Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine Sodium 25 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 micrograms levothyroxine sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.
6.0 mm, white to off white, round, '25' inscription on one side and deep bisect on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of euthyroid goitre, especially in adults, if iodine is not indicated.
- Recurrent prophylaxis after goitre resection, depending on postoperative hormone status.
- Substitution with hypothyroidism.
- Suppression treatment in thyroid carcinoma.
- Substitution during concomitant treatment with thyreostatic agents in hyperthyroidism.

4.2 Posology and method of administration

Posology

In order to treat each patient according to their individual need, tablets are available with a levothyroxine sodium content ranging from 25 to 100 microgram.

The doses listed below are guidelines.

The individual daily dose should be determined by laboratory tests and clinical investigations.

Because a number of patients exhibit an increased concentration of T_4 and free T_4, the basal thyroid stimulating hormone (TSH) serum concentration is a more reliable basis for treatment.

Thyroid hormone therapy should be started at a low dose and gradually increased every 2 to 4 weeks until the full replacement dose is reached.

Paediatric population
For neonates and young children suffering from congenital hypothyroidism where rapid substitution is important, the recommended starting dose - 10 to 15 microgram per kg body weight per day - should be given for the first 3 months. Afterwards, the dosage must be adjusted per individual, related to the clinical outcomes, thyroid hormone and the TSH level.

Elderly
In elderly patients, in patients with cardiac disorders and in patients with severe or long-standing hypothyroidism, particular caution is required when initiating thyroid hormone therapy. This means
that a low starting dose (for example 12.5 microgram/day) should be given, which is slowly increased with long intervals (for example a gradual increase of 12.5 microgram every 2 weeks). Thyroid hormones should be monitored regularly. Therefore, a lower than the optimal dosage that provides complete replacement should be considered, resulting in an incomplete correction of the TSH level.

Experience has shown that a lower dose is sufficient in patients with low weight and in patients with a large nodular goitre.

Indication	**Recommended dose (microgram levothyroxine sodium/day)**			
Treatment of euthyroid goitre	75 – 200			
Recurrent prophylaxis after goitre resection	75 – 200			
Substitution in hypothyroidism in adults - starting dose - maintenance dose	25 – 50 100 – 200			
Substitution in children with acquired hypothyroidism - starting dose - maintenance dose	12.5 – 50 100 – 150 microgram/m2 body surface area			
Substitution during concomitant treatment with thyreostatic agents in hyperthyroidism	50 – 100			
Suppression treatment in thyroid cancer	150 – 300			
Suppression treatment in thyroid cancer	Week 4 before the test	Week 3 before the test	Week 2 before the test	Week 1 before the test
Levothyroxine sodium 100 microgram	---	---	2 tab/day	2 tab/day

Method of administration

The daily doses can be given in a single administration.

Intake: one daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with some liquid (for example half a glass of water).

Children receive the entire dose in one go, at least half an hour before the first meal of the day. The tablets should be dissolved in some water and the formed suspension, which should be prepared at the time it is needed, should be taken with more liquid.

The duration of treatment is generally life-long in the event of substitution in hypothyroidism, post- strumectomy or thyroidectomy and upon recurrent prophylaxis after goitre resection.

Concomitant treatment of hyperthyroidism after euthyroidism has been reached is indicated during the period of thyreostatic administration.

Benign euthyroid goitre requires a treatment duration of 6 months to 2 years. To prevent a recurrent goitre, prophylaxis with a low dose of iodine (100 - 200 microgram/day) is recommended after the goitre size has decreased. If the medical treatment during this period proves insufficient, surgery or treatment with radioactive iodine should be considered.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Untreated adrenal insufficiency, untreated pituitary insufficiency and untreated thyrotoxicosis.
- The treatment with levothyroxine should not be started with acute myocardial infarction, acute myocarditis and acute pancarditis.
- Combination therapy of levothyroxine with a thyreostatic agent is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Before starting treatment with thyroid hormones or before performing a thyroid suppression test, the following disorders should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, hypophyseal insufficiency (hypopituitarism), adrenal insufficiency, autonomic thyroid gland functioning. In case of adrenocortical dysfunction, this must be treated before treatment with levothyroxine is initiated by adequate replacement therapy to prevent acute adrenal insufficiency (see section 4.3).

