SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eltroxin® Tablets 50mcg
Eltroxin® Tablets 100mcg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levothyroxine sodium 50 micrograms or 100 micrograms.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

non-scored tablets

The tablets are round, white to off-white and biconvex. The tablet with 50 micrograms is engraved with “GS 11E” on one side and with “50” on the other. The tablet with 100 micrograms is engraved with “GS 21C” on one side and with “100” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypothyroidism, cretinism and juvenile myxoedema.

4.2 Posology and method of administration

Posology

General
If the dose is increased too rapidly symptoms such as diarrhoea, nervousness, high heart rate, insomnia, tremor and at times pain in the heart with latent myocardial ischaemia may occur. In such cases the dose should be reduced or treatment omitted for one or two days and then restarted at a lower dose. ECG changes caused by hypothyroidism may be confused with ECG signs of ischaemia. Therefore, it is recommended to have an ECG performed prior to start of Eltroxin.

In patients on medicines including levothyroxine and known interfering substances administration should be at least 4 hours apart (see section 4.5 Interactions).

Adults
The treatment is initiated with 50-100 micrograms daily, which is increased by 50 micrograms in intervals of 4 to 6 weeks until clinical and biochemical euthyroidism is obtained. This may require doses of 100-200 micrograms daily.

Elderly patients and patients with heart disease or serious, prolonged hypothyroidism
Use with caution in patients over 50 years old, patients with heart disease and patients with serious or prolonged hypothyroidism.

For patients over 50 years it is not recommended to initially exceed 50 micrograms daily. For heart disease 50 micrograms every second day is more suitable, and the dose may be increased by 50 micrograms every second day with intervals of around four weeks.

Paediatric population
For congenital hypothyroidism and juvenile myxoedema the largest dose not leading to a toxic effect is given. The dose is depending on clinical response, assessment of growth and relevant tests of thyroid function. Clinically normal pulse rate and absence of diarrhoea or constipation are the most useful indicators.
As a consequence of the readjustment of the hypothalamic-pituitary axis the thyrotropin level may remain elevated during the first year of life in children with neonatal hypothyroidism.

A suitable initial dose for infants with congenital hypothyroidism would be 50 micrograms levothyroxine sodium every second day. This is increased with 50 micrograms every second day at two-to-four-week intervals until optimal response is achieved.
The same procedure can be used for children with juvenile myxoedema, except that the initial dose in children over 1 year of age is 2.5-5 micrograms/kg/day.

The calculated daily dose equivalent should be rounded to the nearest 25 micrograms to determine the actual prescribed dose.

Eltroxin tablets should not be divided. If a dosage of 25 micrograms is required, other registered products containing Levothyroxine 50mcg that can be divided to 25 mcg, can be used.

Administration

For oral administration.

As limited data are available Eltroxin tablets should not be crushed, and Eltroxin tablets without a scoreline should not be divided.

Eltroxin tablets should preferably be taken in the fasting state.

If a dose is forgotten it should be taken as soon as the patient remembers it, unless it is almost time for the patient's next dose. A double dose should not be taken.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Untreated adrenal insufficiency
- Untreated pituitary insufficiency
- Untreated thyrotoxicosis.
- Untreated hypertension
- Acute myocardial infarction
- Acute myocarditis
- Acute pancarditis.

Combination treatment of levothyroxine and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Laboratory monitoring
Eltroxin has a narrow therapeutic index. Optimal Eltroxin dosing is based on a clinical assessment and laboratory monitoring of tests of thyroid function. During the initial titration period a careful dose titration and monitoring is necessary to avoid the consequences of excessive or inadequate treatment. The symptoms of a high dosage can be compared to many of the traits observed for endogenous thyrotoxicosis.

Interference with laboratory tests:
Biotin may interfere with thyroid immunoassays based on the interaction of biotin with streptavidin, leading to either falsely low or falsely high test results. The risk of interference increases with higher doses of biotin.

When interpreting laboratory test results a possible interference with biotin should be taken into account, in particular if an inconsistent correlation with the clinical presentation is observed.

For patients taking products containing biotin, laboratory personnel should be informed when a thyroid test is requested. Alternative tests that are not sensitive to interference with biotin should be used if available (see section 4.5).

Levothyroxine should not be used for treatment of obesity or weight loss.
Thyroid hormones are not suitable for weight reduction. In euthyroid patients, treatment with levothyroxine will not result in weight loss. Higher doses can cause serious and even life-threatening side effects, especially if treated concomitantly with certain weight-reducing agents, and in particular with sympathomimetic amines.

