

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine 50 micrograms/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains 50micrograms levothyroxine sodium.

Excipients with known effect:

Sodium methyl parahydroxybenzoate 10.3 mg/5ml

Sodium propyl parahydroxybenzoate 1.12 mg/5ml

Propylene glycol 100 mg/5ml

Maltitol 3,350 mg/5ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hypothyroidism (congenital or acquired)
- Diffuse non toxic goitre
- Goitre associated with Hashimoto's thyroiditis
- Suppression therapy in thyroid carcinoma

Levothyroxine 50 micrograms/5ml oral solution in this formulation is not suitable for children under the age of five years due to the excipient content (see section 4.4). Alternative formulations of levothyroxine 50 micrograms/5ml oral solution exist, with a different excipient content, that are more suitable for the paediatric population under five years of age.

4.2 Posology and method of administration

Posology

The treatment of any thyroid disorder should be determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring.

The individual daily dose should be determined on the basis of laboratory tests and clinical examinations. As a number of patients show elevated concentrations of T4 and fT4, basal serum concentration of thyroid-stimulating hormone provides a more reliable basis for following treatment course.

Patients switching from the oral solution to the tablet form or from the tablet form to the oral solution should be monitored closely.

Levothyroxine is best taken as a single dose on an empty stomach, usually before breakfast.

Hypothyroidism (congenital or acquired)

Adults, children over 12 years

Initial dose:	50 - 100 micrograms daily before breakfast.
Usual maintenance dose:	100 - 200 micrograms daily.

The initial dose is adjusted by 25 to 50 microgram increments at 3 – 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose established.

Diffuse non toxic goitre or goitre associated with Hashimoto's thyroiditis

The recommended dose is 50-200 micrograms/day.

Suppression therapy in thyroid carcinoma

The recommended dose is 150-300 micrograms/day.

Use in special populations

In elderly patients, in patients with coronary heart disease, and in patients with severe or long-existing hypothyroidism, special caution is required when initiating therapy with thyroid hormones, that is, a low initial dose (for example 12.5 microgram/day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 microgram/day fortnightly) with frequent monitoring of thyroid hormones. A dosage, lower than optimal dosage giving complete replacement therapy, consequentially not resulting in a complete correction of TSH level, might therefore need to be considered.

Paediatric population (5 – 12 years)

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.

Levothyroxine 25 micrograms/5ml; 50 micrograms/5ml; 100 micrograms/5ml oral solution is not suitable for children under five years of age due to the presence of propylene glycol as an excipient in amounts that would lead to exposure in excess of recommended daily limits for propylene glycol exposure 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. Duration of treatment is usually for life in the case of hypothyroidism, non-toxic goitre and goitre associated with Hashimoto's thyroiditis.

For patients with non-toxic diffuse goitre and normal T4 and TSH levels treatment with levothyroxine can be considered. If no discernible decrease in size of the goitre occurs after 6 to 12 month, thyroxine therapy should be stopped.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In patients with adrenal insufficiency without adequate corticosteroid cover.
- 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

Thyroid treatments should be used with caution in patients with cardiovascular disorders, including myocardial insufficiency and hypertension.

Thyroid replacement therapy should be introduced gradually in elderly patients, and those with severe long standing hypothyroidism. Special care is needed when there are symptoms of myocardial insufficiency or ECG evidence of myocardial infarction and for similar reasons the treatment of hypothyroidism in the elderly should be initiated cautiously.

Patients with adrenal insufficiency may react unfavourably to levothyroxine treatment so it is advisable to initiate corticosteroid therapy before giving levothyroxine.

Caution should also be exercised when administering levothyroxine to diabetics or patients on glycosides.

Sub-clinical 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 a 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 re-growth usually occurs.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases. In the case of secondary hypothyroidism the cause must be determined before replacement therapy is given and if necessary replacement treatment of a compensated adrenal insufficiency must be commenced.

Where thyroid autonomy is suspected a TRH test should be carried out or a suppression scintigram obtained before treatment.

Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9).

