SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levothyroxine Abdi 25 microgram tabletten
Levothyroxine Abdi 50 microgram tabletten
Levothyroxine Abdi 75 microgram tabletten
Levothyroxine Abdi 100 microgram tabletten
Levothyroxine Abdi 125 microgram tabletten
Levothyroxine Abdi 150 microgram tabletten
Levothyroxine Abdi 175 microgram tabletten
Levothyroxine Abdi 200 microgram tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet Levothyroxine Abdi 25 micrograms contains 25 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 50 micrograms contains 50 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 75 micrograms contains 75 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 100 micrograms contains 100 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 125 micrograms contains 125 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 150 micrograms contains 150 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 175 micrograms contains 175 micrograms of levothyroxine sodium.
Each tablet Levothyroxine Abdi 200 micrograms contains 200 micrograms of levothyroxine sodium.

Excipients with known effect:.

Each tablet Levothyroxine Abdi 25 micrograms contains 62.63 mg of lactose.
Each tablet Levothyroxine Abdi 50 micrograms contains 62.60 mg of lactose.
Each tablet Levothyroxine Abdi 75 micrograms contains 62.58 mg of lactose.
Each tablet Levothyroxine Abdi 100 micrograms contains 62.55 mg of lactose.
Each tablet Levothyroxine Abdi 125 micrograms contains 62.54 mg of lactose.
Each tablet Levothyroxine Abdi 150 micrograms contains 62.51 mg of lactose.
Each tablet Levothyroxine Abdi 175 micrograms contains 62.49 mg of lactose.
Each tablet Levothyroxine Abdi 200 micrograms contains 62.46 mg of lactose.

For the full list of other excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Levothyroxine Sodium 25 mcg Tablets are round and white tablets debossed on one side with “25” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 50 mcg Tablets are round and white tablets debossed on one side with “50” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 75 mcg Tablets are round and white tablets debossed on one side with “75” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 100 mcg Tablets are round and white tablets debossed on one side with “100” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 125 mcg Tablets are round and white tablets debossed on one side with “125” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 150 mcg Tablets are round and white tablets debossed on one side with “150” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 175 mcg Tablets are round and white tablets debossed on one side with “175” and scored in the shape of “+” sign on the other side.

Levothyroxine Sodium 200 mcg Tablets are round and white tablets debossed on one side with “200” and scored in the shape of “+” sign on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levothyroxine Abdi 25 – 200 micrograms:

- Treatment of benign goiter (thyroid enlargement) with euthyroid function
- Prophylaxis of recurrent goiter after resection of the goiter with euthyroid function, depending on the postoperative hormonal status
- Thyroid hormone replacement in hypothyroidism
- Suppression treatment in thyroid malignancy

Levothyroxine Abdi 25 – 100 micrograms:

- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism

Levothyroxine Abdi 100/150/200 micrograms:

- Diagnostic use for thyroid suppression test

4.2 Posology and method of administration

Posology

In order to treat each patient individually according to needs of the patient, tablets with a gradually-increasing content of 25 to 200 micrograms of levothyroxine sodium are available, so generally only one tablet should be taken daily.

The dosing recommendations provided in this document are for guidance purposes only.

Individual daily dose should be determined by laboratory tests and clinical examinations.

Since some patients who are undergoing treatment have elevated T4 and fT4 levels, the determination of the basal serum concentration of the thyroid-stimulating hormone (TSH) is a more reliable basis for the further therapeutic approach.

Treatment with thyroid hormones should be started at a low dose and gradually increased every 2 to 4 weeks in order to reach to the targeted dose.

Elderly population:

In patients with coronary heart disease and in patients with severe or long-existing hypothyroidism, treatment with thyroid hormones should be started with special care. At first, a low initial dose (e.g., 12.5 micrograms/day) should be administered, and then it should be increased slowly and at longer intervals (e.g., a gradual dose increase of 12.5 micrograms every 14 days) with frequent control of thyroid hormone levels. Dosage below the dose required for complete substitution and therefore insufficient to fully normalize TSH value must be considered here.

