SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine 25 micrograms/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains 25 micrograms of levothyroxine sodium.

Excipients with known effect:

Each 5 ml of oral solution contains 10 mg sodium methyl parahydroxybenzoate, 1.10 mg sodium propyl parahydroxybenzoate, 100 mg propylene glycol and 3394.54 mg maltitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear, colourless solution

4.1 Therapeutic indications

Levothyroxine Oral Solution is indicated in adults and children 5 years of age and above for:

- Control of hypothyroidism
- Congenital hypothyroidism
- Acquired hypothyroidism in children and juvenile myxoedema.

4.2 Posology and method of administration

Posology

In younger patients, and in the absence of heart disease, a serum Levothyroxine (T4) level of 70 to 160 nanomoles per litre, or a serum thyrotrophin level of less than 5 milli-units per litre should be targeted. A pretherapy 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.

Adults
Patients under 50 years age:
Initially 100 micrograms daily, preferably taken before breakfast or the first meal of the day. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained.
The final daily dose may be up to 100 to 200 micrograms.
Patients over 50 years age:

a) *Without cardiac disease*: Initially, it is not advisable to exceed 50 micrograms daily. In this condition, the daily dose may be increased by 50 micrograms at intervals of every 3-4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

b) *With cardiac disease*: Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In this conditions, the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather that serum levels.

Elderly
Same as that for patients aged over 50 years.

Paediatric population
The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated. Regular monitoring using serum TSH levels, as in adults, is required to make sure he/she gets the right dose. Infants should be given the total daily dose at least half an hour before the first meal of the day.

Acquired hypothyroidism in children over 5 years of age:
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.

Juvenile myxoedema in children over 5 years of age:
The initial recommended dosage is 25 micrograms daily. In such conditions, the daily dose may be increased by 25 micrograms at intervals of every 2 – 4 weeks, until mild symptoms of hyperthyroidism is seen. The dose will then be reduced slightly.

Children under 5 years
Levothyroxine 25 micrograms/5 ml oral solution is not suitable for children under five years of age due to the presence of propylene glycol in the formulation in an amount that exceeds recommended daily limits in this age group if prescribed in accordance with the recommended posology (see section 4.4). Alternative formulations of levothyroxine oral solution exist that do not contain propylene glycol.

Method of administration
For oral administration

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Thyrotoxicosis
- Adrenal gland disorder or adrenal insufficiency.
- Treatment with Levothyroxine Oral Solution must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.
- Combination therapy of levothyroxine and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Levothyroxine should be introduced very gradually in patients aged over 50 years (see section 4.2) 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.
Special care is needed for the elderly and for patients with symptoms of myocardial insufficiency, or ECG evidence of myocardial infarction.

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.
See note above regarding withdrawal of treatment.

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.

Care is required when levothyroxine is administered to patients with known history of epilepsy. Seizures have been reported rarely in association with the initiation of

levothyroxine sodium therapy and may be related to the effect of thyroid hormone on seizure threshold.

Haemodynamic parameters should be monitored when levothyroxine therapy is initiated in very low birth weight preterm neonates as circulatory collapse may occur due to the immature adrenal function.

A small number of patients report adverse events on changing between different levothyroxine products. In some cases, symptoms are reported despite thyroid function tests within the reference range. If patients report side effects on switching between products, consider thyroid function testing. For patients who are persistently symptomatic after switching, whether they are
biochemically euthyroid or have evidence of abnormal thyroid function, consider consistently prescribing a specific levothyroxine product that is well tolerated by the patient. If symptoms or poor control of thyroid function persist despite adhering to a specific product, prescription of levothyroxine in an oral solution formulation should be considered.

Thyroid hormones should not be given for weight reduction. In euthyroid patients, treatment with levothyroxine does not cause weight reduction. Substantial doses may cause serious or even life-threatening undesirable effects, particularly in combination with certain substances for weight reduction, and especially with sympathomimetic amines.

Interferences with laboratory test:

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

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

For patients taking biotin-containing products, laboratory personnel should be informed when a thyroid function test is requested. Alternative tests not susceptible to biotin interference should be used, if available, (see section 4.5)

Excipient Warnings:
Sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217): May cause allergic reactions (possibly delayed).

