

New Zealand Data Sheet

EUTROXSIG

Tablets, thyroxine sodium 50 µg, 75 µg, 100 µg or 200 µg

PRESENTATION

50 microgram, white, biconvex, round tablet, scored and marked "50" on one side, plain on the other side in blister packs of 200. The blister packs of 200 tablets are presented as 8 blister strips, each strip containing 25 tablets.

75 microgram, white, biconvex, round tablet, scored and marked "75" on one side, plain on the other side in blister packs of 200. The blister packs of 200 tablets are presented as 10 blister strips, each strip containing 20 tablets.

100 microgram, white, biconvex, round tablet, scored and marked "100" on one side, plain on the other side in blister packs of 200. The blister packs of 200 tablets are presented as 10 blister strips, each strip containing 20 tablets.

200 microgram, white, biconvex, round tablet, scored and marked "200" on one side, plain on the other side in blister packs of 200. The blister packs of 200 tablets are presented as 10 blister strips, each strip containing 20 tablets.

Excipients:

EUTROXSIG tablets contain the following excipients: starch-maize, lactose, dextrin and magnesium stearate.

USES

Actions:

EUTROXSIG is used as thyroid replacement therapy for the treatment of hypothyroidism. The principal pharmacological effect of thyroid hormones is to increase the metabolic rate of body tissues. Thyroid hormones are also involved in the regulation of cell growth and differentiation. Thyroxine is the major component of normal secretions of the thyroid gland; therefore it is the essential determinant of normal thyroid function.

Pharmacokinetics:

Absorption

Thyroxine sodium is variably but adequately absorbed from the gastrointestinal tract following oral administration. Approximately 50 to 75% of thyroxine sodium is absorbed. Studies in humans indicate that thyroxine sodium is absorbed from the jejunum and ileum, and in the duodenum. Fasting will only increase the extent of absorption, whereas malabsorption will only cause a decrease in absorption. Following the initiation of therapy, thyroxine sodium has a slow onset of action as the peak therapeutic effect occurs between 3 to 4 weeks. It also has a long duration of action occurring between 1 to 3 weeks, even following the discontinuance of the drug.

Distribution

Thyroxine sodium apparently undergoes enterohepatic circulation. Once inside the circulation, thyroxine is extensively protein bound, principally to thyroxine-binding globulin (TBG) and also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin. Thyroxine is distributed into most body tissues and fluids with the highest concentration occurring in the liver and kidneys. A minimal amount of thyroxine is distributed into breast milk.

Elimination

Thyroxine sodium has a plasma half-life in euthyroidism of about 6 to 7 days. In hypothyroidism, the half life is prolonged between 9 to 10 days. However, the half-life is reduced between 3 to 4 days in hyperthyroidism. Thyroxine is primarily metabolised in the liver and in the kidney to tri-iodothyronine. Approximately 40% of thyroxine sodium is metabolised to the inactive reverse tri-iodothyronine, which both undergo further deiodination to inactive metabolites. About 85% of the thyroxine sodium metabolised daily is deiodinated. Thyroxine is reported to undergo enterohepatic recycling and is excreted in faeces.

INDICATIONS

EUTROXSIG is indicated for the management of demonstrated thyroid hormone deficiency.

EUTROXSIG is also used to suppress thyrotropin (TSH) for the management of TSH-responsive tumours of the thyroid.

EUTROXSIG has also been used in the management of thyroiditis such as Hashimoto's disease.

DOSAGE AND ADMINISTRATION

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

The dose should be individualised on the basis of clinical response and biochemical tests. Regular monitoring of TSH and thyroxine is recommended when starting therapy or changing the dose.

Thyroxine therapy should normally be initiated with low doses (eg 25 or 50 µg/day). The lower dose is particularly important in the elderly and patients with ischaemic heart disease. In adult patients under 60 years of age, in the absence of ischaemic heart disease, therapy can be commenced with 50 to 100µg/day.

Wherever possible, whole tablets should be taken (eg if the dose required is 150 µg then 1 x 100 µg tablet and 1 x 50 µg tablet should be taken, rather than 1 ½ x 100 µg tablets).

When there is no contraindication to full thyroxine replacement, a TSH level of about 1 mU/L with a serum thyroxine level in the high-normal range, usually indicates optimal therapy.

Maintenance doses

Adults:

100 to 150 µg per day.

Children:

Congenital and acquired hypothyroidism

Age	Thyroxine dose/kg/day
0-6 months	8 µg approximately
6-12 months	6 µg approximately
1-5 years	5 µg approximately
6-12 years	4 µg approximately
12 years and over	2 µg approximately

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

Elderly: 75-125 µg per day.

