For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

THYOBUILD
(Levothyroxine Sodium 25, 50, 75, 100mcg tablets)

COMPOSITION

THYOBUILD 25

Each uncoated tablet contains:
Thyroxine Sodium I.P. equivalent to anhydrous Thyroxine Sodium ……25mcg
(Synthetic Thyroid Hormone)
Excipients…… q.s.
Colour: Sunset Yellow FCF

THYOBUILD 50

Each uncoated tablet contains:
Thyroxine Sodium I.P. equivalent to anhydrous Thyroxine Sodium ……50mcg
(Synthetic Thyroid Hormone)
Excipients…… q.s.
Colour: Sunset Yellow FCF

THYOBUILD 75

Each uncoated tablet contains:
Thyroxine Sodium I.P. equivalent to anhydrous Thyroxine Sodium ……75mcg
(Synthetic Thyroid Hormone)
Excipients…… q.s.
Colour: Brilliant Blue FCF

THYOBUILD 100

Each uncoated tablet contains:
Thyroxine Sodium I.P. equivalent to anhydrous Thyroxine Sodium …….....100mcg
(Synthetic Thyroid Hormone)
Excipients…… q.s.
Colour: Quinolline Yellow WS

INDICATIONS

Recommended clinical indications: Control of hypothyroidism, congenital hypothyroidism and juvenile myxoedema.

DOSAGES AND ADMINISTRATION

Adults:

Initially 50 to 100 micrograms daily, preferably taken before breakfast. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained: this may require doses of 100 to 200 micrograms daily.

For patients over 50 years, it is not advisable to exceed 50 micrograms daily initially and where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable initially. In this condition the daily dose may be increased by 25 micrograms at intervals of perhaps 4 weeks. For patients younger than 50 years, and in the absence of heart disease, a serum Levothyroxine (T4) level of 70 to 160 nanomols per litre, or a serum thyrotropin level of less than 5 mili-units per litre should be targeted. For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather than serum levels.

A pre-therapy ECG is valuable because ECG changes due to hypothyroidism may be confused with ECG evidence of cardiac ischaemia. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors, and sometimes anginal pain where there is latent cardiac ischaemia), dosage must be reduced, or withheld, for a day or two, and then re-started at a lower dose level.

Elderly:

As for patients aged over 50 years. Paediatric patients the maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Infants should be given the total daily dose at least half an hour before the first meal of the day.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients.

- Thyrotoxicosis
- Adrenal gland disorder or adrenal insufficiency

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Levothyroxine should be introduced very gradually in patients aged over 50 years and those with long standing hypothyroidism to avoid any sudden increase in metabolic demands.

Patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may react to levothyroxine treatment, and it is advisable to start corticosteroid therapy before giving levothyroxine to such patients.

Levothyroxine sodium should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, hypertension, and in the elderly who have a greater likelihood of occult cardiac disease.

To minimise the risk of adverse effects of undetected overtreatment, such as atrial fibrillation and fractures associated with low serum levels of thyroid stimulating hormone (TSH) in older patients, it is important to monitor serum TSH and adjust the dose accordingly during long term use

In individuals suspected to have cardiovascular disease or to be at high risk, it is important to perform an ECG prior to commencement of levothyroxine treatment in order to detect changes consistent with ischaemia in which case, levothyroxine should be initiated at a low dose, followed by cautious dose escalation to avoid worsening of ischaemia or precipitation of an infarct

Thyroid replacement therapy may cause an increase in dosage requirements of insulin or other anti-diabetic therapy (such as metformin). Care is needed for patients with diabetes mellitus, and diabetes insipidus.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Parents of children receiving thyroid agent 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.

DRUG INTERACTION

Interactions affecting other drugs:

Levothyroxine increases the effect of anticoagulants (Warfarin) and it may be necessary to reduce the anticoagulation dosage if excessive, hypoprothrombinaemia and bleeding are to be avoided.

Blood sugar levels are raised and dosage of anti-diabetic agents may require adjustment.

Tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) response may be accelerated because levothyroxine increases sensitivity to catecholamines; concomitant use may precipitate cardiac arrhythmias.

The effects of sympathomimetic agents (e.g. adrenaline or phenylephrine) are also enhanced

If levothyroxine therapy is initiated in digitalised patients, the dose of digitalis may require adjustment. Hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin.

False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.

Beta Blockers: levothyroxine (thyroxine) accelerates metabolism of propranolol, atenolol and sotalol.

Isolated reports of marked hypertension and tachycardia have been reported with concurrent ketamine administration.

Interactions affecting Levothyroxine:

Amiodarone may inhibit the de iodination of thyroxine to tri iodothyronine resulting in a decreased concentration of tri iodothyronine, thereby reducing the effects of thyroid hormones.

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 dosage requirements.