Experiences have shown that a lower dose is sufficient even with low body weight and with a large nodular goiter.

Paediatric population:

In newborns and children with congenital hypothyroidism requiring rapid substitution, an initial dose of 10 to 15 micrograms/kg of body weight per day is recommended for the first 3 months. Afterwards, the dose should be adjusted based on individual clinical findings, and thyroid hormone and TSH levels.

Indication	Recommended dosage (levothyroxine sodium microgram /day)				
Benign goiter with euthyroid function	75 – 200				
Prophylaxis of recurrent goiter after resection of the goiter with euthyroid function	75 – 200				
Thyroid hormone replacement in Hypothyroidism in adults: – Initial dose – Maintenance dose	25 – 50 100 – 200				
Thyroid hormone replacement in hypothyroidism in children: – Initial dose – Maintenance dose	12,5 – 50 100– 150 micrograms/m^2 body surface				
Supplementation therapy with antithyroid drug treatment in hyperthyroidism	50 – 100				
Suppression treatment in thyroid malignancy	150 – 300				
Diagnostic application as part of the thyroid suppression test		Week 4 prior to test	Week 3 prior to test	Week 2 prior to test	Week 1 prior to test

	Levothyroxine Abdi 200 micrograms	–	–	1 Tablet/ Day	1 Tablet/ Day
	Levothyroxine Abdi 100 micrograms	–	–	2 Tablets /Day	2 Tablets/ Day
	Levothyroxine Abdi 150 micrograms	½ Tablet/ Day	½ Tablet/ /Day	1 Tablet/ Day	1 Tablet/ Day

Method of administration

Total daily dose can be administered at once.

Usage: Total daily dose is taken in the morning on an empty stomach at least half an hour before breakfast with some amount of liquid (e.g.: half a glass of water).

Children should receive the total daily dose at least 30 minutes before the first meal of day. For this, the tablets are disintegrated in some water and the resulting fine distribution is administered (should be freshly prepared for each use!) with a little more liquid.

Duration of use: It is mostly used throughout one's life in hypothyroidism, after strumectomy or thyroidectomy, and for the prevention of relapse after resection of a goiter with euthyroid function. After reaching euthyroid function, a concomitant therapy for the treatment of hyperthyroidism is indicated for the duration of thyrostatic medication.

For benign goiter with euthyroid function, a treatment duration of 6 months to 2 years is required. If drug treatment is insufficient during this period, surgery or radioiodine therapy of the goiter should be considered.

4.3 Contraindications

– In case of hypersensitivity to the active substance or any of the other excipients listed in section 6.1.

– Untreated adrenal insufficiency, untreated pituitary insufficiency and untreated hyperthyroidism.

– Treatment with Levothyroxine Abdi should not be started in acute myocardial infarction, acute myocarditis and acute pancarditis.

– Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Before initiating thyroid hormone treatment or performing a thyroid suppression test, the following diseases or medical conditions should be excluded or treated: Coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary or adrenocortical insufficiency. Thyroid autonomy should also be excluded or treated prior to treatment with thyroid hormones.

When initiating thyroid hormone treatment in patients at risk for psychotic disorders, it is recommended to start with a low levothyroxine dose and slowly increase the dose from the baseline

of the treatment. Follow-up of the patient is indicated. If psychotic disorder symptoms appear, adjustment of levothyroxine dosage should be considered.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence, frequent examination of the thyroid hormone parameters is recommended.

In case of secondary hypothyroidism, the cause must be clarified before initiation of substitution treatment. 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). And, if necessary, appropriate replacement treatment must be initiated in the presence of compensated adrenocortical insufficiency.

If thyroid autonomy is suspected, a TRH test or suppression scintigraphy should be performed.

In levothyroxine treatment on postmenopausal women with hypothyroidism, who have an increased risk of osteoporosis; thyroid function should be closely monitored in order to avoid supraphysiological blood levels of levothyroxine.