CONTRAINDICATIONS

Known hypersensitivity to thyroxine, which has been described rarely, is a contraindication.

EUTROXSIG is contraindicated in the following conditions:

- Untreated hyperthyroidism
- Uncorrected adrenal insufficiency
- Thyrotoxicosis
- Acute myocardial infarction uncomplicated by hypothyroidism

WARNINGS AND PRECAUTIONS

Initiation of therapy:

Thyroxine therapy should normally be initiated with low doses (eg 25 or 50 µg/day). In the elderly or patients with ischaemic heart disease, EUTROXSIG should not be initiated at more than 50 µg/day, and dose then be gradually increased. (see DOSAGE & ADMINISTRATION).

Presence of cardiac disorder:

Extreme caution is required in patients with a cardiovascular disorder. In the event of cardiovascular effects, the dosage of EUTROXSIG should be lowered. Even smaller initial dosage (eg 12.5 to 25 µg/day) should be used with increments of not more than 25 µg/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. The use of a β blocker may help to control angina.

Cortisone deficiency:

Corticosteroid replacement therapy must precede initiation of EUTROXSIG 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 thyroxine replacement therapy, there are grounds for using radioimmunoassay monitoring of T₄, T₃, TSH and response to TRH. Blood sampling times should be related to time of ingestion. Pregnancy status should be disclosed. 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 (see **Dosage and Administration**).

Diabetes:

Caution is also required when EUTROXSIG is given to patients with diabetes mellitus or diabetes insipidus, as it may cause the required dosage of insulin and oral antidiabetic agents to be increased. Careful monitoring of diabetic control is recommended, especially when EUTROXSIG therapy is initiated, changed or discontinued. Adjustments in the dosage of these agents should only be made accordingly if necessary.

Renal Disorder:

There is no evidence that EUTROXSIG dosage should be 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 EUTROXSIG metabolism, there is no evidence that dosage should be modified in the presence of cirrhosis. However, thyroid function tests may be influenced and need careful interpretation.

Hyperthyroidism:

Lower doses of EUTROXSIG may be required in patients with a history of hyperthyroidism, as such patients may have residual autonomous thyroid function.

Thyrotoxicosis:

Patients who have thyrotoxicosis who are being treated with anti-thyroid medication, may have increased sensitivity to EUTROXSIG.

Long-standing Hypothyroidism and Myxedema:

Caution is also required for patients with long-standing hypothyroidism or myxedema, as they are more sensitive to thyroid hormones.

Carcinogenicity, Mutagenicity and Impairment to Fertility:

Animal studies to determine the carcinogenic or mutagenic potential of thyroid agents have not been established. However, there is epidemiological evidence against the

use of thyroid supplements enhancing the risk of breast cancer. There is no information available on the possible effects of thyroxine on human fertility.

Use in Pregnancy (Category A):

If overt hypothyroidism is diagnosed during pregnancy, thyroid function test results should be normalised as rapidly as possible. In newly-diagnosed hypothyroidism in pregnancy, thyroxine dosage should be titrated rapidly, for example 1.5–2.0 µg/kg/day may be required for initial replacement. If hypothyroidism has been diagnosed before pregnancy, thyroxine therapy should be optimised before conception and monitored during pregnancy by measurement of serum TSH and thyroxine levels. The thyroxine dose commonly needs incremental adjustments by 4–6 weeks of gestation and may require a 25-40% increase in dosage. It is recommended that those levels should be re-evaluated every 3 to 4 weeks during the first and second trimesters, with thyroxine dosage changes as appropriate. The requirement is likely to decrease post-partum.

Monitoring of TSH concentrations can give guidance. TBG increases during pregnancy and therefore total T₄ and T₃ may appear to be elevated. Measurement of free T₄ and T₃ may be more appropriate. There is contradictory evidence concerning the passage of T₄ and T₃ across the placenta but it is unlikely that the fetus is at risk. Clinical experience does not indicate any adverse effects on the fetus when thyroxine is administered during pregnancy.

Australian categorisation definition of:

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Use in Lactation: There is contradictory evidence concerning the secretion of T₄ and T₃ in human breast milk. However, T₄ and T₃ have been demonstrated in one case. Although minimal amounts of thyroid hormones are distributed in breast milk, thyroid agents should be used with caution in women who are breast-feeding.

Use in Children: Studies performed have not yet demonstrated paediatric-specific problems that would limit the usefulness of thyroid hormones in children. However, neonates should be carefully observed for evidence of altered thyroid functions. This caution is required, as the infant pituitary gland is relatively insensitive to negative feedback effects of thyroid hormones. The parents of children who are receiving the thyroid agent need to be aware that partial loss of hair may occur during the first few months of therapy. However this effect is usually transient and subsequent regrowth usually occurs.