At the start of levothyroxine treatment in patients at risk of psychotic disorders, it is recommended to start with a low dose of levothyroxine and to gradually increase the dose at the start of the treatment. It is recommended to monitor the patient. In the event of symptoms of psychotic disorders, adjustment of the dosage of levothyroxine should be considered.

Even mild hyperthyroidism caused by drugs should be avoided in patients with coronary insufficiency, cardiac insufficiency or tachycardia arrhythmias. Therefore, in this case, regular checks of thyroid hormone parameters should be performed.

In the case of secondary hypothyroidism, the cause should be determined before replacement therapy is given and, if necessary, replacement therapy of compensated adrenal insufficiency should be initiated.

If an autonomously functioning thyroid gland is suspected, a thyreotropin 'releasing' hormone (TRH) test or a suppression scintigram should be performed before treatment.

Haemodynamic parameters should be monitored when levothyroxine therapy is initiated in preterm neonates with a very low birth weight, as circulatory collapse due to an underdeveloped adrenal function may occur.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, serum supraphysiological levothyroxine levels should be avoided, therefore thyroid function should be closely monitored.

Levothyroxine should not be given in any other hyperthyroid state, except for concomitant addition during thyrostatics treatment of hyperthyroidism.

Thyroid hormones should not be given for weight loss. In euthyroid patients, treatment with levothyroxine does not cause weight loss. High doses can cause serious or even life-threatening side effects. Levothyroxine at high doses should not be combined with certain weight loss substances, such as sympathomimetics (see section 4.9).

If a switch to another levothyroxine-containing product is required, close monitoring, including clinical and biological monitoring, is necessary during the transition period due to a potential risk of thyroid imbalance. A dose adjustment may therefore be required in some patients.

Hypothyroidism and/or impaired control of hypothyroidism may occur with concomitant administration of orlistat and levothyroxine (see section 4.5). Patients taking levothyroxine should be advised to consult their physician before initiating, stopping, or adjusting treatment with orlistat because orlistat and levothyroxine may need to be taken at different times and levothyroxine dosing may need to be adjusted. Furthermore, it is recommended to monitor the patient by checking hormonal serum levels.

For diabetic patients and patients receiving anticoagulant therapy, see section 4.5.

Interference with laboratory tests:
Biotin can interfere with thyroid immunoassays based on a biotin/streptavidin interaction, leading to erroneously reduced or erroneously increased test results. The risk of interference increases with higher doses of biotin.
Potential biotin interference should be considered when interpreting laboratory test results, particularly when a lack of correlation with clinical presentation is observed.
If patients are taking drugs containing biotin, the laboratory staff should be informed when a thyroid function test is requested.
If available, alternative tests that are not sensitive to biotin interference should be used (see section 4.5).

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, meaning it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Antidiabetic agents:
Levothyroxine may reduce the effect of drugs that lower blood sugar levels. For this reason, blood glucose levels should be monitored regularly at the start of thyroid hormone therapy and, if necessary,
the dosage of the antidiabetic agent should be adjusted.

Coumarin derivatives:
The effect of anticoagulation therapy may be potentiated as levothyroxine displaces anticoagulants from the plasma protein, which may increase the risk of bleeding, e.g., in CNS or gastrointestinal

bleeding, especially in elderly patients. Therefore, it is necessary to regularly monitor blood clotting parameters at the start of and during concomitant treatment. If necessary, the dosage of the anticoagulant should be adjusted.

Protease inhibitors:
Protease inhibitors (e.g., ritonavir, indinavir, lopinavir) may impact the effect of levothyroxine. Accurate monitoring of thyroid hormone levels is recommended. If necessary, the dose of levothyroxine will have to be adjusted.

Phenytoin:
Phenytoin can impact the effect of levothyroxine by displacing levothyroxine from plasma proteins, resulting in an increase in free T_3 and free T_4 fractions. On the other hand, phenytoin increases the liver metabolism of levothyroxine. Therefore, careful monitoring of thyroid hormone parameters is recommended.

Bileacid binding sequestrants:
Bile acid binding sequestrants (e.g., cholestyramine or cholestipol) inhibit the absorption of levothyroxine sodium. Therefore, levothyroxine sodium should be taken 4 to 5 hours before administration of these types of agents.