A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. If too rapid an increase of metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

Excipient warnings

- Parahydroxybenzoates. These may cause allergic reactions (possibly delayed).
- Propylene glycol. This medicine contains 100mg propylene glycol in each 5ml of oral solution, which is equivalent to 20mg/ml.
- Maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 1mg/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.

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.

4.5 Interaction with other medicinal products and other forms of interactions

The absorption of levothyroxine is reduced by sucralfate, sodium polystyrene sulphonate or colestyramine binding within the gut.

- Cimetidine, aluminium hydroxide, calcium carbonate and ferrous sulphate also reduce absorption of levothyroxine from the G.I. tract. Dosages should be separated by an interval of several hours.
- The concurrent use of carbamazepine, phenytoin, phenobarbital, primadone or rifampicin with levothyroxine have been found to increase levothyroxine metabolism.
- Effects of levothyroxine may be decreased by concomitant sertraline. Some drugs such as lithium act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.
- Increased thyroid-stimulating hormone concentration has been noted after the use of chloroquine with proguanil for malaria prophylaxis in a patient stabilised on levothyroxine.
- Protease inhibitors (e.g. ritonavir, indinavir, lopinavir) may influence the effect of levothyroxine. Close monitoring of thyroid hormone parameters is recommended. If necessary, the levothyroxine dose has to be adjusted.
- Sevelamer may decrease levothyroxine absorption. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine dose has to be adjusted.

- Tyrosine kinase inhibitors (e.g. imatinib, sunitinib) may decrease the efficacy of levothyroxine. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine dose has to be adjusted.
- Enzyme inducing medicinal products such as barbiturates or carbamazepine can increase hepatic clearance of levothyroxine.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.
- Soy-containing compounds can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of Levothyroxine Oral Solution may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.
- Oestrogen, oestrogen containing products and oral contraceptives may increase the requirement of thyroid therapy dosage.
- Conversely, androgens and corticosteroids may decrease serum concentrations of thyroxine-binding globulins.
- The effects of warfarin, dicoumarol, acenocoumarol, phenindione and probably other anticoagulants are increased by the concurrent use of thyroid compounds.
- The antidepressant response to imipramine, amitriptyline and possibly other tricyclic antidepressants can be accelerated by the concurrent use of levothyroxine.
- A possible interaction occurs with hypoglycaemic agents, hence diabetic patients should be monitored for increased requirements of insulin or oral hypoglycaemic agents.
- If levothyroxine therapy is initiated in digitalised patients, the dose of digoxin may require adjustment, hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds, because initially patients are relatively sensitive to digoxin.
- Isolated reports of marked hypertension and tachycardia has been reported with concurrent ketamine administration.
- Lovastatin has been reported to cause one case each of hypothyroidism and hyperthyroidism in two patients taking levothyroxine. False low total plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.
- Levothyroxine accelerates the metabolism of propranolol.
- False low total plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.
- Thyroid drugs increase metabolic demands and should therefore be used with caution with other drugs known to influence cardiac function, such as the sympathomimetics, as they may enhance this effect. In addition, thyroid hormones may increase receptor sensitivity to catecholamines.
- Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone and iodine containing contrast media: These substances inhibit the peripheral conversion of T4 to T3. Due to its high iodine content amiodarone can trigger hyperthyroidism as well as hypothyroidism. Particular caution is advised in the case of nodular goitre with possibly unrecognized autonomy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Women on a maintenance dose for hypothyroidism who become pregnant, must be monitored closely. Levothyroxine sodium does not readily cross the placenta in the second and third trimester, but may do so in the first.

Levothyroxine sodium is not known to have either carcinogenic or tetragenic effects.

Treatment with levothyroxine should be given consistently during pregnancy and breast-feeding in particular. Dosage requirements may even increase during pregnancy.

Experience has shown that there is no evidence of drug-induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose level.

Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on foetal and postnatal development.

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

Thyroid suppression diagnostic tests should not be carried out during pregnancy, as the application of radioactive substances in pregnant women is contraindicated.