Propylene glycol (E1520): This medicinal product contains 100 mg propylene glycol in each 5 ml of oral solution, which is equivalent to 20 mg/ ml. Young children under the age of five years, and neonates in particular, possess immature elimination pathways involving alcohol dehydrogenase metabolism, and reduced renal clearance also, which are required for safe elimination of propylene glycol. Current recommendations are that children under five years of age should be exposed to propylene glycol at no more than 50 mg/kg/day and even lower at 1 mg/kg/day in the neonatal population. This formulation contains propylene glycol in amounts that lead to exposure exceeding currently recommended limits, if prescribed in accordance with the recommended posology for treatment of hypothyroidism in this age group.

Liquid maltitol (E965): Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml of dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of 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

Cardiac glycosides: 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.
NSAIDs: 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.

General anaesthetics: 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 triiodothyronine resulting in a decreased concentration of tri iodothyronine, thereby reducing the effects of thyroid hormones.

Anti-convulsants, such as carbamazepine and phenytoin, enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anti-convulsant therapy may alter levothyroxine dosage requirements.

Effects of Levothyroxine may be decreased by concomitant sertraline.

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

Proton pump inhibitors (PPIs):

Co-administration with PPIs may cause a decrease in the absorption of the thyroid hormones, due to the increase of the intragastric pH caused by PPIs.
Regular monitoring of thyroid function and clinical monitoring is recommended during concomitant treatment. It may be necessary to increase the dose of thyroid hormones. Care should also be taken when treatment with PPI ends.

Metabolism of levothyroxine (thyroxine) is accelerated by rifampicin, barbiturates, products containing St John's Wort (Hypericum perforatum L.) and primidone. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these products are given concurrently.

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

Beta blockers may decrease the peripheral conversion of levothyroxine to triiodothyronine.

Lipid regulating drugs: Lovastatin has been reported to cause one case each of hypothyroidism and hyperthyroidism in two patients taking levothyroxine.

Sex Hormones: 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.

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.

Interferences with laboratory test:
Biotin may interfere with thyroid immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see section 4.4).

4.6 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.

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy. Such combination would require higher doses of antithyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

Breast-feeding
Levothyroxine is excreted in breast milk in low concentrations, and it is contentious whether this can interfere with neonatal screening.
Fertility
No data available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following side effects are usually due to excessive dosage, and correspond to symptoms of hyperthyroidism. 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. These reactions usually disappear after dose reduction or withdrawal of treatment.

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, alopecia, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones
ATC code: H03AA01

The thyroid gland is dependent upon 2 active principles for its main hormone activity these are Levothyroxine (tetraiodothyronine) 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 deiodinated in peripheral tissues to form Tri-iodothyronine which is thought to be the active tissue form of thyroid hormone.

Pharmacodynamic effects Tri-iodothyronine is certainly more rapid acting and has a shorter duration of action than Levothyroxine. The chief action of Levothyroxine is to increase the rate of cell metabolism

5.2 Pharmacokinetic properties

Absorption
Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract.

Distribution

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.

Biotransformation

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.

Elimination
Levothyroxine is excreted in the urine as free drug, deiodinated metabolites and conjugates. Some Levothyroxine is excreted in the faeces. There is limited placental transfer of Levothyroxine.

5.3 Preclinical safety data

Not applicable since Levothyroxine has been used in clinical practice for many years and its effects in man are well known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)

Sodium hydroxide (E524)

Sodium methyl parahydroxybenzoate (E219)

Sodium propyl parahydroxybenzoate (E217)

Maltitol liquid (E965)

Citric acid monohydrate (E330)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months
Discard 60 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottles: Type III amber glass bottle

Closure: Tamper evident, child resistant white plastic cap with polypropylene inner, polyethylene outer and expanded polyethylene (EPE) liner

Dosing device: 5 ml oral syringe with 0.1 ml graduation mark and a syringe adaptor

Pack size: 100 ml

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 39307/0092

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2021

10 DATE OF REVISION OF THE TEXT

01/05/2025