

**The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it on February 2016.**

## **Summary of Product Characteristics**

### **1. NAME OF THE MEDICINAL PRODUCT**

**Eltroxin<sup>®</sup>** Tablets 50mcg  
**Eltroxin<sup>®</sup>** Tablets 100mcg

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Eltroxin Tablet containing 50 mcg (0.05mg) or 100 mcg (0.1mg) anhydrous thyroxine sodium respectively, which is the monosodium salt of the levorotary isomer of thyroxine

### **3. PHARMACEUTICAL FORM**

non-scored tablets

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Treatment of hypothyroidism, cretinism and juvenile myxoedema

#### **4.2 Posology and method of administration**

If the dose of thyroxine is increased too rapidly, symptoms such as diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia, may occur, and the dosage must be reduced or withheld for a day or two, then restarted at a lower level. A pre-therapy ECG is valuable, as changes induced by hypothyroidism may be confused with ECG evidence of ischaemia.

Due to a lack of data it is not appropriate to crush thyroxine tablets and thyroxine tablets without a score-line must not be halved.

Thyroxine tablets should preferably be taken on an empty stomach.

## **Missed dosage**

If a scheduled daily dose is missed, the dose should be taken as soon as the patient remembers, unless it is almost time for the patient's next dose. Two doses should not be taken together.

## **Populations**

### **• Adults**

Initially 50 to 100 micrograms daily and adjust at 4 to 6 week intervals by 50 micrograms until attainment of clinical and biochemical euthyroidism. This may require doses of 100 to 200 micrograms daily.

With patients aged over 50 years, it is not advisable to exceed 50 micrograms a day initially. Where there is cardiac disease, 50 micrograms on alternate days is more suitable. In this condition the daily dosage may be increased by 50 micrograms on alternate days, at intervals of approximately 4 weeks.

### **• Children**

In congenital hypothyroidism and juvenile myxoedema, the largest dose consistent with freedom from toxic effects should be given. The dosage is guided by clinical response, growth assessment and appropriate thyroid function tests – clinically normal pulse rate and absence of diarrhoea or constipation are the most useful indicators. Thyrotrophin levels may remain elevated during the first year of life in children with neonatal hypothyroidism due to resetting of the hypothalamic-pituitary axis.

For infants with congenital hypothyroidism a suitable starting dose is 50 micrograms thyroxine sodium on alternate days, with increments of 50 mcg on alternate days at intervals of every two to four weeks until optimal response is achieved. The same dosing regimen applies to juvenile myxoedema, except that the starting dose for children older than one year may be 2.5 to 5 micrograms/kg/day. The calculated daily dose equivalent should be rounded to the nearest 25 micrograms to determine the actual prescribed dose.

## **Method of Administration**

For oral administration.

### **4.3 Contraindications**

- Hypersensitivity to any component of the preparation.
- Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Eltroxin must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.
- Combination therapy of levothyroxine and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

### **4.4 Special warnings and special precautions for use**

#### **Laboratory Monitoring**

Thyroxine has a narrow therapeutic index. Appropriate thyroxine dosage is based upon clinical assessment and laboratory monitoring of thyroid function tests. During the initial

titration period, careful dosage titration and monitoring is necessary to avoid the consequences of under- or over-treatment. The symptoms of excessive thyroxine dosage are the same as many features of endogenous thyrotoxicosis.

Thyroid Hormones are not suitable for treatment of Obesity or weight reduction.

In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for anorectic effects.

In order to ensure the continuity of different products of levothyroxine sodium in individual patients it should be emphasized that if patients are changed from one levothyroxine sodium product to another it should be done only with specific counseling and tight monitoring from their healthcare professional.

Before starting therapy with thyroid hormones or before performing a thyroid suppression test, the following diseases or medical conditions should be excluded or treated: coronary failure, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency. Thyroid autonomy should also be excluded or treated before starting therapy with thyroid hormones.

#### Special patient populations

Treatment with thyroxine in patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may cause reactions, including dizziness, weakness, malaise, weight loss, hypotension and adrenal crisis. It is advisable to initiate corticosteroid therapy before giving thyroxine in these cases.

