SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eltroxin 100 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 micrograms anhydrous levothyroxine sodium.
Excipients with known effect: lactose monohydrate 48.86mg
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

A white uncoated biconvex tablet with the words 'Eltroxin 100' engraved on one face and with a breakline on the other face.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Recommended clinical indications: Control of hypothyroidism, congenital hypothyroidism in infants, acquired hypothyroidism in children and juvenile myxoedema.

4.2 Posology and method of administration

Posology

A pre-therapy ECG is valuable because ECG changes due to hypothyroidism may be confused with ECG evidence of cardiac ischaemia. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors, and sometimes anginal pain where there is latent cardiac ischaemia) dosage must be reduced, or withheld, for a day or two, and then re-started at a lower dose level.

Initial monitoring and dose adjustments.

It is especially necessary when starting Eltroxin to establish a maintenance dose. The timing of this blood test depends on patients symptoms. If their symptoms have improved after starting Eltroxin, patients should have their TSH level measured at around 6 weeks after starting Eltroxin. If a patient still has symptoms 2-3 weeks after starting Eltroxin, they will need a TSH level taken earlier.

Adults (under 50 years age)

Initially 50 to 100 micrograms daily, preferably taken before breakfast or the first meal of the day. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained: The final daily dose may be up to 100 to 200 micrograms. In younger patients and in the absence of heart disease, a serum thyroxine (T4) level of approximately 70 to 160 nanomoles per litre, or a serum thyrotropin (TSH) level of less than 5 (mIU/L) should be targeted.

Patients over 50 years: It is not advisable to exceed 50 micrograms daily initially. In this condition, the daily dose may be increased by 50 micrograms at intervals of every 3-4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms. For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criterion of dosage, rather than serum levels.

Patients with cardiac disease:

Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable initially. In this condition the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

Elderly: As for patients aged over 50 years.

Paediatric population

The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated. Regular monitoring is required to make sure he/she gets the right dose. Infants should be given the total daily dose at least half an hour before the first meal of the day. In children under 5 years of age, the administration of whole tablets is not recommended. It is also not recommended that tablets are crushed and dispersed in water or other liquids, owing to limited solubility which could lead to dosing inaccuracy. In this age group it is preferable to administer an approved oral solution of levothyroxine. *Regular monitoring* ***using serum TSH levels, as in adults,*** *is required to allow dose adjustment.*

<u>Congenital hypothyroidism in infants:</u>

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

<u>Acquired hypothyroidism in children:</u>

For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Thyrotropin levels may remain elevated during the first year of life in children with neonatal hypothyroidism due to re-setting of the hypothalamic-pituitary axis.

Treatment with Eltroxin should be withdrawn, when appropriate, by gradual reduction of dosage over several weeks to avoid possible effects of rebound hypothyroidism and interaction with other therapies due to sudden withdrawal of levothyroxine treatment.

Method of administration:

Oral.

Where applicable (e.g. difficulty in swallowing tablets), tablets can be disintegrated in some water (10 to 15 mL) and the resultant suspension, must be prepared freshly as required and administered with some more liquid (5 to 10 mL). Eltroxin should be taken on an empty stomach, ideally an hour before breakfast and not right before a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Thyrotoxicosis.

Uncorrected adrenal gland disorder or uncorrected adrenal insufficiency

Treatment with Eltroxin must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.

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

4.4 Special warnings and precautions for use

Levothyroxine should be introduced very gradually in patients aged over 50 years (see section 4.2) and those with long standing hypothyroidism to avoid any sudden increase in metabolic demands.

Patient with panhypopituitarism or other causes predisposing to adrenal insufficiency may react to levothyroxine treatment, and it is advisable to start corticosteroid therapy before giving levothyroxine to such patients.

Levothyroxine sodium should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, hypertension, and in the elderly who have a greater likelihood of occult cardiac disease.