Aluminium, iron and calcium salts:
Aluminium-containing agents (antacids, sucralphate) have been reported in relevant literature to potentially reduce the effect of levothyroxine. Levothyroxine-containing agents should therefore be taken at least 2 hours before administration of aluminium-containing agents.
The same applies to medicinal products that contain iron and calcium salts.

Salicylates, dicoumarol, furosemide, clofibrate:
Salicylates, dicoumarol, furosemide at high doses (250 mg), clofibrate and other substances may displace levothyroxine from the plasma protein, resulting in an increased free T_4 fraction.

Proton pump inhibitors (PPIs):
Co-administration with PPIs may cause a decrease in the absorption of thyroid hormones due to the increase in 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.
Caution is also advised when treatment with a PPI is stopped.

Orlistat:
Hypothyroidism and/or decreased control of hypothyroidism may occur with concomitant intake of orlistat and levothyroxine. Reduced absorption of iodine salts and/or levothyroxine could be the cause.

Sevelamer:
Sevelamer may reduce the absorption of levothyroxine. As a result, it is recommended to monitor patients for changes in thyroid function at the beginning or end of concomitant treatment. If necessary, the levothyroxine dose should be adjusted.

Tyrosine kinase inhibitors:
Tyrosine kinase inhibitors (e.g., imatinib, sunitinib) may reduce the efficacy of levothyroxine. As a result, it is recommended to monitor patients for changes in thyroid function at the beginning or end of concomitant treatment. If necessary, the levothyroxine dose should be adjusted.

Propylthiouracil, glucocorticoids, betasympatholytics, amiodaroneand iodine-containingcontrast agents:
These substances inhibit the peripheral conversion of T_4 into T_3. Amiodarone may cause both hyperthyroidism and hypothyroidism due to its high iodine levels. Particular caution should be exercised in case of nodular goitre with potentially unrecognised autonomy.

Sertraline, chloroquine/proguanil:
These substances reduce the efficacy of levothyroxine and increase serum TSH levels.

Enzyme-inducing medicinal products:
Barbiturates, products containing St John's wort (*Hypericum perforatum*), and other agents with liver enzyme-inducing properties may increase hepatic levothyroxine clearance, resulting in reduced serum

concentrations of thyroid hormone.
Therefore, patients receiving thyroid replacement therapy may require a higher dose of thyroid hormone if administered concomitantly.

Oestrogens:
Women using oestrogen-based contraceptives, and postmenopausal women receiving hormonal replacement therapy, may need more levothyroxine.

Soy-containing products:
Soy-containing products may reduce the intestinal absorption of levothyroxine. Therefore, the dosage of levothyroxine sodium may need to be adjusted, especially at the start or after discontinuation of a soy supplement diet.

Interference with laboratory tests:
Biotin can interfere with thyroid immunoassays based on a biotin/streptavidin interaction, leading to erroneously reduced or erroneously increased test results (see section 4.4).

4.6 Fertility, pregnancy and lactation

Levothyroxine therapy should be continued consistently during pregnancy and especially during breast-feeding. During pregnancy, the dose may even need to be increased. As serum TSH levels may increase as early as the fourth week of pregnancy, pregnant women taking levothyroxine should have their TSH levels measured each trimester to confirm that the mother's serum TSH level is within the specific pregnancy reference limits for that trimester. An elevated serum value for TSH should be adjusted by increasing the levothyroxine dose. Given that the postpartum concentrations for TSH are similar to the values prior to conception, the levothyroxine dose should be reset to the pre-pregnancy value immediately after giving birth. TSH levels should be measured again 6 to 8 weeks postpartum.

Pregnancy
The development of the child depends on the thyroid function of the mother. Thyroxine is necessary to ensure the child's proper brain development. Therefore, thyroid hormone therapy should be continued during pregnancy. The dosage requirement may even increase during pregnancy. To date, there have been no reports of any risk after extended use during pregnancy.

Breast-feeding
Levothyroxine sodium can be used during lactation. Levothyroxine is excreted in breast milk at low concentrations. Even with high-dose levothyroxine therapy, the amount of thyroxine excreted in breast milk during lactation is not sufficient to cause the child to develop hyperthyroidism or suppression of TSH secretion.

