# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**L-THYROXINE SERB**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml contains 0.2 mg of Levothyroxine sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion.

Clear solution, practically colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

- Replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology.
- Myxedema coma.

### 4.2. Posology and method of administration

**Posology**

- Before treatment and in order to adjust the dose, it is recommended that testing of T3, T4 and TSH levels be performed.
- The administered doses vary depending on the degree of hypothyroidism, the subject's age and individual tolerance.
- Daily administration of levothyroxine injection should be continued until the patient is able to tolerate an oral dose and is clinically stable.

Adults

Myxedema coma:

An initial loading dose of 500 micrograms the first day is recommended, as a slow intravenous infusion in 250 ml of saline solution to achieve a concentration of the diluted solution of 2 micrograms/ml. Due to an increased risk of serious cardiovascular events or death, this loading dose must not exceed 500 µg.

- Maintenance treatment should then be initiated at a daily dose of 100 µg on average.

Replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology:

- Gastrointestinal absorption of oral levothyroxine tablet is approximately 70%–80% in healthy fasting adults (see section 5.2).
- Complete hormone replacement therapy in adults requires 100 to 150 µg as a single daily dose, on average.

  This dosage will be established gradually and with caution: start with 25 µg per day, then increase the daily dose by 25 µg at weekly intervals.
- Once the dosage has been stable for a long enough period, repeat testing of thyroid hormones levels. Monitor T3 and T4 levels to check that there is no overdose and monitor normalisation of TSH levels in the event of peripheral hypothyroidism.

Elderly patients

More gradual dosing schedules may be proposed, particularly in elderly subjects with known cardiovascular risk factors (see section 4.4), for whom treatment should be initiated at lower doses, and follow more gradual increments. A maintenance dose lower than that required to normalise TSH levels may be considered.

Patients with renal / hepatic insufficiency

Experience in patients with renal and/or hepatic insufficiency is limited.

Paediatric population

Myxedema coma:
Experience in children treated for myxedema coma is very limited.

Replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology:

The maintenance dose is generally 100 to 150 micrograms per m² of body surface area.

- For neonates and infants with congenital hypothyroidism, in whom rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg bodyweight per day for the first 3 months. Thereafter, the dose should be individually adjusted based on clinical and laboratory findings (thyroid hormones and TSH).
- For children with acquired hypothyroidism, the recommended initial dosage is 12.5 to 50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks based on clinical and laboratory findings (thyroid hormones and TSH) until the full replacement dose is reached.

In all cases, the dose should be adjusted on the basis of the needs of each individual.

**Method of administration**

Intravenous injection.

Intramuscular injection possible.

For the treatment of myxedema coma, a slow intravenous infusion in 250 ml of saline solution is recommended for the loading dose.

## 4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Decompensated cardiac diseases (e.g. acute myocardial infarction, acute myocarditis, acute pancarditis).
- Untreated adrenal insufficiency (see section 4.4).
- Untreated hyperthyroidism.
- Untreated pituitary insufficiency (when leading to adrenal insufficiency requiring treatment).

Combination of levothyroxine with an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

## 4.4. Special warnings and precautions for use

Before starting a thyroid hormone therapy, the following diseases or conditions should be excluded or treated:

- Coronary heart disease,
- angina pectoris,
- hypertension,
- pituitary and/or adrenal insufficiency,
- thyroid autonomy.

It is essential that even mild, drug-induced hyperthyroidism be avoided in patients with coronary heart disease, heart failure, tachyarrhythmias, myocarditis of non-acute course, chronic hypothyroidism or in patients who have already suffered a myocardial infarction. In these patients, more frequent monitoring of thyroid hormone parameters is essential during thyroid hormone therapy (see section 4.2).

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.

If a switch to another levothyroxine-containing product is required, there is a need to undertake a close monitoring including a clinical and biological monitoring during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment could be necessary.

Due to the difference of bioavailability of the oral dosage form versus injectable form, the dose should be carefully adapted when switching from one form to another (See section 4.2).

Patients with cardiovascular disorders or with a history of cardiovascular disorders

Levothyroxine by the intravenous/intramuscular route can be associated with cardiac toxicity (in particular arrhythmia, tachycardia, myocardial ischaemia and myocardial infarction or exacerbation of congestive heart failure and death) in patients with underlying cardiovascular disease (in particular coronary disorders, arrhythmias, hypertension, decompensated heart failure).

Due to the increased prevalence of cardiovascular diseases in the elderly, caution is required when administering levothyroxine solution for injection or concentrate for solution for infusion in elderly patients or those with known cardiac risk factors. Cautious use may be required in these populations, including at doses at the lower end of the recommended dosage range (see section 4.2).