Weight loss medicine: Orlistat may reduce the absorption of levothyroxine, which may lead to hypothyroidism. To avoid this, orlistat and levothyroxine should be administered at least 4 hours apart. Regular monitoring of changes in the thyroid function is required (see section 4.5).

If switching to another medicinal product containing levothyroxine is necessary, close monitoring, including clinical and biological monitoring during the transitional period, is necessary due to a potential risk of thyroid disorders. In some patients, a dose adjustment may be necessary.

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. Thyroid autonomy should also be excluded or treated before starting therapy with thyroid hormones.

Special patient populations
Treatment with Eltroxin in patients with pituitary insufficiency or other causes of adrenal insufficiency may cause dizziness, weakness, malaise, weight loss, hypotension and Addison's crisis. Treatment with glucocorticoids should therefore be initiated prior to starting treatment with levothyroxine. In case of adrenocortical dysfunction, this should be treated with appropriate replacement therapy prior to initiation of levothyroxine therapy to prevent acute adrenal insufficiency (see section 4.3).

Eltroxin should be used with caution to 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 a sudden increase in blood pressure. 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.

In cases of secondary hypothyroidism, the cause must be found prior to giving replacement treatment, and treatment of a compensated adrenal insufficiency should be initiated if necessary.

Patients with myxoedema have increased sensitivity to thyroid hormones. In these patients, the initial dose should be low and dose escalation should take place slowly.

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

In patients treated with levothyroxine the thyroxine level in serum may decrease and the TSH level increase during pregnancy. When pregnancy is established, the dose of levothyroxine should be increased. TSH should be measured more frequently during pregnancy and an increased level must immediately be corrected by increasing the dose of levothyroxine. Post-partum the dose of levothyroxine may be reduced to the level before pregnancy.

Haemodynamic parameters should be monitored when initiating levothyroxine treatment in premature neonates with a very low birth weight, as circulatory collapse may occur due to immature function of the adrenals.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions reducing the absorption of thyroxine.

Cholestyramine, colestipol
Concomitant administration of cholestyramine or colestipol reduces the absorption of levothyroxine.

Calcium, aluminium, magnesium, iron supplements, polystyrene sulfonates, bile acid binding agents, anion / cation exchangers, sucralfate, lanthanum, and proton pump inhibitors.

Proton pump inhibitors (PPI):

Concomitant administration of PPI may cause a decrease in uptake of thyroid hormones due to the increase in intragastric pH caused by PPI.

Regular monitoring of thyroid function and clinical monitoring are recommended during concomitant therapy. It may be necessary to increase the dose of thyroid hormones.

Caution should also be exercised when terminating treatment with PPI.

These medicinal products reduce the absorption of levothyroxine. Therefore, it is necessary to increase the dose of levothyroxine with concomitant administration. 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 and the above medicinal products as much as possible (see section 4.2).

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.

Ciprofloxacin:
Ciprofloxacin may reduce serum concentrations of levothyroxine.

Products containing soy and a diet with a high fibre content
Products containing soy and a diet with a high fibre content may reduce the intestinal absorption of levothyroxine. Therefore, a dose adjustment of Eltroxin may be warranted, especially in the initial phase or after supplementation with soy containing products has been discontinued.

Weight loss medicinal products
Orlistat may reduce the absorption of levothyroxine, which may lead to hypothyroidism. To avoid this, orlistat and levothyroxine should be administered at least 4 hours apart. Regular monitoring of changes in the thyroid function is necessary.

Interactions affecting thyroxine

Carbamezapine, phenytoin
Anticonvulsants such as e.g. carbamezapine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may therefore require adjustment of levothyroxine dose.

Barbiturates, rifampicin
Effects of medicinal products that induce cytochrome P-450: Enzyme-inducing medicinal products such as barbiturates, other substances such as rifampicin and products containing St. John's wort (Hypericum perforatum L.) may increase the hepatic clearance of levothyroxine, resulting in decreased serum thyroid hormone concentrations.

Therefore, it may be necessary to simultaneously increase the dose of thyroid hormone in patients receiving thyroid replacement therapy.

Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone *, lithium and iodine as well as contrast agents containing iodine*
These substances inhibit the peripheral conversion of T_4 to T_3. Due to the high content of iodine amiodarone may trigger hyperthyroidism as well as hypothyroidism.
Should be used with special caution in case of nodular goitre with possible not known autonomy.

Amiodarone
Treatment with amiodarone in patients with hypothyroidism leads tomultiple effects on thyroid function including an increased need for levothyroxine.