Application as adjuvant to thyreostatic agents
During pregnancy and lactation, levothyroxine sodium should not be given concomitantly with medication for the treatment of hyperthyroidism (thyreostatics) (see section 4.3). Since thyreostatic agents, compared to levothyroxine, are much better able to cross the placenta at effective doses, hypothyroidism may develop in the foetus. Because additional administration of levothyroxine may increase the required dose of the thyreostatics, only thyreostatics should be given in case of hyperthyroidism during pregnancy.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency category for the undesirable effects below is not known (cannot be estimated from the available data).

Immune system disorders	Hypersensitivity
Skin and subcutaneous tissue disorders	Angioedema Skin rash Urticaria

If the individual tolerance limit of levothyroxine sodium is exceeded or in the event of an overdose, the following clinical symptoms, characteristic of hyperthyroidism, may occur, particularly if the dose is increased too quickly at the start of treatment.

In such cases, the daily dose should be reduced, or the medication stopped for several days. Treatment may be carefully restarted once these effects have disappeared.

Endocrine disorders	Hyperthyroidism Irregular periods
Nervous system disorders	Headache Benign intracranial hypertension Tremor Restlessness Insomnia
Cardiac disorders	Arrhythmia Atrial fibrillation Extrasystoles Tachycardia Palpitations Angina pectoris
Gastrointestinal disorders	Vomiting Diarrhoea
Skin and subcutaneous tissue disorders	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle weakness Muscle spasms
General disorders and administration site conditions	Excessive flushing Pyrexia
Investigations	Weight loss

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

An increased T_3 level is a more reliable indication of an overdose than an increased T_4 or free T_4 concentration.
In case of an overdose, the patient shows symptoms of a marked increase in basal metabolism. Depending on the extent of the overdose, it is recommended that treatment with the tablets be stopped, and an examination be performed.

Several cases of sudden death due to cardiac disorders have been reported in patients after years of levothyroxine abuse.

Symptoms suggestive of obvious beta-sympathomimetic effects, such as tachycardia, anxiety, agitation and hyperkinesis, can be managed with beta-blockers.

In the event of extreme overdose, plasmaphaeresis may be useful, but haemodialysis and haemoperfusion are not effective and peritoneal dialysis is not sufficiently effective.

In exceeding the individual tolerance level, isolated cases of seizures have been reported in patients predisposed to this.

Overdose of levothyroxine could lead to symptoms of hyperthyroidism and to acute psychosis, particularly in patients at risk of psychotic disorders.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: thyroid hormones, ATC Code: H03AA01

The effect of the synthetic levothyroxine in Levothyroxine Sodium is equivalent to that of the naturally occurring essential hormone secreted by the thyroid gland. Like the endogenous hormone, it is converted into T_3 in the peripheral organs and develops its specific effect through the T_3 receptors. The body cannot distinguish between endogenous and exogenous levothyroxine.

5.2 Pharmacokinetic properties

With oral intake, levothyroxine is absorbed almost entirely in the upper part of the small intestine. Depending on the galenic form, the absorption is up to 80%. Tmax is approximately 5 to 6 hours.

After oral administration, the onset of action occurs after 3 to 5 days. Levothyroxine exhibits an extremely strong binding of approximately 99.97% to specific carrier proteins. This protein hormone binding is not covalent, and thus the bound hormone in the plasma is exchanged continuously and very rapidly with the free hormone fraction. The volume of distribution is approximately 10-12 L.

Because of the high degree of protein binding, levothyroxine does not undergo haemodialysis or haemoperfusion.

The half-life of levothyroxine is approximately 7 days. In hyperthyroidism, this is shorter (3 to 4 days). In hypothyroidism, this is longer (approximately 9 to 10 days). The liver contains 1/3 of the entire extrathyroid levothyroxine. This is rapidly exchangeable with the levothyroxine in the serum. Thyroid hormone is primarily metabolised in the liver, kidneys, brain and muscles. The metabolites are excreted in the urine and faeces. The total metabolic levothyroxine clearance is approximately 1.2 L of plasma per day.

5.3 Preclinical safety data

There is no preclinical data of interest to the prescriber besides the data presented in other sections of this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (PH-101 & PH-102)
Povidone
Sodium starch glycolate
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25˚C.

6.5 Nature and contents of container

High density polyethylene (HDPE) containers with a polypropylene child-resistant cap and a desiccant canister containing 100 tablets.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
12 Crowe Street
Dundalk
Co. Louth
A91 NN29
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22865/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th August 2026

10 DATE OF REVISION OF THE TEXT