Eltroxin should be used with caution in the elderly and in patients where heart insufficiency, myocardial infarction or ischaemia as well as diabetes mellitus or insipidus is present. An excessive initial dose or a too rapid dose escalation may cause or aggravate symptoms such as angina pectoris, arrhythmia, myocardial infarction, heart insufficiency or sudden blood pressure elevation. See section 4.2.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases.

Thyroxine raises blood sugar levels and this may upset the stability of patients receiving anti-diabetic agents.

In the case of secondary hypothyroidism the cause must be determined before replacement therapy is given and if necessary replacement treatment of a compensated adrenal insufficiency must be commenced. Patients with myxoedema have increased sensitivity to thyroid hormones. In these patients the initial dose must be low and dose escalation should take place slowly.

Absorption of thyroxine is reduced in patients with malabsorption. It is recommended to treat the malabsorption condition to ensure an effective thyroxine treatment.

In patients treated with levothyroxine the thyroxine level in serum may decrease and the TSH level increase during pregnancy. The increase in serum TSH levels should be measured more frequently during pregnancy and an increased level must immediately be

corrected by increasing the dose of levothyroxine. At post-partum the dose of levothyroxine may be reduced to the level before pregnancy.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely.

Where thyroid autonomy is suspected a TRH test should be carried out or a suppression scintigram obtained before treatment.

Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

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

- The effect of anticoagulants may be intensified as levothyroxine displaces anticoagulants from plasma proteins. It is therefore necessary to monitor coagulation parameters regularly when initiating and discontinuing treatment with thyroid hormone. The anticoagulant dose may have to be adjusted. Phenytoin levels may be increased by thyroxine.
- Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter thyroxine dose requirements.
- Barbiturates and other substances such as rifampicin, capable of inducing liver enzymes, may increase the hepatic clearance of levothyroxine.
- If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.
- The effect of sympathomimetic agents are also enhanced.
- Thyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants.
- Aluminium, Calcium, magnesium, iron-containing drugs, (antacids, sucralfate) have been reported in the pertinent literature as potentially decreasing the effect of levothyroxine. Drugs containing levothyroxine should therefore be administered at least 2 hours prior to the administration of these drugs.
- Ingestion of ion exchange resins such as, kayexalate, sevelamer, lanthanum and bile acid sequestrants such as cholestyramine, colestipol and proton pump inhibitors inhibits the absorption of levothyroxine sodium. To avoid interaction between the medicinal products in the stomach or in the small intestine it should be attempted to separate the dosages of Levothyroxine sodium and it should therefore be taken 4-5 hours before administration of such products.

- Sevelamer may decrease levothyroxine absorption. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine dose has to be adjusted.
- Salicylates, dicumarol, furosemide in high doses (250 mg), clofibrate and other substances can displace levothyroxine sodium from plasma proteins, resulting in an elevated fT4 fraction.
- Co-administration of oral contraceptives or post-menopausal women treated with hormone replacement therapy as well as a number of other drugs, including oestrogen, tamoxifene, clofibrate, methadone, and 5-fluorouracil may increase serum concentration of thyroxine-binding globulin, and therefore increase thyroxine dosage requirements.
- Reports indicate that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase thyroid hormone requirements in patients receiving thyroxine therapy. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate thyroxine dose adjustments may be necessary when thyroxine and statins are co-prescribed.
- Treatment with tyrosine kinase inhibitors (e.g., imatinib and sunitinib) was associated with increased thyroxine dosage requirements in hypothyroid patients.
- Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone, lithium, and iodine as well as contrast media containing iodine : These substances inhibit the peripheral conversion of T4 to T3. Due to its high iodine content amiodarone can trigger hyperthyroidism as well as hypothyroidism. Particular caution is advised in the case of nodular goitre with possibly unrecognized autonomy.
- Anti-diabetic agents: Levothyroxine may reduce the effect of antidiabetic agents. For this reason, blood glucose levels should be checked frequently at the start of thyroid hormone therapy and the dosage of the antidiabetic agent has to be adapted, if necessary.
- Protease inhibitors (e.g. ritonavir, indinavir, lopinavir) may influence the effect of levothyroxine. Close monitoring of thyroid hormone parameters is recommended. If necessary, the levothyroxine dose has to be adjusted.
- Sertraline, chloroquine/ proguanil: These substances decrease the efficacy of levothyroxine and increase the serum TSH level.
- Soy-containing compounds and diet with high fibre content can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of Eltroxin may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

