SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levothyroxine 50 microgram Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 microgram of Levothyroxine Sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round biconvex tablets with scoreline on one side and marking 50 on the other side of the tablet.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Recommended clinical indications: Control of hypothyroidism, congenital hypothyroidism in infants, 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 nanomols per litre, or a serum thyrotrophin level of less than 5 milli-units per litre should be targeted. 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.

Adults

Patients under 50 years of age:

Initially 50 to 100 micrograms daily, preferably taken on an empty stomach, at least 30 minutes and preferably 1 hour before food, ideally taken before breakfast or your 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. The dose may need to be increased during pregnancy.

Patients aged over 50 years:
For patients over 50 years, 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.

Patients over 50 years with cardiac disease:
Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In this condition, the daily dose may be increased by 25 microgram increments 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 than 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 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.

Congenital hypothyroidism in infants:
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.

Acquired hypothyroidism in children:
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.

Juvenile myxoedema in children:

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 are seen. The dose will then be reduced slightly.

Method of administration
For oral administration.

In children under 5 years of age, the administration of whole tablets is not recommended. It is also not recommended that levothyroxine tablets are crushed and dispersed in water or other liquids, owing to limited solubility which could lead to dosing inaccuracy. In this age group it is preferable to administer an approved oral solution of levothyroxine.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
In addition Levothyroxine is contra-indicated in:

- thyrotoxicosis
- adrenal gland disorder or untreated adrenal insufficiency
- treatment with this medicinal product must not be initiated in acute myocardial infarction, acute myocarditis and acute pancarditis
- combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in 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 pectoris, arteriosclerosis, coronary artery disease, hypertension, symptoms or ECG evidence of myocardial infarction and in older people who have a greater likelihood of occult cardiac disorders. A patient with prolonged myxoedema should be restored to normality only gradually.

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.

In case of adrenocortical dysfunction, this should be treated before starting the therapy with levothyroxine by adequate replacement treatment to prevent acute adrenal insufficiency (See section 4.3).

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).

Paediatric population
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 subsequently regrowth usually occurs.

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23mg) per tablet, 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.

Treatment with Levothyroxine may result in an increase in dosage requirements of insulin or oral hypoglycaemic agents.

As levothyroxine increases receptor sensitivity to catecholamines, the response to tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) may also be accelerated; concomitant use may precipitate cardiac arrhythmias.

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

Cardiac glycosides: The toxicity of digitalis is enhanced by levothyroxine, therefore, in digitalised patients the dose of digitalis may need adjusting (gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin) if levothyroxine therapy is required.

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 triiodothyronine, 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).
<u>Proton pump inhibitors (PPIs):</u>
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, barbituarates, 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.

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

Interactions affecting levothyroxine:

Amiodarone and propranolol may inhibit the de-iodination of levothyroxine to triiodothyronine resulting in a decreased concentration of triiodothyronine, therefore reducing the effects of thyroid hormones.

Metabolism of thyroid hormones may be enhanced by anticonvulsants such as phenytoin and carbamazepine. The levothyroxine dose may need adjustment after initiating or terminating anticonvulsant therapy which may also displace them from plasma proteins.

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.

Effects of levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine 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).

Barbiturates, primidone and enzyme inducing drugs such as rifampicin enhance thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones (may increase requirements for levothyroxine (thyroxine) in hypothyroidism).

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

An increased dosage of levothyroxine may be required when co-administered with oral contraceptives, Oestrogen, oestrogen containing product (including hormone replacement therapy). Conversely, androgens and corticosteroids may decrease serum concentrations of levothyroxine-binding globulins.

Thyroid function tests may be affected by a number of drugs. This should be taken into account when monitoring a patient's response to levothyroxine therapy.

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

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

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.

Orlistat

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

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 during pregnancy has not been established. Any possible risk of congenital abnormalities should be assessed against the possible consequences 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 anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

Breast-feeding
Levothyroxine is excreted into breast milk in low concentrations and screening for congenital hypothyroidism might be affected.