Tyrosine kinase inhibitors
In patients with hypothyroidism, treatment with imatinib and sunitinib is associated with a need for an increased levothyroxine dose. Patients treated with sunitinib may need an increased levothyroxine dose.

Sertraline, chloroquine /proguanil
These substances reduce the effect of levothyroxine and increase the level of serum TSH.

Oestrogens
Women taking contraceptive agents containing oestrogen or postmenopausal women treated with hormone replacement therapy may have an increased need for levothyroxine.

Administration of other medicinal products such as tamoxifen, clofibrate, methadone and 5-fluorouracil may increase the serum concentration of thyroxine-binding globulin, and therefore increase the need for levothyroxine.

Simvastatin, lovastatin
Reports have shown that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase the need for thyroid hormone in patients treated with levothyroxine. It is unknown if this applies to all statins. Close monitoring of thyroid function and appropriate levothyroxine dose adjustment may be necessary when levothyroxine and statins are co-administered.

Protease inhibitors
Post-marketing cases have been reported, suggesting possible interactions between medicinal products containing ritonavir and levothyroxine. Thyroid stimulating hormone (TSH) should be monitored in patients treated with levothyroxine, for at least the first month after initiation and/or discontinuation of treatment with ritonavir, indinavir, lopinavir.

A number of medicinal products may affect the results of tests of thyroid function, and this should be considered when monitoring patients treated with levothyroxine.

Interaction with other medicinal products

Antidiabetics
Levothyroxine may increase the need for antidiabetic medicinal products in patients with diabetes. A reduction of the levothyroxine dose may cause hypoglycaemia if the dose of antidiabetics remain unchanged.

Salicylates, furosemide, clofibrate
Salicylates, dicumarol, furosemide in high dose (250 mg) and other substances may displace levothyroxine sodium from plasma proteins. This leads to an increased fT_4-fraction.

Coumarin derivatives
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, during and discontinuing treatment with thyroid hormone. The anticoagulant dose may have to be adjusted.

Phenytoin
Levothyroxine may increase the phenytoin concentration.

Cardiac glycosides
With concomitant administration of levothyroxine and cardiac glycosides it may be necessary to adjust the dose of cardiac glycosides.

Tricyclic antidepressants
The receptor sensitivity to catecholamines is increased, and the effect of tricyclic antidepressants is hereby enhanced. The effects of sympathomimetics are also enhanced.

Interactions in laboratory tests

Androgens, anabolic steroids
A number of medicinal products, such as androgens and anabolic steroids, may reduce the serum concentration of thyroxine-binding globulin, and would therefore require a reduction of levothyroxine dose.

With concomitant treatment with levothyroxine and anti-inflammatory substances such as phenylbutazone or acetylsalicylic acid, falsely low plasma concentrations of thyroid hormones have been observed. Concomitant administration of acetylsalicylic acid and levothyroxine results in an initial transient increase of free T4 in serum. Continued administration leads to normal concentrations of free T4 and TSH, and the patients will therefore become clinically euthyroid.

Interference with laboratory tests:

Biotin may interfere with thyroid immunoassays based on interaction between biotin and streptavidin, resulting in leading to either falsely low or falsely high test results (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:
A large number of pregnant and fertile women have been treated with levothyroxine without so far observing disturbances to the reproductive process.
However, hypo- or hyperfunction of the thyroid gland in pregnant women may be detrimental to the development and well-being of the foetus.

The risk of the untreated disease is deemed to be greater than the risk to the foetus from the treatment.

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

Levothyroxine should not be taken with medicinal products used for treating hyperthyroidism (antithyroid medicine) during pregnancy, as supplementing treatment with levothyroxine may necessitate an increased dose of the antithyroid medicinal products .

Breast-feeding:
Eltroxin can be used during the breast-feeding period. Eltroxin 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 or use machines

No labelling.
Eltroxin has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The undesirable effects disappear when reducing the daily dose or upon discontinuation.

Classification of side effects into exact estimates of frequency is not possible due to insufficient clinical data.