Breast-feeding

Levothyroxine is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant. Levothyroxine can be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, since levothyroxine is identical to the naturally occurring thyroid hormone, it is not expected that Levothyroxine Oral Solution has any 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:

- arrhythmias, anginal pain, tachycardia, disorders of menstruation, pseudotumor cerebri, cramps in skeletal muscles, headache, restlessness, excitability, flushing, sweating, diarrhoea, excessive weight loss and muscular weakness, insomnia, tremor, fever, vomiting, palpitations and heat intolerance.

These reactions usually disappear after dose reduction or withdrawal of treatment.

Hypersensitivity reactions including rash, pruritus and oedema have also been reported.

Thyroid crisis has occasionally been reported following massive or chronic intoxication and cardiac arrhythmias, heart failure, coma and death have occurred.

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 HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

An elevated T3 value is a more reliable indicator of overdose than elevated T4 or fT4 values.

In the event of an overdose, symptoms displaying a marked increase in metabolic activity occur (see section 4.8). Depending on the extent of the overdose, it is recommended that the patient stops taking the product and undergoes a check-up.

Symptoms may manifest themselves as marked beta-adrenergic effects, such as tachycardia, anxiety states, agitation and hyperkinesia. The symptoms may be reduced by beta-receptor blockers. At extreme doses, plasmapheresis may be useful.

Following overdose in humans (with suicidal intent) doses of 10 mg levothyroxine were tolerated without complications.

There are some reports of sudden cardiac death in patients who have misused levothyroxine over many years.

Management

Overdosage following recent ingestion can be treated using gastric lavage/emesis. Propranolol and other supportive measures are used to maintain the circulation. Antithyroid drugs such as propylthiouracil and lithium are unlikely to be of benefit to prevent thyrotoxic crisis due to delayed absorption/onset of action.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Thyroid hormones

ATC Code: H03AA01

Thyroxine (T4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T3) in the peripheral tissues. Receptors for T3 are found on cell membranes, mitochondria and cell nuclei. Thyroid hormones are required for normal growth and development of the body, especially the nervous system. They increase the basal metabolic rate of the whole body and have stimulatory effects on the heart, skeletal muscle, liver and kidney.

The synthetic levothyroxine contained in Levothyroxine Oral Solution is identical in effect with the naturally occurring thyroxine secreted by the thyroid.

5.2 Pharmacokinetic properties

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. Levothyroxine is extensively metabolised in the thyroid, liver, kidney and anterior pituitary. Some enterohepatic re-circulation occurs. Part of the levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine and faeces, partly as free drug and partly as conjugates and de-iodinated metabolites.

It has a half life of 7 days but this may be shortened or prolonged depending on the disease condition. Levothyroxine is almost completely bound to plasma protein, mainly thyroxine binding globulin, with approx. 0.03% of levothyroxine unbound. The unbound levothyroxine is converted to triiodothyronine.

There are four main pathways of metabolism:

- 1) Deiodination to triiodothyronine (active) - T3 or to reverse triiodothyronine (inactive). Further deiodination of T3 leads to the formation of thyroacetic acid.
- 2) Deamination to the tetrone.
- 3) Conjugation to the glucuronide or sulphate.
- 4) Ether bond cleavage to diiodotyrosines.

The most important metabolic pathway is deiodination. Between 30 - 55% of the levothyroxine dose is excreted in the urine and 20 - 40% in the faeces.

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

Citric acid monohydrate
Sodium methyl parahydroxybenzoate
Sodium propyl parahydroxybenzoate
Propylene glycol
Maltitol, Liquid
Sodium Hydroxide
Hydrochloric Acid

Sodium Hydroxide
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months
After opening: three months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The finished product is packed in either 100ml and 150ml conventional amber soda glass (Type III) bottles fitted with 28mm child resistant tamper evident caps.

A 5ml oral dosing pipette is provided. A pipette adaptor will be fitted to the bottle neck in order to allow the dosing device to be used.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/044/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2016

10 DATE OF REVISION OF THE TEXT

June 2020