יוני 2022

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר:

L-THYROXINE SERB

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא.

התוספות סומנו בצבע כחול, ההחמרות סומנו בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:

www.health.gov.il וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, רחוב המתכת 6, א.ת. קדימה.

בברכה,

אריאל מימון

מנהלת מחלקת רישום

מרכיב פעיל וחוזק:

LEVOTHYROXINE SODIUM 0.2 MG / 1 ML

התוויה מאושרת:

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

להלן העדכונים המהותיים שבוצעו בעלון לרופא:

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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. ~~radio-immunological assays of T3, T4 and TSH levels be performed or, otherwise, assay of hormonal iodine levels.~~

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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: ~~Other indications:~~

- 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 ~~biological assay~~ of thyroid hormones levels. Monitor ~~Perform~~ T3 and T4 levels ~~assays~~ to check that there is no overdose and monitor normalisation of TSH levels in the event of peripheral hypothyroidism.

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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 mycoarditis, acute pancarditis).
- Untreated adrenal insufficiency.
- 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).

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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 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).

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) which may affect the thyroid function. See also section 4.5.
For diabetic patients and patients under anticoagulant therapy, see section 4.5.

~~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

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.

~~• 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. Levothyroxine does not readily cross the placenta and its administration in appropriate doses has no effects on the foetus. ~~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.~~ 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.

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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 200 micrograms/ml solution for injection/infusion, 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

~~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/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.

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