Thyrox®

(Levothyroxine sodium)

PRESENTATION

Each white tablet contains 50 micrograms Levothyroxine sodium USP.

INDICATION

Thyrox® is indicated for the management of demonstrated thyroid hormone deficiency.

Thyrox® may be used to suppress Thyrotropin (Thyroid Stimulating Hormone, TSH). For the management of TSH- responsive tumors of the thyroid.

Thyrox® may be used in the management of thyroiditis such as Hashimoto's disease.

DOSAGE AND ADMINISTRATION

Initiation of therapy

Levothyroxine therapy should be initiated at low dosage(e.g. 25 or 50 micrograms/day) and increased at intervals of not less than two weeks, by not more than 50 micrograms increments (see PRECAUTIONS AND WARNINGS).

Maintenance therapy

Adults

100 to 150 micrograms/day

Children

Congenital and acquired hypothyroidism

Note: The lowest dose compatible with clinical euthyroidism and satisfactory laboratory values should be used.

Age	Levothroxine dosage microgram/kg/day
0-6 months	approximately 8
6-12 months	approximately 6
1-5 years	approximately 5
6-12 years	approximately 4
12 years and over	approximately 2

The elderly

75-125 micrograms/day (see PRECAUTIONS AND WARNINGS).

Administration

Levothyroxine can be taken as a single daily dose and is best ingested in the fasting state since food will impair absorption.

CONTRA-INDICATIONS

Known hypersensitivity to 1-throxine, which has been described rarely, is a contraindication to the use of Thyrox®.

PRECAUTIONS AND WARNINGS

Initiation of therapy

In all cases, Thyrox® should be initiated at not more than 50 micrograms/day and gradually increased as described under DOSAGE AND ADMINISTRATION.

Presence of cardiac disorder

Even smaller initial dosage (e.g. 12.5 to 25 micrograms/day) should be used with increments of not more than 25 micrograms/day at not less than two week intervals.

If this routine is not tolerated because of angina, increments should be further reduced with prolongation of the intervals between changes. Use of a beta blocker may help to control angina.

Cortisone deficiency

Corticosteriod replacement therapy must precede initiation of Thyrox® therapy to avoid Addisonian crisis in such conditions as hypopituitarism and adrenal insufficiency.

Monitoring

Because both clinically occult hyper-and hypothyroidism have been described in recipients of Levothroxine replacement therapy, there are grounds for using radioimmunoassay monitoring of T_4, T_3, TSH and response to thyrotropin releasing hormone (TRH). Blood sampling times should be related to time of ingestion. Monitoring may assist management in malabsorption syndromes and the rare cases of tissue resistance.

Monitoring may avoid development of side effects which resemble clinical thyrotoxicosis.

Variability in clinical response

Individual patients vary in response to both the maintenance dose of Thyrox® and to the size and frequency of dose increments. Too large an increment or too high a replacement dose can lead to manifestations of thyrotoxicosis which include:

Cardiovascular:

Tachycardia, cardiac arrhythmias, palpitations, angina, myocardial ischaemia, myocardial infarction, death;

Nervous system:

Anxiety, restlessness, tremors, headache, poor concentration, emotional liability, sleep disturbance, mania, psychosis, psychotic depression, seizures, petit mal, status epilepticus, pseudotumor cerebri (especially in children);

Gastrointestinal system:

Diarrhea, vomiting, malabsorption;

Skin:

Warmth, erythema, telangiectasia, hyperhydrosis, alopecia, hyperpigmentation;

Respiratory system:

Increased minute ventilation, tachypnoea;

Neuromuscular system:

Myopathy, lid lag;

Reproductive system:

Amenorrhoea, decreased libido, gynaecomastia ;

Metabolic:

Fever, glucose intolerance, weight loss, premature craniosynostosis (in children), TRH suppression;

Renal disorder:

There is no evidence that **Thyrox®** dosage should modified in the presence of renal failure. However, thyroid function tests may be influenced and need careful interpretation.

Liver disorders:

In spite of the major involvement of the liver in **Thyrox®** metabolism, there is no evidence that dosage should be modified in the presence of cirrohosis.. However, thyroid function tests may be influenced by the cirrhosis itself and need careful interpretation.

Carcinogenicity

There is epidemiological evidence against the use of thyroid supplements enhancing the risk of breast cancer.

Pregnancy and lactation

There is no evidence that change of dosage is required during pregnancy provided adequate replacement was established before conception. Monitoring of TSH concentrations can give guidance. Levothyroxine binding globulin (TBG) increases during preganancy and therefore total T_4 and T_3 may appear to be elevated. Measurement of free T_4 and T_3 may be more appropriate. There is contradictory evidence concerning the passage of T_4 and T_3 across the placenta but it is unlikely that the fetus is at risk.