Use in the Elderly:

These patients may be more sensitive to the effects of thyroid hormones. EUTROXSIG should be gradually introduced in the elderly and in those with long-standing hypothyroidism, so that any sudden increases in metabolic demands may be avoided. Individualisation of dosage is recommended and caution is required, as occult cardiac disease may be present.

Risk of Osteoporosis:

Subclinical hyperthyroidism may be associated with bone loss. To minimise the risk of osteoporosis, dosage of levothyroxine should be titrated to the lowest possible effective level.

ADVERSE REACTIONS

Individual patients vary in response to both the maintenance dose of EUTROXSIG 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:

Chest pain, tachycardia, cardiac arrhythmias, palpitations, angina, myocardial ischaemia, myocardial infarction, heart failure, death.

Nervous system:

Irritability, anxiety, nervousness, excitability, restlessness, tremors, headache, poor concentration, emotional lability, sleep disturbance, insomnia, mania, psychosis, psychotic depression, seizures, petit mal status epilepticus, pseudotumour cerebri (especially in children).

Gastrointestinal system:

Diarrhoea, vomiting, malabsorption.

Skin:

Warmth, erythema, telangiectasia, hyperhidrosis, alopecia, hyperpigmentation.

Respiratory system:

Increased minute ventilation, tachypnoea, and shortness of breath.

Neuromuscular system:

Myopathy, lid lag, muscle weakness and cramps.

Reproductive system:

Amenorrhoea, menstrual irregularities, decreased libido, gynaecomastia (in male).

Metabolic:

Fever, glucose intolerance, weight loss, premature craniosynostosis (in children) TRH suppression, heat intolerance, sweating, flushing.

INTERACTIONS

Oral anticoagulants, coumarin or indandione derivative eg. warfarin:

Depending on the thyroid status of the patient, concurrent use of oral anticoagulants with EUTROXSIG will increase the therapeutic effects of oral anticoagulants. Therefore, an increase in the dosage of EUTROXSIG may necessitate a decrease in

the oral anticoagulant dosage. Adjustment of oral anticoagulant dosage is recommended on the basis of prothrombin time. Patients should be observed closely for adverse effects.

SSRIs *eg. sertraline:*

The effects of EUTROXSIG in hypothyroid patients may be decreased by concomitant use of sertraline, therefore resulting in an increase in EUTROXSIG requirements.

Insulin and Antidiabetic agents *eg. sulfonylurea:*

EUTROXSIG may increase the required dosage of insulin and other oral antidiabetic drugs. Therefore, careful monitoring of diabetic control is recommended.

Beta-adrenergic blocking agents *eg. propranolol:*

These agents may decrease the peripheral conversion of thyroxine to triiodothyronine.

Ion-exchange resins *eg. cholestyramine, sodium polystyrene sulphonate or colestipol:*

Due to concurrent use of ion-exchange resins with EUTROXSIG, the effects of EUTROXSIG may be reduced due to the resin binding to EUTROXSIG in the gastrointestinal tract, causing a delay or impairment in EUTROXSIG absorption. An interval of 4 to 5 hours between the administration of the two medications is recommended.

Corticosteroids *eg. prednisolone and dexamethasone:*

The clearance of corticosteroids may be increased in hyperthyroid patients, and decreased in hypothyroid patients, solely due to the administration, changes in dosage and discontinuation of EUTROXSIG. Therefore, corticosteroid dosage may need to be adjusted.

Oestrogen:

In patients with a non-functioning thyroid gland, oestrogen may increase the serum thyroxine-binding globulin, therefore generating an increase in EUTROXSIG requirements.

Antiepileptics *eg. phenytoin, carbamazepine and barbiturates:*

These agents may increase the hepatic degradation of EUTROXSIG, therefore resulting in an increase in EUTROXSIG requirements.

Ritonavir:

Ritonavir may interact with EUTROXSIG, therefore resulting in an increase in EUTROXSIG requirements.

Antimalarials:

The combined use of chloroquine and proguanil may increase the hepatic degradation of EUTROXSIG, therefore resulting in an increase in EUTROXSIG requirements.

Antibacterials *eg. rifampicin and ciprofloxacin:*

Rifampicin may increase the hepatic degradation of EUTROXSIG, therefore resulting in an increase in EUTROXSIG requirements.

Oral ciprofloxacin may decrease the absorption of EUTROXSIG. An interval of 6 hours between the administration of the two medications is recommended.

Androgens:

Androgens may decrease the concentration of the serum thyroxine-binding globulin, therefore generating a decrease in EUTROXSIG requirements.