Regular and careful monitoring of cardiac conditions is necessary at treatment initiation and throughout treatment.

Patients with adrenal insufficiency

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

*As an adrenal insufficiency linked with myxedema coma can occur, an empiric intravenous glucocorticoid treatment should be administered in association to levothyroxine until confirmation or exclusion of adrenal insufficiency.*

Low birth weight preterm neonates

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.

Diabetes

The addition of levothyroxine to an anti-diabetic treatment or insulin therapy can lead to an increase in insulin or anti-diabetic drug requirements. Careful monitoring of metabolic control is recommended in diabetic patients (see section 4.5).

Patients with a history of epilepsy

Due to the risk of seizures in patients with a history of epilepsy, monitoring of these patients is recommended throughout treatment with levothyroxine.

Hypersensitivity
Hypersensitivity reactions (including angioedema), sometimes serious, have been reported with L-THYROXINE SERB. If signs and symptoms of allergic reactions occur, treatment with L-THYROXINE SERB must be discontinued and appropriate symptomatic treatment initiated (see Section 4.3 and 4.8).

Pregnant women

Clinical and laboratory monitoring must be reinforced at the most earliest stage possible in pregnant women, particularly during the first half of the pregnancy, in order to adjust the treatment if necessary (see section 4.6).

Osteoporosis
During levothyroxine therapy of postmenopausal women with increased risk of osteoporosis, dosage of levothyroxine sodium should be titrated to the lowest possible effective level and thyroid function should be monitored more frequently to avoid levels of levothyroxine above the physiological range (see section 4.8).

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 and other treatments
Monitoring is required in patients receiving concomitant administration of levothyroxine and medicinal products (such as amiodarone, tyrosine kinase inhibitors, salicylates and furosemide at high doses, selpercatinib, …) which may affect the thyroid function. See also section 4.5.
For diabetic patients and patients under anticoagulant therapy, see section 4.5.

For patients receiving selpercatinib, hypothyroidism has been reported. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice, however patients could have an insufficient response to substitution with levothyroxine (T4) as selpercatinib may inhibit the conversion of levothyroxine to liothyronine (T3) and supplementation with liothyronine may be needed (see section 4.5).

Important information about some of the ingredients
SodiumThis medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium-free’.

## 4.5. Interaction with other medicinal products and other forms of interaction

**Combinations not recommended**

**St. John's Wort (Hypericum perforatum L.)**

Risk of increased hepatic clearance of levothyroxine resulting in reduced serum concentrations of thyroid hormone and risk of decreased clinical effects. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these products are given concurrently.

**Combinations requiring precautions for use**

**Anti-diabetic agents**

Levothyroxine can reduce the blood sugar-lowering effect of antidiabetics (e.g. metformin, glimepiride, glibenclamide and insulin). Therefore, blood sugar levels in diabetic patients must be regularly checked, particularly at the start and at the end of thyroid hormone treatment. The dose of the blood sugar-lowering drug should also be adapted.

**Coumarin derivatives**

Levothyroxine can intensify the effect of coumarin-derivatives through plasma protein binding displacement. Therefore, regular blood coagulation checks are necessary in the case of simultaneous treatment; the dose of the anticoagulant must be adapted, if necessary (dose reduction).

**Propylthiouracil, glucocorticoids and beta-receptor blockers (especially propranolol)**

These substances inhibit the conversion of T4 into T3 and can result in a lowered T3 serum concentration.

**Amiodarone and contrast media containing iodine**

Due to their iodine content, these agents can trigger hyperthyroidism as well as hypothyroidism. Special care should be taken in the case of nodular goiter with possibly undetected functioning autonomies. Amiodarone inhibits the conversion of T4 into T3, resulting in a lowered T3 serum concentration and an increased TSH serum level.

**Salicylate, dicumarol, furosemide, clofibrate**

Levothyroxine can be displaced from the plasma protein binding through salicylate (particularly in doses greater than 2.0 grams per day), dicumarol, high doses (250 milligrams) of furosemide, clofibrate and other substances. This can lead to an initial, temporary increase of free thyroid hormones, jointly followed by a decrease of the total thyroid hormone level.

**Contraceptives containing oestrogen, drugs for post-menopausal hormone substitution**

The levothyroxine demand can increase during the intake of contraceptives containing oestrogen or during post-menopausal hormone replacement treatment. There may be increased binding of levothyroxine, which may lead to diagnostic and therapeutic errors.

**Sertraline, chloroquine/proguanil**

These substances reduce the efficacy of levothyroxine and increase the TSH serum level.

**Enzyme inducing drugs**

Barbiturates, rifampicin, carbamazepine, phenytoin and other drugs with liver enzyme-inducing characteristics can increase the hepatic clearance of levothyroxine and result in a decreased plasma level.