Levothyroxine should not be administered to patients with hyperthyreotic state metabolism, other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

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.

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.

In the case of existing, discontinued levothyroxine treatment, it is recommended to adjust the dosage according to clinical response of the patient and laboratory values.

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.

Concurrent usage of orlistat and levothyroxine may result in hypothyroidism and / or decreased control of hypofunction (see section 4.5). Patients taking levothyroxine should consult a physician before initiating the treatment, discontinuing the treatment or changing the treatment with orlistat, as orlistat and levothyroxine may need to be taken with intervals and the levothyroxine dosage may need to be adjusted. In addition, it is recommended to monitor the patient's serum hormone levels.

<u>Interferences with laboratory test:</u>
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 lactose. Patients with rare hereditary problems such as galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Levothyroxine Abdi.

Information on diabetic patients and patients taking anticoagulants can be found in section 4.5.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’

4.5 Interaction with other medicinal products and other forms of interaction

Antidiabetics:

Levothyroxine may reduce the effects of anti-diabetic drugs. Therefore, blood sugar levels must be checked frequently at the beginning of thyroid hormone treatment and if necessary, the dosage of the blood sugar-lowering drugs can be adjusted.

Coumarin derivatives:

Since levothyroxine displaces anticoagulants from plasma proteins, the effect of anticoagulant therapy may be enhanced, which may increase the risk of bleeding especially in the elderly, such as central nervous system bleeding or gastrointestinal bleeding. Therefore, periodic controls of the coagulation parameters are required at the beginning of therapy and throughout combination treatment, and if necessary, anticoagulant drug dosage may be adjusted.

Protease inhibitors(e.g. ritonavir, indinavir, lopinavir):

Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.*Phenytoin*:

Phenytoin can influence the action of levothyroxine by suppression of plasma protein binding, which leads to an increase in the fT4 and fT3 proportion. Rapid intravenous administration of phenytoin may increase the level of free levothyroxine in plasma and, in rare cases, may lead to arrhythmias. On the other hand, phenytoin leads to an increased metabolism of levothyroxine in the liver. Close monitoring of thyroid hormone levels is recommended.

Cholestyramine, Colestipol:

Intake of ion exchange resins such as cholestyramine and colestipol inhibit the absorption of levothyroxine. Therefore, Levothyroxine should be taken 4 to 5 hours before taking such medicines.

Aluminum, iron and calcium:

In the literature, it has been reported that preparations containing aluminum (antacids, sucralfate) may reduce the efficacy of levothyroxine administration. Therefore, levothyroxine should be taken at least 2 hours before the administration of aluminum-containing products.

The same applies to iron and calcium salt-containing medicinal products.

Salicylates, dicoumarol, furosemide, clofibrate:

Salicylates, dicoumarol, furosemide (250 mg) in high doses, clofibrate and other

substances can suppress levothyroxine from plasma protein binding, leading to an increase in fT4 content.

Orlistat:

Concurrent usage of orlistat and levothyroxine may result in hypothyroidism and / or decreased control of hypofunction. This may be due to decreased absorption of iodine salts and/or levothyroxine.

Sevelamer:

Sevelamer may lead to reduced absorption of levothyroxine. Therefore, it is recommended that patients should be monitored for changes in thyroid function in the beginning and end of combination treatment. If necessary, the levothyroxine dose must be adjusted

Tyrosine kinase inhibitors:

Tyrosine kinase inhibitors (e.g., imatinib, sunitinib) may decrease the efficacy of levothyroxine. Therefore, it is recommended that patients should be monitored for changes in thyroid function in the beginning and end of combination treatment. Where appropriate, levothyroxine dose must be adjusted.

Propylthiouracil, glucocorticoids, beta-sympatholytic agents, amiodarone and iodine-containing contrast agents:

These substances inhibit the peripheral conversion of T4 into T3.

Due to its high iodine content, amiodarone can cause both hyperthyroidism and hypothyroidism. Particular caution should be exercised in nodular goiter with possibly unrecognized autonomy.

