NEW ZEALAND DATA SHEET

Eltroxin® Tablets

(***Levothyroxine Tablets 50 mcg, 100 mcg)***

PRESENTATION

Tablets containing 50 micrograms (0.05 mg) or 100 micrograms (0.1 mg) anhydrous levothyroxine sodium, which is the monosodium salt of the levorotary isomer of thyroxine.

Eltroxin 50 microgram (0.05 mg) tablets are white to off-white, round, biconvex tablets, imprinted with GS 11E on one face and 50 on the other.

Eltroxin 100 microgram (0.1 mg) tablets are white to off-white, round, biconvex tablets, imprinted with GS 21C on one face and 100 on the other.

USES

Pharmacodynamic Properties

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

Levothyroxine (T4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone triiodothyronine (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 mcg levothyroxine is equivalent in activity to 20 to 30 mcg liothyronine/triiodothyronine or 60 mg Thyroid BP and/or local pharmacopoeia specification.

Pharmacokinetic Properties

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

Levothyroxine is nearly totally bound to serum protein.

Metabolism and Elimination
The main pathway for the metabolism of levothyroxine (T4) is its conversion, by deiodination, to the active metabolite triiodothyronine (T3). Further deiodination of T4 and T3 leads to production of inactive products.

Levothyroxine is eliminated slowly from the body with a half-life of approximately 7 days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients.

Renal or hepatic disease do not appear to have any significant effect on the disposition of levothyroxine.

In man approximately 20-40% of levothyroxine is eliminated in the faeces and approximately 30-55% of a dose of levothyroxine is excreted in the urine.

INDICATIONS

Levothyroxine is indicated for the treatment of hypothyroidism.

DOSAGE AND ADMINISTRATION

If the dose of thyroxine 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.

Eltroxin tablets should be swallowed whole, and taken with a full glass of water. Eltroxin tablets should not be split.

Thyroxine 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.

Use in Adults

Initially 50 to 100 micrograms daily and adjusted at four or six 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 25 micrograms, given as 50 micrograms on alternate days, is more suitable. In this condition the daily dosage may be slowly increased by 25 micrograms increments (given as 50 micrograms on alternate days) at intervals of perhaps four weeks. This dosing regimen is illustrated in Table 1 below;

DAILY DOSE	DOSING REGIMEN
25 microgram	One 50 microgram tablet on alternate days
50 microgram	One 50 microgram tablet daily
75 microgram	One 50 microgram tablet daily and one 50 microgram tablet on alternate days
100 microgram	One 100 microgram tablet daily
125 microgram	One 100 microgram tablet daily and one 50 microgram tablet on alternate days

Use in 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 micrograms levothyroxine sodium given as 50 micrograms every other day is advisable. This may be slowly increased by increments of 25 micrograms (given as 50 micrograms on alternate days) every two to four weeks until optimal response is achieved. This dosing regimen is illustrated in Table 1 above. 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 any component of the preparation. Thyrotoxicosis.

WARNINGS AND PRECAUTIONS

Thyroxine has a narrow therapeutic index. Appropriate thyroxine 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 thyroxine dosage are the same as many features of endogenous thyrotoxicosis.

Treatment with thyroxine 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.

Special care is needed in the elderly and in patients with symptoms of myocardial insufficiency or ECG evidence of myocardial infarction or ischaemia and also those with diabetes mellitus or insipidus.

Levothyroxine raises blood sugar levels and this may upset the stability of patients receiving antidiabetic agents.

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

Parents of children receiving levothyroxine 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.

Use during Pregnancy and Lactation

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 fetal outcome or well-being.

Lactation

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.

ADVERSE 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.

Immune system disorders:	Hypersensitivity reactions such as skin rash and pruritis
Metabolism and nutrition disorders:	Increased appetite, abdominal cramps, nausea, vomiting and diarrhoea
Nervous system disorders:	Excitability, insomnia, restlessness, headache, tremors, seizure, psychotic depression, rare cases of pseudotumor cerebri (benign intracranial hypertension) have been reported especially in children.
Cardiac disorders:	Anginal pain, cardiac arrhythmias, palpitations, tachycardia, increased blood pressure, heart failure, myocardial infarction
Respiratory, thoracic and mediastinal disorders:	Dysponea
Skin and subcutaneous tissue disorders:	Sweating, flushing, hair loss
Musculoskeletal, connective tissue and bone disorders :	Cramps in the skeletal muscle, muscular weakness, decreased bone mineral density. Excessive dose may result in craniosynostosis in infants, and premature closure of epiphyses in children with compromised adult height.
Reproductive system and breast disorders:	Menstrual irregularity, impaired fertility
General disorders and administration site conditions:	Fatigue, heat intolerance, fever, excessive loss of weight

INTERACTIONS

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.

Anticonvulsants such as carbamezapine 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.

If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside

may be necessary.

The effects of sympathomimetic agents are also enhanced.

Levothyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants.

Cholestyramine given concurrently reduces the gastrointestinal absorption of levothyroxine.

A number of other drugs may decrease absorption of thyroxine sodium, and therefore increase thyroxine dosage requirements including antacids (eg. aluminium hydroxide), bile acid segestrants (eg. colestipol), cation exchange resins (eg. kayexalate), sucralfate, calcium carbonate and ferrum sulphate.

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 thyroxine dosage requirements.

Reports indicate that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase thyroid hormone requirements in patients receiving thyroxine therapy. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate thyroxine dose adjustments may be necessary when thyroxine and statins are co-prescribed.

A number of drugs may decrease serum concentration of thyroxine-binding globulin, and therefore decrease thyroxine dosage requirements, including androgens and anabolic steroids.

Treatment with imatinib was associated with increased thyroxine dosage requirements in hypothyroid patients.

Treatment with amiodarone has been associated with multiple effects on thyroid function including increased thyroxine dosage requirements in hypothyroid patients.

A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on levothyroxine sodium therapy.

OVERDOSE

Symptoms and Signs

In addition to exaggeration of side effects the following symptoms may 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.

Treatment

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

Treatment is symptomatic, and tachycardia has been controlled in adults by 40mg doses of propranolol given every 6 hr and other symptoms by diazepam and/or chlorpromazine as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Pharmaceutical Precautions

Shelf life:

24 months

Storage conditions:

Store below 25 °C. Protect from light.

MEDICINES SCHEDULE

Prescription Only Medicine

PACKAGE QUANTITIES

50 mcg tablets in a polypropylene bottle fitted with a tamper evident, push-fit, white opaque low-density polyethylene (LDPE) closure containing 1000 tablets.

100 mcg tablets in a polypropylene bottle fitted with a tamper evident, push-fit, white opaque low-density polyethylene (LDPE) closure containing 1000 tablets.

FURTHER INFORMATION

100 mcg levothyroxine is equivalent in activity to 20 to 30 mcg liothyronine or 60 mg thyroid BP.

Excipients

Microcrystalline cellulose, Pregelatinised maize starch, Talc, Colloidal anhydrous silica, Magnesium stearate.

SPONSOR DETAILS

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DATE OF PREPARATION

9 October 2008
Date of most recent amendment: 31 July 2014