**Protease inhibitors**

There are reports stating that protease inhibitors can result in a loss of the therapeutic effect of levothyroxine if simultaneously administered with lopinavir/ritonavir. Therefore, careful monitoring of clinical symptoms and thyroid function should be carried out in patients who use levothyroxine and protease inhibitors simultaneously.

**Tyrosine kinase inhibitors** (e.g. Imatinib, sunitinib, sorafenib, motesanib)

These agents can reduce the efficacy of levothyroxine. Therefore, careful monitoring of clinical symptoms and thyroid function should be carried out in patients who use levothyroxine and tyrosine kinase inhibitors simultaneously.

**Selpercatinib**

Levothyroxine may be less effective when given with selpercatinib.

Selpercatinib could inhibit D2 deiodinase and thereby decrease the conversion of levothyroxine (T4) to liothyronine (T3). Patients could therefore have an insufficient response to substitution with levothyroxine and supplementation with liothyronine may be needed (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**

Data concerning the use of levothyroxine injections in pregnant women are limited. Levothyroxine does not readily cross the placenta and its administration in appropriate doses has no effects on the foetus. Animal studies do not provide adequate data concerning reproductive toxicity (see section 5.3).

It is essential that thyroid hormone treatment be continued throughout pregnancy to maintain the balance required in the mother to ensure a healthy pregnancy (and, in particular, to reduce the risk of foetal hypothyroidism). Clinical and laboratory monitoring must be reinforced as soon as possible, particularly during the first half of the pregnancy, so that the treatment can be adjusted if necessary. In all cases, it is recommended that a thyroid assessment be performed on the newborn infant.

During pregnancy, levothyroxine must not be combined with anti-thyroid agents for hyperthyroidism. Only small quantities of levothyroxine cross the placenta, whereas large quantities of anti-thyroid drugs cross from the mother to the infant. This can cause foetal hypothyroidism.

**Breast-feeding**

In breast-feeding women with balanced T4 levels, levothyroxine is secreted into breast milk in low concentrations. Consequently, replacement therapy using levothyroxine is possible while breast-feeding.

**Fertility**

No fertility studies have been performed with this medicinal product. Hypothyroidism or hyperthyroidism are liable to affect fertility.

## 4.7. Effects on ability to drive and use machines

L-THYROXINE SERB has no effect or a negligible effect on the ability to drive and use machines.

## 4.8. Undesirable effects

If the patient does not tolerate the dosage given or overdosage occurs, the typical symptoms of hyperthyroidism may occur, especially if the dose is increased too rapidly at the start of treatment. In these cases, the daily dosage should be reduced, or the medication should be stopped for several days. Treatment may be restarted with cautious dose adjustment once the side effects have disappeared.

In case of hypersensitivity against levothyroxine or against other ingredients of L-THYROXINE SERB, allergic reactions on the skin (e.g. angioedema, rash, urticaria) and on the respiratory tract may occur.

Adverse reactions are classified into the following categories in order of frequency:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders
not known: hypersensitivity

Endocrine disorders
common: hyperthyroidism

Psychiatric disorders
very common: insomnia
common: nervousness
not known: agitation

Nervous system disorders
very common: headache
rare: pseudotumor cerebri particularly in children
not known: tremors

Cardiac disorders
very common: palpitations
common: tachycardia
not known: cardiac arrhythmias, anginal pain

Vascular disorders
not known: flushing, circulatory collapse in low birth weight preterm neonates (see section 4.4)

Gastrointestinal disorders
not known: diarrhoea, vomiting and nausea

Skin and subcutaneous disorders
Not known: angioedema, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders
not known: muscle weakness and cramps, osteoporosis at suppressive doses of levothyroxine, especially in postmenopausal women, mainly when treated for a long period.

Reproductive system and breast disorders
not known: menstrual irregularities

General disorder and administration site conditions
not known: heat intolerance, fever.

Investigations
not known: weight loss

**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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

## 4.9. Overdose

This is manifested in adults by thyrotoxicosis. In the event of a thyrotoxic crisis (thyroid storm), substantially reduce the doses or suspend treatment for a few days, then resume it at lower doses, following biological monitoring.

Treatment with levothyroxine solution for injection or concentrate for solution for infusion must be adjusted (dose reduction or temporary suspension) in the event of severe overdose. In addition, appropriate supportive measures including, in particular, beta-blockers, should be initiated on the basis of the patient's clinical condition. An elevated T3 level is a reliable indicator of overdosage, more than elevated T4 or fT4 levels.

In overdosage and intoxication, symptoms of moderate to severe increases in metabolism occur (see section 4.8). Depending on the extent of the overdosage it is recommended that treatment is interrupted and that tests are carried out.