#### Interactions in laboratory tests

- A number of drugs may decrease serum concentration of thyroxine-binding globulin, and therefore decrease thyroxine dosage requirements, including androgens and anabolic steroids.

- When treating concomitantly with thyroxine and anti-inflammatory drugs such as phenylbutazone or acetylsalicylic acid false concentrations of thyroid hormones have been observed. Concomitant ingestion of acetylsalicylic acid and thyroxine in an initial transient increase of free T4 in serum. Continued administration lead to normal concentrations of free T4 and TSH, and the patients will therefore be clinically euthyroid.

A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on thyroxine therapy.

## **4.6 Pregnancy and lactation**

### Pregnancy

Thyroxine has been taken by a large number of pregnant women and women of childbearing age without any form of definite disturbances in the reproductive process having been observed so far.

Thyroid, hypo- or hyperactivity in the mother may, however, unfavourably influence the foetal outcome or well-being.

The risk of the untreated disease is deemed to be larger than the risk to the foetus during treatment.

Markedly increased levothyroxine doses may have a negative effect on foetal and postnatal development during pregnancy. Treatment during pregnancy requires closed monitoring.

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy. Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

### Lactation

Thyroxine is excreted in breast milk in low concentrations and this may be sufficient to interfere with neonatal screening for hypothyroidism.

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

From the pharmacokinetic and pharmacodynamic properties of thyroxine, treatment with thyroxine sodium would not be expected to interfere with ability to drive or operate machinery.

## **4.8 Undesirable effects**

The frequency classification for these adverse reactions is not known due to a lack of robust clinical trial data to accurately determine frequency estimates.

**Cardiac disorders:** Anginal pain, cardiac arrhythmias, palpitations, tachycardia, increased blood pressure, heart failure, myocardial infarction.

**Endocrine disorders:** Hyperthyroidism (if the initial dose is increased too rapidly).

**Immune system disorders:** Hypersensitivity reactions such as skin rash and pruritus and anaphylactic reactions.

**Metabolism and nutrition disorders:** Increased appetite, excessive loss of weight

**Nervous system disorders:** headache, tremors, seizure. Rare cases of pseudotumor cerebri (benign intracranial hypertension) have been reported especially in children.

**Psychiatric disorders:** Irritability, anxiety, mood disorder, nervousness, excitability, insomnia, restlessness.

**Respiratory, thoracic and mediastinal disorders:** Dyspnoea.

**Gastrointestinal disorders:** Abdominal cramps, nausea, vomiting, diarrhoea.

**Skin and subcutaneous tissue disorders:** Sweating, hair loss.

**Musculoskeletal, connective tissue and bone disorders:** Cramps in the skeletal muscle, muscular weakness, decreased bone mineral density.

Excessive dose may result in craniosynostosis in infants, and premature closure of epiphyses in children with compromised adult height.

**Reproductive system and breast disorders:** Menstrual irregularity, impaired fertility.

**General disorders and administration site conditions:** Fatigue, heat intolerance, fever.

**Vascular disorders:** Redness, hot flashes.

#### 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

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

## **4.9 Overdose**

### **Toxicity:**

In case of poisoning (suicide attempt) in humans doses of 10 mg levothyroxine were tolerated without complications. Several cases of sudden cardiac death have been reported in patients after several years of levothyroxine abuse.