Sertraline, chloroquine / proguanil:

These substances decrease the efficacy of levothyroxine and lead to an increase in TSH.

Drugs with enzyme-inducing effect:

Medicinal products that can induce the enzyme system in the liver, such as barbiturates, carbamazepine or products containing St John’s Wort (Hypericum perforatum L.) may increase the hepatic clearance of levothyroxine.

Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these products are given concurrently.

Estrogens:

In women taking estrogen-containing contraceptives or in post-menopausal women taking hormone replacement treatment, the need for levothyroxine may be increased.

Soy products:

Soy products can reduce the intestinal uptake of Levothyroxine Abdi. Particularly at the beginning or the end of a soy-containing diet, dose adjustment of Levothyroxine Abdi may become necessary.

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).

Proton pump inhibitors (PPIs):

Co-administration with PPIs may cause a decrease in the absorption of the thyroid hormones, due to the increase of the 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.
Care should also be taken when treatment with PPI ends.

4.6 Fertility, pregnancy and lactation

Treatment with levothyroxine must be carried out consistently, especially during pregnancy and lactation. A dose increase may be required during pregnancy. Elevated serum TSH levels may occur as early as the 4th week of pregnancy. Therefore, pregnant women taking levothyroxine should have their TSH levels checked to confirm that maternal serum TSH levels are within the trimester-specific pregnancy reference range during each trimester. Elevated serum TSH levels should be corrected by increasing the levothyroxine dose. Since postpartum TSH levels are similar to those before conception, levothyroxine dose should be switched to the dose before the pregnancy immediately after birth. Serum TSH levels should be determined 6 to 8 weeks after birth.

Pregnancy

Experiences have shown that there is no evidence of substance-induced teratogenicity and/or fetotoxicity in humans in the recommended dose range. Excessive levothyroxine levels during pregnancy can have a negative effect on fetal and postnatal development.

Concomitant treatment with levothyroxine and antithyroid drugs in hyperthyroidism is not indicated during pregnancy. Such concomitant treatment requires a higher dosage of antithyroid drugs, which is known to be placental and may trigger hypothyroidism in the child.

Diagnostic use in the context of the thyroid suppression test must be avoided during pregnancy, as the use of radioactive substances in pregnant women is contraindicated.

Breast-feeding

Levothyroxine is secreted into breast milk, but the concentrations achieved at the recommended dose range are not sufficient to cause hyperthyroidism or TSH suppression in the infant.

4.7 Effects on ability to drive and use machines

There are no studies conducted on the impact on the ability to drive and the operate machinery. Since levothyroxine is identical to the naturally occurring thyroid hormone, Levothyroxine Abdi is not expected to affect the ability to drive and operate machinery.

4.8 Undesirable effects

If in individual cases, the dose strength is not tolerated or if there is an overdose case, especially if the dose is increased too quickly at the beginning of the treatment, symptoms may be experienced, such as occurrence in overactivity of thyroid glands: Cardiac arrhythmias (e.g., atrial fibrillation and extrasystoles), tachycardia, palpitations, pectanginous conditions, headache, muscle weakness and spasms, flushing, fever, vomiting, menstrual disorders, pseudotumor cerebri, tremor, inner restlessness, insomnia, hyperhidrosis, weight loss, diarrhea.

In these cases, the daily dose should be reduced or the medication should be discontinued for several days. Once the adverse effect has disappeared, the treatment can be restarted with a more careful dosing.

In case of hypersensitivity to any of the components of Levothyroxine Abdi, allergic reactions of the skin and respiratory tract may occur. Angioedema, rash and urticaria cases have been reported (frequency of incidences is 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 Nederlands Bijwerkingen Centrum Lareb at: www.lareb.nl.

4.9 Overdose

An elevated T3 value is a more reliable indicator of overdose compared to elevated T4 or fT4 levels.

Overdose causes symptoms of distinct increase in the metabolism (see section 4.8). These signs can occur with delay of 2 to 5 days after levothyroxine overdose. Depending on the degree of overdose, it is recommended to discontinue the administration of tablets, and follow up is recommended.