In incidents of poisoning in humans, oral doses of 10 mg levothyroxine were tolerated without complications. Severe complications involving a threat to vital functions (respiration and circulation) are not to be expected, except in coronary heart disease. However, there exist reports on cases of thyrotoxic crisis, cramps, cardiac insufficiency and coma. Isolated cases of sudden cardiac death have been reported in patients with many years of levothyroxine abuse.

In case of acute overdosage, treatment is generally symptomatic and supportive. Beta-blockers may be given if severe beta-sympathomimetic symptoms such as tachycardia, anxiety, agitation and hyperkinesia occur.

Antithyroid drugs are not appropriate, because of prior complete inactivation of the thyroid.

In cases of intoxication with extremely high doses, plasmapheresis may be helpful.

Levothyroxine overdosage requires a prolonged monitoring period. Owing to the gradual transformation of levothyroxine into liothyronine, symptoms may occur with a delay of up to six days.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: thyroid hormones, ATC code: H03AA01

**Mechanism of action**

Thyroid hormones exert their physiological effects via the control of DNA transcription and protein synthesis. Triiodothyronine (T3) is diffused in the nucleus of the cell and binds to protein thyroid receptors bound to the DNA. This hormone-receptor complex present in the nucleus activates genetic transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological effects of thyroid hormones are mainly due to T3, predominantly derived (around 80%) from T4 by deiodination in the peripheral tissues.

**Pharmacodynamic effects**

The primary pharmacodynamic response to levothyroxine, solution for injection or concentrate for solution for infusion, has been the subject of studies in patients with myxedema coma or hypothyroidism, which have demonstrated the capacity of intravenous levothyroxine to increase blood concentrations of T4 and simultaneously reduce TSH levels in these types of patients.

The secondary pharmacokinetic response has been the subject of in vitro studies, which highlighted binding sites shared by levothyroxine and oestradiol 17β-glucuronide ($E_2$17βG), a conjugated sterol, in the OATP 1C1 blood-brain barrier transporters, suggesting competition between levothyroxine and other substances when crossing the blood-brain barrier.

## 5.2. Pharmacokinetic properties

**Absorption**

After parenteral administration, synthetic levothyroxine cannot be differentiated from the natural hormone secreted endogenously.

**Distribution**

Over 99% of circulating thyroid hormones are bound to plasma proteins, in particular to thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA) and albumin, whose binding capacities and affinities vary depending on the hormones. Thyroid hormones bound to plasma proteins remain inversely correlated with low free hormone concentrations. Only the latter are metabolically active.

Following intravenous administration, the distribution volume is estimated to be 11.6 litres in healthy subjects and 14.7 litres in patients with hypothyroidism.

**Biotransformation**

The main metabolic pathway for thyroid hormones is sequential deiodination. Around 80% of circulating T3 is derived from peripheral T4 by monodeiodination. The liver is the main site for the degradation of T4 and T3, with deiodination of T4 also occurring in a certain number of other sites, in particular the kidneys and other tissues. Around 80% of T4 daily dose is deiodinised to obtain equal quantities of T3 and rT3 (reverse T3). T3 and rT3 are then deiodinised and turn into diiodothyronine (T2). Thyroid hormones are also metabolised by conjugation with sulfate and glucuronic acid and directly excreted in the bile and intestine where they undergo entero-hepatic recirculation.

**Elimination**

Levothyroxine clearance is estimated to be around 0.050 litres/hour in euthyroid patients; it is slightly higher (0.053 litres/hour) in hypothyroid patients. The elimination half-life of levothyroxine is estimated to be 6 to 7 days in healthy subjects and 9 to 10 days in patients with myxedema coma.

## 5.3. Preclinical safety data

In non-clinical studies, the adverse reactions of treatment with high doses of T4 were due to an excessive pharmacological effect of the hormone, and therefore they are not expected to occur at therapeutic doses.

The repeated-dose toxicity data in animals in the scientific literature have not revealed any specific risk to humans.

Conventional genotoxicity, carcinogenicity and reprotoxicity studies have not been conducted with levothyroxine.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. List of excipients

Sodium hydroxide, water for injection.

## 6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## 6.3. Shelf life

The expiry date of the product is indicated on the packaging material.
After opening and/or dilution: the product must be used immediately.

## 6.4. Special precautions for storage

Store below 25°C. Protect from light.

## 6.5. Nature and contents of container

Type I uncolored glass, 1ml ampoule.

Each package contains 6 ampoules.

## 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 and IMPORTER

RAZ PHARMACEUTICS LTD.,
31 Gesher Haetz, Industrial Park, Emek Hefer, Israel

## 8. MARKETING AUTHORISATION NUMBER(S)

165-27-35356-00

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