

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine 25 micrograms/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Levothyroxine 25 micrograms/5ml Oral Solution contains 5 micrograms levothyroxine sodium.

Each 5 ml of Levothyroxine 25 micrograms/5ml contains 25 micrograms levothyroxine sodium.

Excipients with known effect:

Sodium methyl parahydroxybenzoate (E219): 14.58 mg per 5 ml dose.

Sodium propyl parahydroxybenzoate (E217): 2.915 mg per 5 ml dose

Glycerol (E422): 3,780 mg per 5 ml dose.

This medicinal product contains 0.945 mmol (or 21.7 mg) sodium per 5 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

A clear, colourless to pale yellow liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levothyroxine Oral Solution is indicated for:

- i) hypothyroidism (congenital or acquired)
- ii) diffuse non toxic goitre
- iii) goitre associated with Hashimoto's thyroiditis
- iv) Suppression therapy in thyroid carcinoma

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 T_4 and fT_4 , 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.

Susceptible patient 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 micrograms/day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 micrograms/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

The maintenance dose is generally 100 to 150 micrograms per m² 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.

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.

Method of administration

For oral use only.

No studies have been undertaken into mixing this drug product with food or drink as it is intended that the product is dispensed directly from the pipette into the mouth.

Your doctor, pharmacist or nurse will show you how to administer this medicine. The box containing this medicine will contain a 10 ml graduated dosing pipette and a dosing adaptor.



10 ml pipette, each numbered section is 1 ml and the smaller increments are 0.25 ml

Levothyroxine 25 micrograms/5ml Oral Solution: 1 ml is equivalent to 5 micrograms and 0.25 ml is equivalent to 1.25 micrograms

Instructions are provided below for using the dosing pipette. If you have any questions about the dose you should use or how to use the pipette, you should ask your doctor or pharmacist.

Instructions for use:

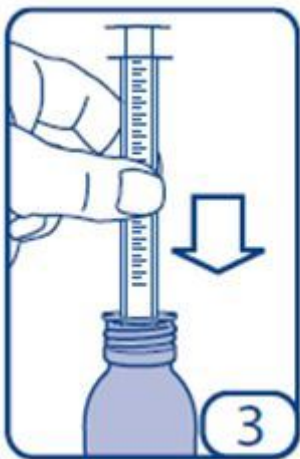
- Open the bottle: press the cap and turn it anticlockwise (figure 1)



- On using the bottle for the first time, the pipette adaptor must be fitted. It will then stay in place for future doses. Holding the bottle, take the plastic pipette adaptor from the box and insert the adaptor into the bottle neck (figure 2). Ensure it is well fixed.



- Take the pipette and put it in the adaptor opening (figure 3).



- Hold the pipette in place and turn the bottle upside down. Fill the pipette with a small amount of the suspension by pulling the piston down (figure 4), then push the piston up in order to remove any possible air.
- Still holding the pipette in place, pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (figure 4).



- Turn the bottle the right way up. Remove the pipette from the adaptor (figure 5).



- Administer the contents of the pipette into the mouth by pushing the piston to the bottom of the pipette and ensure the medicine is swallowed.

Do not remove the adaptor from the bottle neck, it is intended to stay in place. Close the bottle with the plastic screw cap.

Wash the pipette with warm water. Dry it with a clean paper towel and replace into the box with your medicine.

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.

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.

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).

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.

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.

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.

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.

This medicinal product contains:

- Parahydroxybenzoates. These may cause allergic reactions (possibly delayed).
- Glycerol – This may cause headache, stomach upset and diarrhoea.
- Sodium – contains 21.7 mg sodium per 5 ml, equivalent to 1.1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. The maximum daily dose of 300 micrograms of levothyroxine (60 ml of product) contains 260.4 mg of sodium which is the equivalent of 13.0 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. Levothyroxine Oral Solution is available in three strengths 25 micrograms/5 ml, 50 micrograms/5 ml and 100 micrograms/5 ml; caution is advised in ensuring that the correct strength is given to the patient. The doctor should prescribe the most appropriate strength based upon the clinical requirements of the patient (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interactions

Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone and iodine containing contrast media:

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These substances inhibit the peripheral conversion of T_4 to T_3 .

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.

- 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

Soy-containing compounds:

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.

Enzyme inducing medicinal products:

Enzyme inducing medicinal products such as barbiturates or carbamazepine can increase hepatic clearance of levothyroxine.

- 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
- 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.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.
- 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.
- False low total plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.
- Anti-obesity drugs such as orlistat may decrease levothyroxine absorption which may result in hypothyroidism (monitor for changes in thyroid function).
- 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.

Protease inhibitors

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

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

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.

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Interactions affecting other medications

- 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.
- A possible interaction occurs with hypoglycaemic agents, hence diabetic patients should be monitored for increased requirements of insulin or oral hypoglycaemic agents.
- 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.
- Levothyroxine accelerates the metabolism of propranolol.
- Isolated reports of marked hypertension and tachycardia has been reported with concurrent ketamine administration.
- 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.

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 teratogenic 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 fetotoxicity in humans at the recommended therapeutic dose level. Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on fetal 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.

Breastfeeding

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.

Fertility

There are no fertility data available.

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. Adverse reactions listed below have been observed during 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 reactions including rash, pruritus and oedema
Endocrine disorders	Not known	Thyrotoxic crisis ¹
Psychiatric disorders	Not known	Restlessness, agitation, insomnia
Nervous system disorders	Not known	Tremor, headache
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	Pyrexia, malaise, oedema
Investigations	Not known	Weight decreased

¹ Thyroid crisis have occasionally been reported following massive or chronic intoxication and cardiac arrhythmias, heart failure, coma and death have occurred.

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 HPRa Pharmacovigilance

Website: www.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.

Monitoring

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 (T_4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T_3) in the peripheral tissues.

Receptors for T_3 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) - T_3 or to reverse triiodothyronine (inactive). Further deiodination of T_3 leads to the formation of thyroacetic acid.
- 2) Deamination to the tetrone.
- 3) Conjugation to the glucoronide 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

Glycerol (E422)
Purified water
Citric acid monohydrate (E330)
Sodium hydroxide (E524)
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 15 months

After first opening: 28 days

Store in the original package in order to protect from light.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

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

6.5 Nature and contents of container

Amber glass bottle containing 100 ml, closed with a tamper evident, child resistant screw cap with polyethylene liner.

The bottle is supplied with a CE-marked 10 ml dosing pipette (with 0.25 ml graduations), and a separate 'bung' adaptor which is fitted to the neck of the bottle at first use (i.e. after opening), to ensure proper use of the pipette.

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

JensonR+ (Ireland) Limited
104 Lower Baggot Street
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2282/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2018

10 DATE OF REVISION OF THE TEXT

April 2021