Effects of Levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine (thyroxine) possibly reduced by antacids, proton pump inhibitors, calcium salts, cimetidine, oral iron, sucralfate, colestipol, polystyrene sulphonate resin and cholestyramine (administration should be separated by 4-5 hours).

Metabolism of levothyroxine (thyroxine) accelerated by rifampicin, barbiturates, and primidone. (may increase requirements for levothyroxine (thyroxine) in hypothyroidism)

Imatinib: plasma concentration of levothyroxine (thyroxine) possibly reduced by imatinib.

Beta blockers may decrease the peripheral conversion of levothyroxine to triiodothyronine. Oestrogen, oestrogen containing product (including hormone replacement therapy) and oral contraceptives may increase the requirement of thyroid therapy dosage. Conversely, androgens and corticosteroids may decrease serum concentrations of Levothyroxine-binding globulins.

Anti-obesity drugs such as orlistat may decrease levothyroxine absorption which may result in hypothyroidism (monitor for changes in thyroid function).

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of Levothyroxine treatment during pregnancy is not known, but any possible risk of foetal abnormalities should be weighed against the risk to the foetus of untreated hypothyroidism.

Breast-feeding

Levothyroxine is excreted in breast milk in low concentrations, and it is contentious whether this can interfere with neonatal screening.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Levothyroxine has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Side-effects are usually indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days.

Adverse reactions listed below have been observed during clinical studies and/or during marketed use and are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention:

Not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Immune system disorders	Not known	Hypersensitivity reaction,
Endocrine disorders	Not known	Thyrotoxic crisis[1]
Psychiatric disorders	Not known	Restlessness, agitation, insomnia
Nervous system disorders	Not known	Tremor,
Cardiac disorders	Not known	Angina pectoris, arrhythmia, palpitations, tachycardia
Vascular disorders	Not known	Flushing,
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Gastrointestinal disorders	Not known	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis, rash, pruritus
Musculoskeletal and connective tissue disorder	Not known	Arthralgia, muscle spasm, muscular weakness,
Reproductive system disorders	Not known	Menstruation irregular

General disorders and administration site conditions	Not known	Headache, pyrexia, malaise, oedema
Investigations	Not known	Weight decreased

[1]Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a "thyroid crisis" with any of the following symptoms: Hyperpyrexia, tachycardia, arrhythmia, hypotension, cardiac failure, jaundice, confusion, seizure and coma

Paediatric population

Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children.

OVERDOSE

Symptoms

In most cases there will be no features. Signs of an overdose may include: fever, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea, tremor, insomnia and hyperpyrexia. These signs can take up to 5 days to appear. Atrial fibrillation may develop. Convulsions occurred in one child. There may be increased toxicity in those with pre-existing heart disease.

Management:

Give oral activated charcoal if more than 10mg has been ingested by an adult or more than 5mg by a child, within 1 hour. If more than 10mg has been ingested by an adult or more than 5mg by a child, take blood 6-12 hours after ingestion for measurement of the free thyroxine concentration. The analysis does not need to be done urgently but can wait until the first working day after the incident. Patients with normal free thyroxine concentrations do not require follow up. Those with high concentrations should have outpatient review 3-6 days after ingestion to detect delayed onset hyperthyroidism. Features of clinical hyperthyroidism should be controlled with beta-blockers, e.g. propranolol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC Code: H03AA01

Thyobuild is a tablet containing the hydrated form of Levothyroxine sodium which is used for the treatment of hypothyroidism. The Thyroid gland is dependent upon 2 active principles for its main hormone activity. These are Levothyroxine (Tetra-iodothyronine) and Tri-iodothyronine (see Goodman and Gilman, 1985). These closely related iodine

containing amino acids are incorporated into the glycoprotein thyroglobulin. The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is de-iodinated in peripheral tissues to form Tri-iodothyronine which is thought to be active tissue form of thyroid hormone. Tri-iodothyronine is certainly more rapid acting and has shorter duration of action than Levothyroxine.

Pharmacokinetic properties

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. It is almost completely bound to plasma proteins and has a half-life in the circulation of about a week in healthy subjects, but longer during pregnancy in patients with myxoedema. A large portion of the Levothyroxine leaving the circulation is taken up by the liver. Part of a dose of Levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine as free drug, de-iodinated metabolites and conjugates. Some Levothyroxine is excreted in the faeces. There is limited placental transfer of Levothyroxine.

Preclinical safety data

No further data of relevance.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store below 25℃. Protect from sunlight and moisture. Keep out of reach of children.

PRESENTATION
THYOBUILD 25 is available as bottle of 100 tablets
THYOBUILD 50 is available as bottle of 100 tablets
THYOBUILD 75 is available as bottle of 100 tablets
THYOBUILD 100 is available as bottle of 100 tablets

MARKETED BY
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IN/THYOBUILD 25,50,75,100 mg/AUG-17/02/PI