### **Symptoms and Signs:**

In addition to exaggeration of side effects the following symptoms of a marked increase in the metabolic rate, elevated levels of T<sub>3</sub> increased side effects as well as intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation, and hyperkinesia. Furthermore irritability, sweating, arrhythmias, confusion, hyperactivity, headache, mydriasis, tachypnoea, pyrexia, increased bowel movements and convulsions. The appearance of clinical hyper- thyroidism may be delayed for up to five days. Symptoms of thyrotoxicosis are observed after prolonged overdose

### **Treatment**

The goal of therapy is restoration of clinical and biochemical euthyroid state by omitting or reducing the thyroxine dosage, and other measures as needed depending on clinical status.

Symptomatic treatment:

Symptoms of intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia may be reduced with beta-blockers. After extreme doses plasmapheresis may help.

In adults tachycardia is controlled with propranolol in doses of 40 mg every 5 hours and other symptoms with diazepam and / or chlorpromazine when relevant.

Further treatment is given after clinical indication or as recommended by the national poison center when available.

## **5. PHARMACOLOGICAL PROPERTIES**

Thyroxine sodium is the monosodium salt of the levorotary isomer of thyroxine.

### **5.1 Pharmacodynamic properties**

Thyroxine (T<sub>4</sub>) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone tri-iodothyronine (T<sub>3</sub>) in peripheral tissues. The precise signals controlling the conversion of T<sub>4</sub> to T<sub>3</sub> within the cell are not known. The thyroid hormones are required for normal growth and development, particularly of the nervous system. They increase the resting or basal metabolic rate of the whole organism and have stimulatory effects on the heart, skeletal muscle, liver and kidney. Thyroid hormones enhance lipolysis and the utilization of carbohydrate.

100 mcg thyroxine is equivalent in activity to 20 to 30 mcg liothyronine/tri-iodothyronine or 60mg thyroid BP and/or local pharmacopoeia specification.

### **5.2 Pharmacokinetic properties**

#### **Absorption**

Following oral administration the absorption of thyroxine is incomplete and variable especially when taken with food. The amount absorbed increases during fasting conditions.

#### **Distribution**

Thyroxine is nearly totally bound to serum protein.



## Metabolism

The main pathway for the metabolism of thyroxine ( $T_4$ ) is its conversion, by de-iodination, to the active metabolite tri-iodothyronine ( $T_3$ ). Further de-iodination of  $T_4$  and  $T_3$  leads to production of inactive products.

## Elimination

Thyroxine is eliminated slowly from the body with a half-life of approximately seven days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients.

In man approximately 20-40% of thyroxine is eliminated in the faeces and approximately 30 to 55% of a dose of thyroxine is excreted in the urine.

## Special Patient Populations

- **Renal impairment**

Renal disease does not appear to have any significant effect on the disposition of thyroxine.

- **Hepatic impairment**

Hepatic disease does not appear to have any significant effect on the disposition of thyroxine.

## **5.3 Preclinical safety data**

None stated.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose (in triturate)

Microcrystalline cellulose

Pre-gelatinised starch (Maize starch 1500)

Talc

Silica colloidal anhydrous

Magnesium stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf-life**

24 months.

After first opening can be used for 114 days

### **6.4 Special precautions for storage**

Do not store at temperatures exceeding 25°C.

Store in the original container, protected from light.

Keep the container tightly closed.

### **6.5 Nature and contents of container**

Eltroxin 50 mcg tablets: White Opaque polypropylene bottles with tamper-evident, snap fit, low-density polyethylene closures, containing 100 tablets.

Eltroxin 100 mcg tablets: White Opaque polypropylene bottles with tamper-evident, snap fit, low-density polyethylene closures, containing 100 tablets.

### **6.6 Instruction for use and handling**

No special requirements.

## **7. MANUFACTURER**

Aspen Bad Oldesloe GmbH, Bad Oldesloe, Germany

## **8. REGISTRATION AUTHORISATION HOLDER**

Perrigo Israel agencies Ltd., Lechi 29, Bnei-Brak, Israel.

## **9. REGISTRATION AUTHORISATION NUMBER**

Eltroxin<sup>®</sup> Tablets 50 mcg 55-82-20571

Eltroxin<sup>®</sup> Tablets 100 mcg 27-92-22062

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