In individuals suspected to have cardiovascular disease or to be at high risk, it is important to perform an ECG prior to commencement of levothyroxine treatment in order to detect changes consistent with ischaemia in which case, levothyroxine should be initiated at a low dose, followed by cautious dose escalation to avoid worsening of ischaemia or precipitation of an infarct.

To minimise the risk of adverse effects of undetected overtreatment, such as atrial fibrillation and fractures associated with low serum levels of thyroid stimulating hormone (TSH) in older patients, it is important to monitor serum TSH and adjust the dose accordingly during long term use.

Thyroid replacement therapy may cause an increase in dosage requirements of insulin or other anti-diabetic therapy (such as metformin).Care is needed for patients with diabetes mellitus and diabetes insipidus.

See note above regarding withdrawal of treatment (See section 4.2)

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Subclinical hyperthyroidism may be associated with bone loss. To minimise the risk of osteoporosis, dosage of levothyroxine sodium should be titrated to the lowest possible effective level.

Parents of children receiving thyroid agent should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequent regrowth usually occurs.

Care is required when levothyroxine is administered to patients with known history of epilepsy. Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.

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.

If a switch to another levothyroxine-containing product is required, there is a need to undertake close monitoring including clinical and biological monitoring during the transition period due to a potential risk of thyroid imbalance. In some patients, dose adjustment could be necessary.

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.

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 tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting other drugs:
Levothyroxine increases the effect of anticoagulants (e.g. Warfarin) and it may be necessary to reduce the anticoagulation dosage if excessive, hypoprothrombinaemia and bleeding are to be avoided.

Blood sugar levels are raised and dosage of antidiabetic agents may require adjustment.

Tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) response may be accelerated because levothyroxine increases sensitivity to catecholamines; concomitant use may precipitate cardiac arrhythmias.

The effects of sympathomimetic agents (e.g. adrenaline or phenylephrine) are enhanced.

If levothyroxine therapy is initiated in digitalised patients, the dose of digitalis may require adjustment. Hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin.

False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.

Beta blockers: Levothyroxine (thyroxine) accelerates metabolism of propranolol, atenolol and sotalol.

Isolated reports of marked hypertension and tachycardia have been reported with concurrent ketamine administration.

Interactions affecting Levothyroxine:

Amiodarone may affect thyroid function tests and this must be considered when monitoring a patient on levothyroxine therapy. Amiodarone may inhibit the deiodination of thyroxine to tri iodothyronine resulting in a decreased concentration of tri iodothyronine, thereby reducing the effects of thyroid hormones

Anti-convulsants, such as carbamazepine and phenytoin, enhance the metabolism of thyroid hormones and may displace them from plasma proteins.

Initiation or discontinuation of anti-convulsant therapy may alter levothyroxine dosage requirements.

Effects of Levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine is possibly reduced by cimetidine, antacids, calcium salts, oral iron, polystyrene sulphonate resins, sucralfate, colestipol and cholestyramine (a gap of 4-5 hours is recommended between taking levothyroxine and these medicines, especially if the TSH is still elevated, i.e. if thyroid replacement is not adequate on therapy).

Metabolism of levothyroxine (thyroxine) is accelerated by rifampicin, barbiturates, primidone products containing St John's Wort (Hypericum perforatum L.) and oestrogens, 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.

Imatinib: plasma concentration of levothyroxine (thyroxine) is possibly reduced by imatinib.

Beta blockers may decrease the peripheral conversion of levothyroxine to triiodothyronine. Oestrogen, oestrogen containing products (including hormone replacement therapy) and oral contraceptives may increase the requirement of thyroid therapy dosage. Conversely, androgens and corticosteroids may decrease serum concentrations of levothyroxine binding globulins.

Anti-obesity drugs such as orlistat may decrease levothyroxine absorption which may result in hypothyroidism (monitor for changes in thyroid function).

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.

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.

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
The safety of levothyroxine treatment during pregnancy is not known, but any possible risk of foetal abnormalities should be weighed against the risk to the foetus of untreated hypothyroidism.

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.

Breast-feeding
Levothyroxine is excreted in breast milk in low concentrations, and it is contentious whether this can interfere with neonatal screening.