Fertility
No data available.

4.7. Effects on ability to drive and use machines

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

4.8. 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	Undesirable effects
Immune system disorders	hypersensitivity reactions, allergic reactions of the skin and respiratory tract may occur
Metabolism and Nutrition disorders	increased appetite
Psychiatric disorders	agitation, restlessness, insomnia
Nervous system disorders	tremor, headache, idiopathic intracranial hypertension in children.
Cardiac disorders	angina pectoris, arrhythmia, palpitations, tachycardia, myocardial infarction, cardiac failure
Vascular disorders	flushing, hypertension, cases of circulatory collapse in very low birth weight preterm neonates (see section "Special warnings and precautions for use").
Respiratory, thoracic and mediastinal disorders	dyspnoea
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea
Skin and subcutaneous tissue disorders	angiodema, rash, urticaria, pruritus, hyperhidrosis, alopecia, transient alopecia in children
Musculoskeletal and Connective tissue disorders	arthralgia, muscle spasms, muscular weakness, craniosynostosis in infants, epiphyses premature fusion
Reproductive system and breast disorders	menstruation irregular
General disorders and administration site conditions	headache, pyrexia, malaise, oedema, temperature intolerance
Investigations	weight decreased

Paediatric population

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

Symptoms may not appear until several days after the administration of levothyroxine. All these reactions usually disappear on reduction of the dosage or temporary withdrawal of treatment.

Cardiac disease may be exacerbated by the administration of thyroid hormones resulting in severe angina pectoris, myocardial infarction or sudden cardiac death.

Gross over dosage has been reported to result in a clinical state resembling thyroid storm, and in collapse and coma.

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

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 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. Symptoms of over dosage include exaggeration of its side-effects, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, diarrhoea, tremor, insomnia and hyperpyrexia, agitation, confusion, hyperactivity, irritability, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements. Convulsions occurred in one child. The appearance of clinical hyperthyroidism may be delayed for up to five days. Atrial fibrillation may develop. There may be increased toxicity in those with pre-existing heart disease.

Treatment:

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. Further treatment is symptomatic. Tachycardia has been controlled in an adult by administering beta-blockers (e.g. propranolol) every six hours and other symptoms by diazepam and chlorpromazine as appropriate. Features of clinical hyperthyroidism should be controlled with beta-blockers, e.g. propranolol.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: H03A A01 (Thyroid preparations, thyroid hormones).

Levothyroxine sodium is used for the treatment of hypothyroidism. Levothyroxine is deiodinated in peripheral tissues to form triiodothyronine which is thought to be the active tissue form of thyroid hormone. Triiodothyronine has a rapid action but a shorter duration of activity 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 gastro-intestinal tract. Absorption of orally administered levothyroxine from the gastrointestinal tract ranges from 40% to 80%. The majority of the dose is absorbed from the jejunum and upper ileum. Levothyroxine absorption is increased by fasting, decreased in malabsorption syndrome, by certain foods and decreases also with age.

Distribution
Levothyroxine is almost completely bound to plasma-proteins and has a half-life in the circulation of about a week in healthy persons but longer in patients with myxoedema.

Biotransformation
The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating L-triiodothyronine is derived from peripheral levothyroxine by monodeiodination. The liver is the major site of degradation for both levothyroxine and L-triiodothyronine, with levothyroxine deiodination also occurring at a number of additional sites, including the kidney and other tissues. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination
Levothyroxine is primarily eliminated by the kidneys 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

There are no preclinical data of relevance to the prescriber, which are additional to that already described. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The tablet contains maize starch, mannitol (E421), microcrystalline cellulose, sodium citrate, acacia and magnesium stearate.

6.2. Incompatibilities

None known.

6.3. Shelf life

Blisters packs: 18 months.

6.4. Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

PVC/PE/PVDC/PE/PVC//Al blister strips in packs of 28, 56 and 112 tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/0038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/03/2009

10. DATE OF REVISION OF THE TEXT

09/09/2024