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.

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 radio-immunological assays of T3, T4 and TSH levels be performed or, otherwise, assay of hormonal iodine levels.
- 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 µg the first day is recommended, as a slow intravenous infusion in 250 ml of saline solution. 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.

Other indications:

- 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 biological assay of thyroid hormones levels. Perform T3 and T4 assays 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

Experience in children treated for myxedema coma is very limited.

In other indications:

- 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 myxoedema 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.

Untreated adrenal insufficiency.

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

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.

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

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.

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.

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).

This medicine is not recommended in combination with St. John's Wort (see section 4.5).

This 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)

Risk of decreased clinical effects of thyroid hormones.

Combinations requiring precautions for use

• ENZYME INDUCER ANTICONVULSANT DRUGS (PHENYTOIN, CARBAMAZEPINE, PHENOBARBITAL)

Risk of clinical hypothyroidism in patients with hypothyroidism due to the increased metabolism of thyroid hormones.

Clinical and laboratory monitoring; if necessary, adjustment of the thyroid hormone dosage during treatment with the enzyme inducer and after its discontinuation.

• CHLOROQUINE, PROGUANIL

Risk of clinical hypothyroidism in patients receiving thyroid hormone replacement therapy.

Clinical and laboratory monitoring and, if necessary, adjustment of the thyroid hormone dosage during treatment with the antimalarial drug and after its discontinuation.

• NON-CONTRACEPTIVE OESTROGENS

Risk of clinical hypothyroidism in the event of oestrogen replacement therapy.

Clinical and laboratory monitoring and, if necessary, adjustment of the thyroid hormone dosage for menopausal women treated with oestrogens.

• PROTEASE INHIBITORS BOOSTED BY RITONAVIR

Risk of reduced efficacy of thyroid hormones due to their increased hepatic metabolism induced by ritonavir.

Clinical and laboratory monitoring and, if necessary, adjustment of the thyroid hormone dosage.

• RIFABUTIN, RIFAMPICIN

Risk of clinical hypothyroidism in hypothyroid patients due to the increased metabolism of T3 and T4.

Clinical and laboratory monitoring and, if necessary, adjustment of the thyroid hormone dosage during treatment with rifabutin or rifampicin and after its discontinuation.

• LITHIUM

Lithium blocks the TSH-mediated release of T4 and T3. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual levothyroxine dose may be required.

• AMIODARONE

Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, and decreased or normal free-T3) in clinically euthyroid patients.

Combinations to be taken into account

• ORLISTAT

Risk of thyroid hormone replacement therapy imbalance in the event of treatment with orlistat.

4.6. Fertility, pregnancy and lactation

Pregnancy

Data concerning the use of levothyroxine injections in pregnant women are limited. Thyroid hormones cross the placental barrier to some extent. T4 levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. 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.

Thyroid hormones cross the placental barrier to some extent, whereas large quantities of anti-thyroid drugs cross from the mother to the infant. This can cause foetal hypothyroidism. Therefore, during pregnancy, levothyroxine must not be combined with anti-thyroid agents for hyperthyroidism.

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

The adverse effects listed below are derived from data in the literature and post-market clinical use: their frequency cannot be estimated and is therefore not known.

- Endocrine disorders: if signs of hyperthyroidism, such as tachycardia, insomnia, excitability, headache, rise in temperature, sweating, rapid weight loss or diarrhoea appear, treatment should be suspended for a few days and then resumed at lower doses, following biological monitoring.
- Cardiac disorders: aggravation of any heart disease, myocardial infarction, angina, arrhythmias (such as tachycardia).
- General disorders and administration site conditions: reaction at injection site.
- Skin reactions and subcutaneous tissue disorders: angioedema, rash, urticarial (frequency not known).

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 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.

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, 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 injections.

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 immediately used.

6.4. Special precautions for storage

Store below 25°C. Protect from light.

6.5. Nature and contents of container

1 ml glass ampoule. Each package contains 6 ampoules.

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURER

SERB, 40 AVENUE GEORGE V, 75008 PARIS, FRANCE

8. MARKETING AUTHORISATION HOLDER

RAZ PHARMACEUTICS LTD., 6 Hamatechet st., Kadima, Israel.

9. MARKETING AUTHORISATION NUMBER(S)

165-27-35356-00

Approved on August 2020.

RAZS3155-00