Fertility
No data available

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Side-effects are usually indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days. [1]Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a "thyroid crisis" with any of the following symptoms: Hyperpyrexia, tachycardia, arrhythmia, hypotension, cardiac failure, jaundice, confusion, seizure and coma.

Adverse reactions listed below have been observed during clinical studies and/or during marketed use and are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention:

Not known (cannot be estimated from the available data)

System organ class	**Undesirable effects**
Immune system disorders	Hypersensitivity reaction
Endocrine disorders	Thyrotoxic crisis[1]
Psychiatric disorders	Restlessness, agitation, insomnia
Nervous system disorders	Tremor
Cardiac disorders	Angina pectoris, arrhythmia, palpitations, tachycardia
Vascular disorders	Flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Hyperhidrosis, alopecia, rash, pruritus
Musculoskeletal and connective tissue disorder	Arthralgia, muscle spasm, muscular weakness

Reproductive system disorders	Menstruation irregular
General disorders and administration site conditions	Headache, pyrexia, malaise, oedema
Investigations	Weight decreased

Paediatric population
Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children.

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. Healthcare professionals are asked to report any suspected adverse reactions via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Symptoms
In most cases there will be no features. Signs of an overdose may include: fever, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea, tremor, insomnia and hyperpyrexia. Rarely, features of hyperthyroidism may develop 3-6 days after ingestion. Atrial fibrillation may develop. Convulsions occurred in one child. There may be increased toxicity in those with pre-existing heart disease.

Treatment
Give oral activated charcoal if more than 10mg has been ingested by an adult or more than 5mg by a child, within 1 hour. If more than 10mg has been ingested by an adult or more than 5mg by a child, take blood 6-12 hours after ingestion for measurement of the free thyroxine concentration. The analysis does not need to be done urgently but can wait until the first working day after the incident. Patients with normal free thyroxine concentrations do not require follow up. Those with high concentrations should have outpatient review 3-6 days after ingestion to detect delayed onset hyperthyroidism. Features of clinical hyperthyroidism should be controlled with beta-blockers, e.g. propranolol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Thyroid hormones, ATC Code: HO3AAO1.

Mechanism of action
Eltroxin is a tablet containing the hydrated form of levothyroxine sodium which is used for the treatment of hypothyroidism.
The thyroid gland is dependent upon 2 active principles for it's main hormone activity these are levothyroxine (tetraiodothyronine) and Tri-Iodothyronine (See Goodman and Gilman, 1985).These closely related iodine containing amino acids are incorporated into the glycoprotein thyroglobulin.

Pharmacodynamic effects
The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form Tri-Iodothyronine which is thought to be the active tissue form of thyroid hormone. Tri- Iodothyronine is certainly more rapid acting and has a shorter duration of action than levothyroxine.

5.2 Pharmacokinetic properties

Absorption
Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract.

Distribution
It is almost completely bound to plasma proteins and has a half-life in the circulation of about a week in healthy subjects, but longer during pregnancy in patients with myxoedema.

Biotransformation
A large portion of the levothyroxine leaving the circulation is taken up by the liver. Part of a dose of levothyroxine is metabolised to triiodothyronine.

Elimination
Levothyroxine is excreted in the urine as free drug, deiodinated metabolites and conjugates. Some levothyroxine is excreted in the faeces. There is limited placental transfer of levothyroxine.

5.3 Preclinical safety data

No further data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium citrate
Lactose monohydrate
Maize starch
Powdered acacia
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Tablet containers: Do not store above 25ºC. Keep container in the outer carton in order to protect from light.
Blisters: Do not store above 25ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container
Polypropylene container with tamper-evident low density polyethylene lid, containing 100 and 1000 Eltroxin 100 micrograms tablets. Also 28, 56 and 112 tablets in PVC/PVDC/AL blister packs.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited

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8 MARKETING AUTHORISATION NUMBER

MA625/00403

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 April 2007
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10 DATE OF REVISION OF THE TEXT

December 2025