

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 50 micrograms Levothyroxine sodium.

Excipients with known effect:

Sodium methyl hydroxybenzoate (E219): 9mg per 5ml dose.

Glycerol: 3,780mg per 5ml dose.

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

Levothyroxine is indicated for hypothyroidism (congenital or acquired), diffuse nontoxic goitre, goitre associated with Hashimoto's thyroiditis, suppression therapy in thyroid carcinoma.

4.2 Posology and method of administration

Adults

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..

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.

Duration of treatment is usually for life in the case of hypothyroidism.

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.

Diffuse nontoxic goitre or goitre associated with Hashimoto's thyroiditis

The recommended dose is 50-200 µg/day.

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.

Duration of treatment is usually for life in the case of nontoxic goitre and goitre associated with Hashimoto's thyroiditis.

Suppression therapy in thyroid carcinoma

The recommended dose is 150-300 µg/day.

Adults and Elderly

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.

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, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Levothyroxine 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, pituitary or adrenocortical insufficiency and elderly patients.

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.

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.

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).

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 angular pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

This product contains:

Parahydroxybenzoates
delayed).

These may cause allergic reactions (possibly

Glycerol
diarrhea.

This may cause headache, stomach upset and

4.5 Interaction with other medicinal products and other forms of interaction

The effects of warfarin, dicoumarol, acenocoumarol, phenindione and probably other anticoagulants are increased by the concurrent use of thyroid compounds.

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.

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.

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.

Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.

The antidepressant response to imipramine, amitriptyline and possibly other tricyclic antidepressants can be accelerated by the concurrent use of levothyroxine.

Effects of levothyroxine may be decreased by concomitant sertraline.

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

Some drugs such as lithium act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.

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

Colesevelam: In an interaction study in healthy volunteers, colesevelam reduced the AUC and C_{max} of levothyroxine when administered either concomitantly or after one hour. No interaction was observed when colesevelam was administered at least four hours after levothyroxine.

Cimetidine, aluminium-containing medicines, iron-containing medicines, calcium-containing medicines also reduce absorption of levothyroxine from the G.I. tract. Drugs containing levothyroxine should therefore be administered at least 2 hours prior to the administration of these drugs.

Dosages should be separated by an interval of several hours.

The concurrent use of carbamazepine, phenytoin, phenobarbital, primidone or rifampicin with levothyroxine have been found to increase levothyroxine metabolism.

A possible interaction occurs with hypoglycaemic agents, hence diabetic patients should be monitored for increased requirements of insulin or oral hypoglycaemic agents.

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.

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.

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.

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.

In a crossover interaction study in healthy volunteers, co-administration of 40 mg omeprazole delayed release with 600 µg of levothyroxine oral solution simultaneously or staggered (12 hours between) reduced levothyroxine absorption (C_{max} and AUC_{0-2h}) by less than 10% without affecting total exposure 48 hours post-dosing (AUC_{0-48h}). While this does not suggest a clinically relevant interaction between oral solution of levothyroxine and PPIs, due to the large inter-individual variability in levothyroxine response, an interaction may be present in individual cases.

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.

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.

Enzyme inducing medicinal products:

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

Effects of drugs inducing cytochrome P-450: Enzyme-inducing drugs such as products containing St John's Wort (*Hypericum perforatum* L.) may increase hepatic clearance of levothyroxine, resulting in reduced serum concentrations of thyroid hormone.

Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these products are given concurrently.

Soy-containing compounds:

Soy-containing compounds can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of Levothyroxine may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

Orlistat:

Hypothyroidism and / or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of levothyroxine(see section 4.4).

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

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 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.

Lactation

Levothyroxine is secreted in 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 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 (see section 4.9):

Arrhythmias, angina pectoris, tachycardia, muscles spasms, headache, menstrual disorder, idiopathic intracranial hypertension, restlessness, excitability, flushing, circulatory collapse in low birth weight preterm neonates (see section 4.4), 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, oedema and angioedema have also been reported.

The worsening of cardiopathy (cardiac failure, angina pectoris, arrhythmia) has also been reported. Further, in children, there is a possibility of hypercalciuria occurring.

Thyroid crisis have 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 authorization 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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Acute intoxications are generally of moderate severity in the absence of cardiac history, including during accidental ingestions in children. In symptomatic cases, clinical effects may occur within a few hours or be delayed by a few days in the case of a single dose and may include one or more signs of thyrotoxicosis (see below).

In the event of an overdose, symptoms displaying a marked increase in metabolic activity occur (see section 4.8). In case of repeated doses of suprathreshold doses, the following signs of hyperthyroidism have been observed and in the most severe cases define a state of thyrotoxicosis:

- Digestive disorders: vomiting, abdominal pain, diarrhea, increased appetite, slimming.
- Cardiovascular disorders: tachycardia, atrial fibrillation arrhythmia or extrasystoles, hypertension, chest pain, angina, congestive heart failure, cardiogenic collapse.
- General disorders: fever, redness of the skin, sweating.
- Neurological disorders: irritability, insomnia, headache, agitation, confusion, mydriasis, convulsions in predisposed patients, disturbances of consciousness, coma, acute psychosis.

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.

In case of excessive doses, especially at the time of initiation of treatment, rare cases of seizures have been reported in epileptic patients.

Depending on the extent of the overdose, it is recommended that the patient stops taking the product and undergoes a check-up.

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

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 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 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

Citric acid, Monohydrate

Sodium Methyl Parahydroxybenzoate (E219)

Sodium Hydroxide (for pH-adjustment)

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before opening: 24 months

After opening: 8 weeks

6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light

6.5 Nature and contents of container

Bottles: Amber (Type III) glass bottles

Closures: Tamper evident, child resistant cap(s)

Pack size(s): 75ml, 100ml and 2 x 75 ml

One 5ml oral medication syringe with 0.1ml graduation and the corresponding neck fitted syringe adaptor for the bottle.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
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Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/2543

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