SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine SERB 200 micrograms/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levothyroxine sodium……200 micrograms

For one ampoule of 1 ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Myxoedema coma.
- Hypothyroidism in patients where oral therapy is not feasible, particularly due to difficulties in swallowing or malabsorption.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

- Perform thyroid function test (T3, T4 and TSH levels) before treatment with levothyroxine injection. The starting and maintenance doses depend on the degree of hypothyroidism, the patient's age and individual tolerance.

- Daily administration of levothyroxine injection should be continued until the patient is able to tolerate oral therapy.

Conversion table between micrograms and ml of solution:

Micrograms (µg)	10	25	50	70	75	90	100	125	150	200
Millilitres (ml)	0.05	0.125	0.25	0.35	0.375	0.45	0.5	0.625	0.75	1

Adults

Myxoedema coma:

A loading dose of 200 to 500 micrograms is recommended.

Due to an increased risk of serious cardiovascular events or death, this loading dose must not exceed 500 micrograms. The maintenance dose of parenteral levothyroxine is 1.2 micrograms per kilogram body weight (75-90 micrograms).

Hypothyroidism where oral therapy is not feasible:

Oral to iv conversion: Gastrointestinal absorption of oral levothyroxine tablet is approximately 70%–80% in healthy fasting adults, therefore, parenteral levothyroxine should be administered at an initial dose that corresponds to 70-80% of the patient's oral dose.

- Complete hormone replacement therapy in adults requires 100 to 150 micrograms as a single daily dose, on average.

This dosage will be established gradually and with caution: start with 25 micrograms per day, then increase the daily dose by 25 micrograms at weekly intervals.

- Once the dosage has been stable for a long enough period (4-6 weeks), 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

Myxoedema coma:

Experience in children treated for myxoedema coma is very limited.

Use of parenteral levothyroxine 10 micrograms/kg/day in 3 divided doses for 24 hours as loading dose followed by 3 micrograms/kg/day as maintenance therapy has been reported in published case reports. Dose should be adjusted based on clinical and laboratory findings.

Hypothyroidism where oral therapy is not feasible:
The daily replacement dose of intravenous levothyroxine should be no more than 75% of the oral dose. 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, an initial loading dose is given as a slow intravenous infusion in 100-250 ml of sodium chloride 9 mg/mL (0.9%) solution for injection solution to achieve a concentration of the diluted solution of 2 micrograms/ml.

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 clinical and laboratory monitoring during the transition period due to a potential risk of thyroid imbalance. In some patients, dose adjustment may be necessary.
Due to the difference in bioavailability of the oral dosage form versus injectable form, the dose should be carefully adapted when switching from one form to another (See section 5.2).

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/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 adrenocortical dysfunction occurs concomitantly with myxoedema coma, patients should be treated with glucocorticoids before starting levothyroxine.

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.

The proposed dose of Levothyroxine SERB may be a significant addition to the circulating blood volume of preterm infants. This should be taken into account when calculating daily fluid requirements.

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 Levothyroxine SERB, 200 micrograms/ml solution for

injection/infusion use. If signs and symptoms of allergic reactions occur, treatment with Levothyroxine SERB, 200 micrograms/ml solution for injection/infusion must be discontinued and appropriate symptomatic treatment initiated (see Section 4.3 and 4.8).

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)

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 L.*)

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.

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. Dose adjustments may be required.

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 goitre 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.

Androgens

Use of androgens may decrease serums concentrations of Thyroxin-Binding Globulins.

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.

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

Protease inhibitors

Risk of reduced efficacy of thyroid hormones due to their increased hepatic metabolism induced by 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, selpercatinib)

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.

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. 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 performed 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

Levothyroxine SERB 200 micrograms/ml solution for injection/infusion 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.

Hypersensitivity reactions to levothyroxine or other ingredients in Levothyroxine SERB 200 micrograms/ml solution for injection/infusion include angioedema, rash, urticaria, wheezing.

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).