There is contradictory evidence concerning the secretion of T_4 and T_3 in human breast milk. However, T_4 and T_3 have been demonstrated in one case.

The neonate should be carefully observed for evidence of altered thyroid function.

ADVERSE REACTION

Pseudotumor cerebri and premature craniosynostosis have been referred to under PRECAUTIONS AND WARNINGS as a possible complication of treatment of children. In both instances reduction of dosage and reappraisal of the maintenance needs are indicated.

Slipped capital femoral epiphysis has also been described associated with high dosage.

Allergy to both levothroxine and triiodothyronine has been described and overcome with use of 3.5 diiodo - 3"isopropylthyronine (DIIP).

Both reversible leucopenia and pancytopenia have been reported.

DRUG INTERACTIONS

Levothyroxine can enhance the clinical effect of the following drugs, thus adjustment of dosage may be necessary:- coumarin anticoagulants, meperidine (pethidine), phenobarbitone, methadone, morphine, catecholamines, insulin, tricyclic antidepressants and dihydrotachysterol.

Levothyroxine can reduce the clinical effect of corticosteroids and digoxin, therefore adjustment of dosage may be necessary.

The clinical effect of Levothyroxine can be enhanced by ketamine.

The clinical effect of Levothyroxine can be reduced by cholestyramine, colistepol and soya flour, all of which interfere with its absorption from the gastro-intestinal tract and by propranolol and dexamethasone.

Thyroid function tests can be modified by barbiturates and phenytoin. There are contradictory reports as to whether the clinical effect of Levothyroxine is reduced.

Thyroid function tests can be modified, without changes in clinical effect of Levothyroxine, by rifampicin, salicylates, diazepam, heparin, fenclofenac, fenoprofen and flurbiprofen.

Monitoring

Of the many techniques applied to estimate optimal thyroid replacement therapy, among the more precise are radioimmunoassay of total and free T_4, T_3 and TSH, with or without TRH stimulus.

Both the resin T_3 uptake (RT_3U) and free Levothyroxine index (FT_4I) may be helpful.

OVERDOSAGE

Symptoms

Within three to six days after ingestion, any or all of the symptoms and signs listed under PRECAUTIONS AND WARNINGS may become evident. They may progress to "thyroid storm" with hyperpyrexia, coma and subsequent death.

Treatment

Early treatment has included gastric lavage, induced emesis and ingestion of activated charcoal.

Induction of hypothermia has been used to reduce hyperpyrexia occurring later on in the clinical course.

Of various adrenergic beta-blockers, propranolol has been used commonly to control cardiac arrhythmia and other manifestations. Reserpine, guanethidine and digoxin have also been used.

Exchange transfusion has been recommended for progressive deterioration.

FURTHER INFORMATION

Pharmacology

Thyrox® is synthetic Levothyroxine sodium which can replace natural Levothyroxine (T_4) the principal hormone in thyroglobulin (Tg) produced by the normal thyroid gland.

It is well but variably absorbed (42-74%) and is bound by Levothyroxine binding globulin (TBG), Levothyroxine binding prealbumin (TBPA) and albumin, with about 0.03 to 0.05% remaining as free T_4. About one third of ingested T_4 is converted to triiodothyronine (T_3) by deiodination in peripheral tissues. T_3 is also protein bound but less avidly than T_4 with about 0.2 to 0.5% remaining in the free state. Circulating T_4, and T_3 levels influence the hypothalamic release of thyrotropin releasing hormone (TRH) which in turn influences the release of thyrotropin or thyroid stimulating hormone (TSH) which directly control activity of the thyroid gland.

T_4 plasma half life is about six to seven days whereas that of T_3 is approximately two days. Conjugation in, and clearance by the liver occurs, with no good evidence of a functional enterohepatic circulation. Both free drug and conjugates are found in urine. Variable absorption and deconjugation in the gastrointestinal tract leads to about 20 to 40% recovery of Levothyroxine from stools. There is controversy about the passage of T_4 and TSH accross the placenta but not about the passage of TRH.

There is controversy about the secretion of T_4 and T_3 in human breast milk, but the presence of both has been demonstrated.

The maximum clinical effect of oral T_4 appears in about nine days with an estimated reduction to half maximum effect in 11 to 15 days.

T_4 either directly or by conversion to T_3 influences protein synthesis and development of the nervous system; has calorigenic effects ;influences the cardiovascular system and influences carbohydrate, fat and cholesterol metabolism.

PHARMACEUTICAL PRECAUTIONS AND RECOMMENDATIONS

Recommendations

Storage: Store below 25^0 C. Keep dry. Protect from light.

Package Quantity: Box of 3x30 tablets in blister strips.

® Trade Mark

Manufactured By:
Renata Limited
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Updated September, 2015
C-Code: 105213897/V01