Ketamine:

Cautious administration of ketamine is recommended in patients on EUTROXSIG therapy, as marked hypertension and tachycardia may occur.

Lithium:

Due to the direct action of lithium on the thyroid gland, inhibition of thyroid hormones may result, leading to clinical hypothyroidism.

Tricyclic antidepressants:

Due to concurrent use with EUTROXSIG, an increase in the sensitivity to catecholamines may occur, therefore increasing the therapeutic and toxic effects of both drugs.

Sympathomimetics:

Due to concurrent use with EUTROXSIG, there may be an increase in the effects of both drugs, which may lead to a risk of coronary insufficiency.

Digoxin:

Thyroxine may reduce the clinical effects of digoxin.

Amiodarone:

Amiodarone may decrease the peripheral conversion of thyroxine to triiodothyronine. Therefore, concurrent use of amiodarone with EUTROXSIG may cause a decrease in the effects of EUTROXSIG.

In addition:

Thyroxine can enhance the clinical effects of *pentobarbitone* and *dihydrotachysterol*. Therefore, the adjustment of dosage may be necessary.

The clinical effect of thyroxine can be reduced by soya flour, sucralfate, aluminium hydroxide, magnesium hydroxide, calcium carbonate, and ferrous sulphate - which interfere with absorption from the gastrointestinal tract.

Thyroid function tests can be modified, without changes in clinical effect of thyroxine, by some NSAIDs, salicylates, *diazepam*, *heparin* and *fenclofenac*.

OVERDOSAGE

Within three to six days after ingestion any or all of the symptoms and signs listed under **Precautions** and **Adverse Reactions** may become evident. They may progress to “thyroid storm”, with hyperpyrexia, convulsions, heart failure, coma and subsequent death.

Treatment of overdose:

Early treatment has included gastric lavage, induced emesis and ingestion of activated charcoal. Oxygen may need to be administered and ventilation may need to be maintained. Treatment is usually symptomatic and supportive. Measures to control fever, hypoglycemia or fluid loss should be initiated as necessary. Of various adrenergic β 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.

When overdose does occur, there must be an extended follow-up period as symptoms may be delayed for several days due to the gradual peripheral conversion of thyroxine to tri-iodothyronine.

PHARMACEUTICAL PRECAUTIONS

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Laboratory tests have shown that if not stored correctly, there is a reduction in potency of the active ingredient *thyroxine sodium*.

Blister packs:

A single blister strip can be removed from the carton and stored below 25°C for up to 21 days (3 weeks). After 21 days (3 weeks) of storage below 25 °C, discard any remaining tablets. Where unavoidable (i.e. in warm climates where temperatures regularly exceed 25 °C), a used blister strip (i.e. a blister strip that is being used) of EUTROXSIG tablets may be stored at 2°C to 8°C (Refrigerate. Do not freeze) for up to 21 days (3 weeks).

EUTROXSIG tablets can also be stored in Webster packs for up to 21 days (3 weeks) below 25°C.

Do not store Eutroxsig, or any other medicines in a bathroom or near a sink.

Do not leave it in the car or on windowsills.
Heat and dampness can destroy some medicines.

Keep the medicine where children cannot reach it.

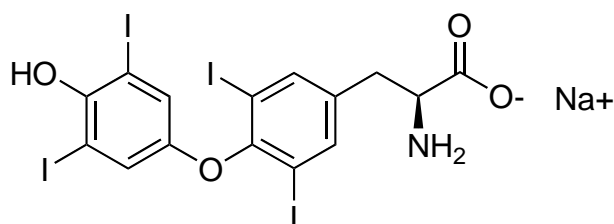
Do not take Eutroxsig tablets if the tablet's colour has changed.

MEDICINE CLASSIFICATION

Prescription Only Medicine

FURTHER INFORMATION

Thyroxine sodium also known as levothyroxine sodium, is a monosodium salt of the *levo* isomer of thyroxine, the principal secretion of the thyroid gland. Thyroxine sodium (CAS-55-03-8) has the following chemical structure:



It has the molecular formula C₁₅H₁₀I₄NNaO₄ and a molecular weight of 798.86.

Thyroxine sodium is almost white to pale brownish-yellow, odourless, tasteless, hygroscopic, amorphous or crystalline powder. On exposure to light, it may acquire a slight pink colour. It is very slightly soluble in water and alcohol, however is insoluble in acetone, chloroform and ether. It dissolves in aqueous solutions of alkali hydroxides and in hot solutions of alkali carbonates.

NAME AND ADDRESS OF SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland, New Zealand

Telephone (09) 9185 100
Fax: (09) 9185 101

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