Symptoms may express themselves as strong beta-sympathomimetic effects, such as tachycardia, anxiety, agitation, and hyperkinesis. The complaints can be relieved by beta-receptor blockers. At extreme doses, plasmapheresis may be helpful.

Seizures have been reported in isolated cases in predisposed patients upon exceeding the individual dose tolerance limit.

Overdose of levothyroxine can lead to symptoms of hyperthyroidism and trigger acute psychosis, especially in patients at risk for psychotic disorders.

There are some reports of sudden cardiac death in patients with a history of years of levothyroxine abuse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC-Code: H03A A01

The synthetic levothyroxine that Levothyroxine Abdi contains is identical to the naturally occurring thyroid hormone predominantly produced by the thyroid gland in terms of its action. It is transformed into T3 in the peripheral organs, and like the natural hormone, shows its characteristic effects at the T3 receptors. Body can not distinguish between endogenous and exogenous levothyroxine.

5.2 Pharmacokinetic properties

Orally administered levothyroxine is almost solely absorbed through the upper small intestine. Depending on the type of pharmaceutical preparation, the absorption rate may be up to a maximum level of 80%. Tmax is approximately 5 to 6 hours.

The onset of action occurs 3 - 5 days after the beginning of oral treatment. Levothyroxine has an extremely high plasma protein binding of 99.97%. There is no covalent bonding, therefore a continuous and very rapid replacement takes place between hormone bound to proteins in the plasma and free hormone content.

Due to its high protein binding, levothyroxine is neither hemodialisable nor can it be removed from the body by hemoperfusion.

The elimination half-life of levothyroxine is 7 days on average. It is shortened (3 - 4 days) in hyperthyroidism and prolonged in hypothyroidism (to about 9 - 10 days). Distribution volume is 10 - 12 L. 1/3 of extra-thyroid levothyroxine is found in the liver, and is rapidly replaceable with serum levothyroxine. Thyroid hormones are primarily metabolized in the liver, kidneys, brain and muscles. The metabolites are excreted through urine and faeces. Metabolic clearance is about 1.2 L plasma/day.

5.3 Preclinical safety data

Acute toxicity:

The acute toxicity of levothyroxine is very low.

Chronic toxicity:

Chronic toxicity studies have been performed on various animal species (rat, dog). At high doses, signs of hepatopathy, increased incidence of spontaneous nephrosis, as well as altered organ weight have been observed in rats.

Reproduction toxicity:

Reproduction toxicology studies have not been performed on animals.

Mutagenicity:

There is no evidence on the mutagenic potential of levothyroxine. Until now, there has been no evidence of damage to the offspring due to changes in the genome by thyroid hormones.

Carcinogenicity:

Long-term animal studies have not been performed with levothyroxine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Maize Starch

Gelatin

Croscarmellose Sodium

Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

PVC/PE/PVDC-Aluminum blister packaging in cartons containing 30, 50, 84, 90, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Abdi Farma, Unip. Lda.

Quinta da Fonte, Rua dos Malhões,

Edifício D. Pedro I

2770-071 Paço de Arcos,

Portugal

8. MARKETING AUTHORIZATION NUMBER(S)

Levothyroxine Abdi 25 microgram tabletten	RVG 123126
Levothyroxine Abdi 50 microgram tabletten	RVG 123129
Levothyroxine Abdi 75 microgram tabletten	RVG 123130
Levothyroxine Abdi 100 microgram tabletten	RVG 123131
Levothyroxine Abdi 125 microgram tabletten	RVG 123132

Levothyroxine Abdi 150 microgram tabletten	RVG 123133
Levothyroxine Abdi 175 microgram tabletten	RVG 123134
Levothyroxine Abdi 200 microgram tabletten	RVG 123135

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Datum van eerste verlening van de vergunning: 14 november 2019
Datum van laatste verlenging: 6 november 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 28 februari 2024