Endocrine disorders Frequency not known (cannot be estimated from the available data)	Hyperthyroidism (if the initial dose is increased too rapidly).
Psychiatric disorders Frequency not known (cannot be estimated from the available data)	Irritability, anxiety, emotional lability, nervousness, restlessness, agitation, insomnia.
Nervous system disorders Rare (>1/10,000 to <1/1,000) Frequency not known (cannot be estimated from the available data)	Benign intracranial hypertension (especially in children). Tremor, seizures (muscular spasms, shaking), cephalalgia.
Cardiac disorders Frequency not known (cannot be estimated from the available data)	Angina pectoris, arrhythmias, palpitations, tachycardia, hypertension, heart insufficiency, myocardial infarction.
Vascular disorders	Redness, hot flashes.
Skin and subcutaneous tissue disorders Frequency not known (cannot be estimated from the available data)	Hyperhidrosis, hair loss, angioedema, rash, urticaria.
Metabolism and nutrition disorders Frequency not known (cannot be estimated from the available data)	Increased appetite, excessive weight loss.
Gastrointestinal disorders	Abdominal pain, nausea, diarrhoea, vomiting
Respiratory, thoracic and mediastinal disorders Frequency not known (cannot be estimated from the available data)	Dyspnoea.
Immune system disorders Frequency not known (cannot be estimated from the available data)	Hypersensitivity reactions: rash, pruritus and anaphylactic reactions.

Musculoskeletal and connective tissue disorders Frequency not known (cannot be estimated from the available data)	Muscular weakness, muscle cramps. An overdose may cause premature epiphyseal closure in children, leading to compromised height.
Reproductive system and breast disorders Frequency not known (cannot be estimated from the available data)	Irregular menstrual periods, infertility.
Congenital, familial and genetic disorders	An overdosage may cause craniosynostosis in infants.
General disorders and administration site conditions Frequency not known (cannot be estimated from the available data)	Tiredness, temperature intolerance, pyrexia.
Investigations Frequency not known (cannot be estimated from the available data)	Reduced bone mineral density

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il

Additionally, you can also report to Padagis via following address: Padagis.co.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 connection with an overdose, symptoms of a marked increase in the metabolic rate, elevated levels of T_3, increased side effects as well as intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia. Furthermore irritability, sweating, arrhythmias, agitation, confusion, hyperactivity, mydriasis, tachypnoea, pyrexia, convulsions and headache may occur. The occurrence of clinical hyperthyroidism may be delayed by to five days.
Symptoms of thyrotoxicosis are observed after prolonged overdose.

Treatment
The goal of treatment is a re-establishment of clinical and biochemical euthyroidism by reducing or omitting levothyroxine dose, 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 as clinically indicated or as recommended by the national poison unit when available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones, ATC code: H 03 AA 01

Levothyroxine sodium is a monosodium salt of levothyroxine. Levothyroxine (T_4) is a naturally occurring thyroid hormone which is converted to the more active hormone liothyronine (T_3) in peripheral tissue. The precise mechanism for the conversion of T_4 to T_3, which takes place within the cell is unknown. The thyroid hormones are necessary for normal growth and development, particularly of the nervous system. They increase the resting metabolic rate for the whole organism and stimulate the heart, liver, kidneys and skeletal muscle. The thyroid hormones increase lipolysis and carbohydrate metabolism.
The activity of 100 micrograms thyroxine corresponds to 20-30 micrograms liothyronine.

5.2 Pharmacokinetic properties

Absorption
The absorption of levothyroxine is incomplete and variable, especially when taken with food. The absorption is increased during fasting conditions.

Distribution
Levothyroxine is almost completely protein bound.

Biotransformation
Metabolism primarily takes place by conversion to the active metabolite, liothyronine (T_3). Both T_3 and T_4 are further degraded (by de-iodination) to inactive metabolites.

Elimination
Levothyroxine is eliminated slowly from the body with a half-life of approximately 7 days in healthy subjects. This may take place more rapidly in hyperthyroid patients, but in hypothyroid patients it may take even longer.
Renal or hepatic disease does not appear to have any significant effect of the excretion of levothyroxine.
Approximately 20-40% of levothyroxine is excreted in faeces and approximately 30-55% in urine.

5.3 Preclinical safety data

None relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Pre-gelatinised starch (Maize starch 1500)
Talc
Microcrystalline cellulose (in triturate)
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package to protect from light.

Keep the bottle tightly closed.

After first opening can be used for 114 days.

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 Special precautions for disposal and other handling

No special precautions.

7. MANUFACTURER

Aspen Bad Oldesloe GmBH, Bad Oldesloe, Germany.

8. REGISTRATION AUTHORISATION HOLDER

Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham, Israel.

9. REGISTRATION AUTHORISATION NUMBER

Eltroxin® Tablets 50 mcg 55-82-20571

Eltroxin® Tablets 100 mcg 27-92-22062

Revised in January 2024 according to MOH guidelines

1.2024