System organ class	**Undesirable side effects**	**Frequency**
Immune system disorders	Hypersensitivity	Not known
Endocrine disorders	Hyperthyroidism	Common
Psychiatric disorders	Insomnia	Very common
	Nervousness	Common
	Agitation	Not known
Nervous system disorders	Headache	Very common
	Pseudotumor cerebri particularly in children	Rare
	Tremors	Not known
Cardiac disorders	Palpitations	Very common
	Tachycardia	Common
	cardiac arrhythmias, anginal pain	Not known
Vascular disorders	Flushing, circulatory collapse in low birth weight preterm neonates (see section 4.4)	Not known
Gastrointestinal disorders	Diarrhoea, vomiting and nausea	Not known
Skin and subcutaneous	Angioedema, rash, urticaria,	Not known

disorders	sweating	
Musculoskeletal and connective tissue disorders	Muscle weakness and cramps, osteoporosis at suppressive doses of levothyroxine, especially in postmenopausal women, mainly when treated for a long period.	Not known
Reproductive system and breast disorders	menstrual irregularities	Not known
General disorder and administration site conditions	Heat intolerance, fever.	Not known
Investigations	Weight loss	Not known

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

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

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, closely monitoring clinical and laboratory response.

Treatment is generally symptomatic and supportive. Beta-blockers may be given if severe beta-sympathomimetic symptoms such as tachycardia, anxiety, agitation and hyperkinesia occur.

Severe complications involving a threat to vital functions (respiration and circulation) are not to be expected, except in coronary heart disease. Isolated cases of sudden cardiac death have been reported in patients with many years of levothyroxine abuse.

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.

An elevated T3 level is a reliable indicator of overdosage, more than elevated T4 or fT4 levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: thyroïd 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/infusion, has been the subject of studies in patients with myxoedema 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 in 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 0.05 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 myxoedema 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

2 years.

After opening and/or dilution: the product must be used immediately.

6.4 Special precautions for storage

Store in the original container protected from light.

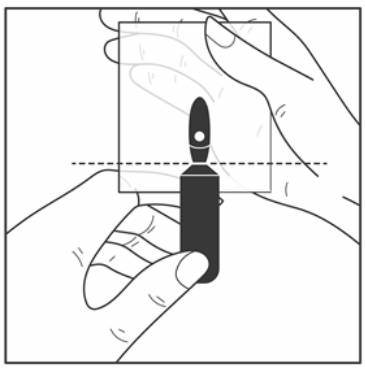
6.5 Nature and contents of container

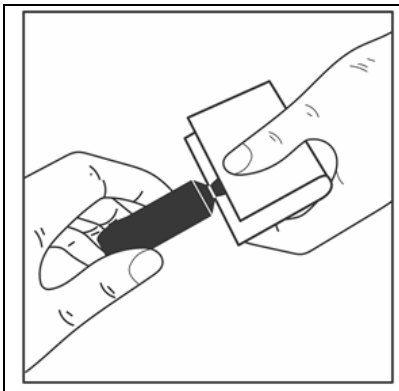
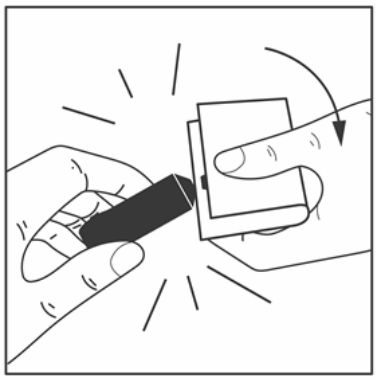
1 ml ampoule (glass). Box of 6.

6.6 Special precautions for disposal

Do not use Levothyroxine SERB 200 micrograms/ml solution for injection/infusion if there is any visible particulate matter or discolouration.

Opening the self-breakable ampoule:

	Hold the body of the ampoule between the thumb and the folded forefinger, with the head of the ampoule facing up and the coloured dot pointing upwards and facing you. Tap the top of the ampoule to make the trapped liquid go down from the head of the ampoule. The break of the ampoule is at the narrowing between the head and the body of the ampoule as indicated in the dotted line on the picture.

	Cover the top of the ampoule with a compress or a cotton ball and place the thumb of one hand on the coloured dot.
	Push back on the neck of the ampoule and it will open easily.

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

7. MARKETING AUTHORISATION HOLDER

SERB
32 rue de Monceau
75008 Paris
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 26080/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/12/2022

10 DATE OF REVISION OF THE TEXT

15/05/2026