch to another levothyroxine-containing product is necessary, close monitoring of laboratory diagnostic and clinical parameters must be performed during the transition period due to the potential risk of thyroid hormone imbalance. A dose adjustment might be required in some patients.

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: 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 levothyroxine 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 levothyroxine sodium in these cases. Adrenocortical dysfunction should be treated with suitable replacement therapy before the start of levothyroxine therapy, in order to avoid acute adrenal insufficiency (See *Contraindications*).

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 thyroxine 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.

Haemodynamic parameters must be monitored when initiating levothyroxine treatment in preterm infants with a very low birth weight, as circulatory collapse due to immature adrenal function may occur.

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 levels.

Interferences with Laboratory Test

Biotin may interfere with immunoassays for assessing thyroid function based on a biotin/streptavidin interaction, thus leading to falsely decreased or falsely increased test results. The risk of interference increases with higher doses of biotin.

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

In patients taking medicines or products containing biotin, the laboratory personnel should be duly informed whenever a thyroid function test is requested. If available, alternative tests not susceptible to biotin interference should be used (See *Interactions with Other Medicinal Products and Other Forms of Interaction*).

Interactions with Other Medicinal Products and Other Forms of Interaction

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), ciprofloxacin and proton pump inhibitors decrease the absorption of levothyroxine. Separate the dosages of levothyroxine and the above-mentioned medicines as much as possible to avoid interaction in the stomach or small bowel.

Proton pump inhibitors (PPIs): Concomitant use with PPIs can lead to a decrease in the absorption of the thyroid hormones, as PPIs cause an increase in pH levels in the stomach.

During concomitant treatment, regular monitoring of thyroid function and clinical monitoring are recommended. It may be necessary to increase the thyroid hormone dose. Caution is also advised when PPI treatment is discontinued.

Hence, the longest possible interval should elapse between taking levothyroxine and any of the above medicinal products, in order to prevent interactions in the stomach and small intestine (See *Posology and Method of Administration*).

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.

Weight loss drug: 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.

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 levothyroxine sodium dose requirements.

Medicinal products with enzyme-inducing properties such as rifampicin increase the metabolism and excretion of thyroxine, which increases levothyroxine requirements.

Effects of cytochrome P450 inducers: Enzyme inducers such as barbiturates and other medicinal products containing St. John's Wort (*Hypericum perforatum L.*) may increase the hepatic clearance of levothyroxine, which may lead to reduced serum concentrations of thyroid hormone.

Therefore, patients receiving thyroid replacement therapy may need an increase in the thyroid hormone dose when these medicinal products are used concomitantly.

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 levothyroxine 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 thyroxine-binding globulin, and therefore increase levothyroxine 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 levothyroxine 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 hypoglycaemia if the insulin or oral antidiabetics dose remains unchanged.

Levothyroxine 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 levothyroxine.

If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.

Levothyroxine 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 ritonavir 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 ritonavir treatment.

Interference with laboratory tests:

Some medicinal products, e.g. androgens and anabolic steroids, can lower the serum concentration of levothyroxine-binding globulin and thus reduce levothyroxine requirements.

Erroneously low plasma levels have been observed with concomitant use of anti-inflammatory agents such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy. The use of acetylsalicylic acid together with levothyroxine initially leads to a transient increase in free T4 serum levels. With continued treatment, levels of free T4 and TSH return to normal and patients subsequently achieve clinical euthyroid status.

Biotin may interfere with immunoassays for assessing thyroid function based on a biotin/streptavidin interaction, thus leading to falsely decreased or falsely increased test results (See *Special Warning and Precautions for Use*).

Fertility, Pregnancy and Lactation

Pregnancy

Levothyroxine 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 foetal outcome or wellbeing.

Breast-feeding

Levothyroxine is excreted in breast milk in low concentrations and this may be sufficient to interfere with neonatal screening for hypothyroidism.

Effects on Ability to Drive and Use Machines

From the pharmacokinetic and pharmacodynamics properties of levothyroxine, treatment with levothyroxine would not be expected to interfere with ability to drive or operate machinery.

Undesirable Effects

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

System Organ Class	Frequency	Side Effects
Cardiac disorders	Not known	Angina pectoris, arrhythmias, palpitations, tachycardia, increased blood pressure, cardiac failure, myocardial infarction
Endocrine disorders	Not known	Hyperthyroidism
Gastrointestinal disorders	Not known	Abdominal pain, nausea, vomiting, diarrhoea
General disorders and administration site conditions	Not known	Fatigue, temperature intolerance, pyrexia
Immune system disorders	Not known	Hypersensitivity reactions such as 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
Investigations	Not known	Bone density decreased
Nervous system disorders	Not known	Headache, tremor, seizure. Rare cases of benign intracranial hypertension have been reported especially in children
Psychiatric disorders	Not known	Anxiety, affect lability, nervousness, agitation, insomnia, restlessness

Reproductive system and breast disorders	Not known	Menstruation irregular, infertility
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis, alopecia, angioedema, rash, urticaria.
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 hyperthyroidism 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 levothyroxine 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

Pharmacodynamic Properties

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

Pharmacotherapeutic group: Thyroid hormone

ATC code: H03AA01

Pharmacodynamic Effects

Thyroxine (T_4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone tri-iodothyronine (T_3) in peripheral tissues. The precise signals controlling the conversion of T_4 to T_3 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.

Pharmacokinetic Properties

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.

Biotransformation

The main pathway for the metabolism of thyroxine (T_4) is its conversion, by de-iodination, to the active metabolite tri-iodothyronine (T_3). Further de-iodination of T_4 and T_3 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 Impairment

Renal disease does not appear to have any significant effect on the disposition of levothyroxine.

Hepatic Impairment

Hepatic disease does not appear to have any significant effect on the disposition of levothyroxine.

Preclinical Safety Data

No additional data of relevance.

PHARMACEUTICAL PARTICULARS

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

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

DISCARD ANY UNUSED TABLETS 3 MONTHS AFTER OPENING.

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.

Nature and Contents of Container

OROXINE Tablets 50mcg and 100mcg are packed into polypropylene bottles with tamper-evident, push-fit, low-density polyethylene closures. Each bottle contains 100 tablets.

Special Precautions for Disposal and Other Handling

None.

Version number of package insert: CCDS16/02/0426
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