1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ELTROXIN NEW FORMULATION 25 µg (tablet)

ELTROXIN NEW FORMULATION 50 µg (tablet)

ELTROXIN NEW FORMULATION 75 µg (tablet)

ELTROXIN NEW FORMULATION 88 µg (tablet)

ELTROXIN NEW FORMULATION 100 µg (tablet)

ELTROXIN NEW FORMULATION 112 µg (tablet)

ELTROXIN NEW FORMULATION 125 µg (tablet)

ELTROXIN NEW FORMULATION 137 µg (tablet)

ELTROXIN NEW FORMULATION 150 µg (tablet)

ELTROXIN NEW FORMULATION 175 µg (tablet)

ELTROXIN NEW FORMULATION 200 µg (tablet)

COMPOSITION

Each tablet of ELTROXIN NEW FORMULATION contains 25 µg, 50 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg, 175 µg, or 200 µg of levothyroxine sodium.

Excipients:

Colloidal silica dioxide, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, talc.

Sugar free.

CATEGORY AND CLASS

A 21.3 Thyroid preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Thyroxine (T_4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone tri-iodothyronine (T_3) in peripheral tissues. The precise signals controlling the conversion of T_4 to T_3 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 utilisation of carbohydrate. 100 µg thyroxine is equivalent in activity to 20 µg to 30 µg liothyronine/tri-iodothyronine or 60 mg thyroid BP.

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

Special 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.

INDICATIONS

ELTROXIN NEW FORMULATION is indicated for untreated hypothyroidism.

CONTRAINDICATIONS

ELTROXIN NEW FORMULATION is contraindicated in:

- Patients with untreated hyperthyroidism.
- Patients with hypersensitivity to levothyroxine sodium or to any of the excipients in ELTROXIN NEW FORMULATION (see COMPOSITION).
- Untreated adrenal insufficiency, untreated pituitary insufficiency.
- Treatment must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.

WARNINGS AND SPECIAL PRECAUTIONS

At the beginning of treatment, ordinary therapeutic doses may cause anginal pain, palpitations and cramps in the skeletal muscle.

Before starting therapy with ELTROXIN NEW FORMULATION the following diseases should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency, thyroid autonomy.

Even slight medicine-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac dysrhythmias.

Hence frequent checks of thyroid hormone parameters must be made in these cases.

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.

Where thyroid autonomy is suspected, a TRH test should be carried out or a suppression scintigram obtained before treatment. In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, supraphysiological serum levels of ELTROXIN NEW FORMULATION should be avoided, and, therefore, thyroid function should be checked regularly.

Thyroid storm (or thyrotoxic crisis) is a medical emergency and has been occasionally reported after massive or chronic intoxication. Convulsions, cardiac dysrhythmias, heart failure, coma and death have occurred (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

ELTROXIN NEW FORMULATION has a narrow therapeutic index. Appropriate ELTROXIN NEW FORMULATION 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 ELTROXIN NEW FORMULATION dosage are the same as many features of endogenous thyrotoxicosis.

Treatment with ELTROXIN NEW FORMULATION 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 ELTROXIN NEW FORMULATION in these cases.

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

It is especially important that children with hypothyroidism have their dosage individualised and treatment monitored.

Parents of children receiving ELTROXIN NEW FORMULATION 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 may occur.

Special care is needed in the elderly and in patients with symptoms of myocardial insufficiency or ECG evidence of myocardial infarction or ischaemia and also those with diabetes mellitus or insipidus.

ELTROXIN NEW FORMULATION raises blood sugar levels and this may upset the stability of patients receiving antidiabetic medicines.

Effects on ability to drive and use machines

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that ELTROXIN NEW FORMULATION does not adversely affect their ability to do so safely (see SIDE EFFECTS).

INTERACTIONS

Warfarin: ELTROXIN NEW FORMULATION increases the effect of warfarin and it may be necessary to reduce the dose of warfarin if excessive hypoprothrombinaemia and bleeding are to be avoided. The INR should be monitored.

Phenytoin and carbamazepine: Phenytoin levels may be increased by ELTROXIN NEW FORMULATION. Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of ELTROXIN NEW FORMULATION and may displace thyroxine from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter thyroxine sodium dose requirements.

Digoxin: If co-administered with digoxin, adjustment of dosage may be necessary.

Sympathomimetic medicines: The effects of sympathomimetic medicines are also enhanced. ELTROXIN NEW FORMULATION increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants (e.g. amitriptyline, imipramine).

Cholestyramine: Cholestyramine given concurrently reduces the gastrointestinal absorption of ELTROXIN NEW FORMULATION.

Other medicines: A number of other medicines may decrease the absorption of ELTROXIN NEW FORMULATION, and therefore increase ELTROXIN NEW FORMULATION dosage requirements including antacids (e.g. aluminium hydroxide), proton pump inhibitors, cimetidine, bile acid sequestrants (e.g. colestipol), cation exchange resins (e.g. kayexalate), sucralfate, calcium carbonate and ferrous sulphate (administration should be separated by 4 to 5 hours).

Co-administration of oral contraceptives, as well as a number of other medicines, including oestrogen, tamoxifen, clofibrate, methadone, and 5-fluorouracil may increase serum concentration of thyroxine-binding globulin, and therefore increase ELTROXIN NEW FORMULATION dosage requirements.

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

Imatinib: Treatment with imatinib was associated with increased ELTROXIN NEW FORMULATION dosage requirements in hypothyroid patients.

Amiodarone: Treatment with amiodarone has been associated with multiple effects on thyroid function including increased ELTROXIN NEW FORMULATION dosage requirements in hypothyroid patients.

Thyroid function tests: A number of medicines may affect thyroid function tests and this should be borne in mind when monitoring a patient on ELTROXIN NEW FORMULATION therapy.

Antibacterials: Enzyme induction by rifampicin enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Oral ciprofloxacin can lead to the development of hypothyroidism in stable patients receiving ELTROXIN NEW FORMULATION.

Antidiabetics: As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any medicine treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their insulin or oral hypoglycaemic requirements.

Antidepressants: Some medicines such as lithium act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism. The effects of ELTROXIN NEW FORMULATION in hypothyroid patients may be decreased by use with sertraline, and the dose of ELTROXIN NEW FORMULATION may need to be increased.

Antivirals: An increased dose of ELTROXIN NEW FORMULATION is necessary with ritonavir whereas a decreased dose is needed with indinavir.

Beta-blockers: Plasma concentrations of propranolol are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance and hypothyroid patients receiving chronic propranolol therapy have a reduction in plasma-propranolol concentrations when given ELTROXIN NEW FORMULATION treatment.

General anaesthetics: Severe hypertension and tachycardia can occur when ketamine is used in patients taking ELTROXIN NEW FORMULATION.

Antimalarials: Increased thyroid-stimulating hormone concentration can occur after the use

of chloroquine with proguanil for malaria prophylaxis.

NSAIDs: Falsely low concentrations of levothyroxine (T_4) or tri-iodothyronine (T_3) can occur during treatment with some anti-inflammatory medicines. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.

Soya-based infant formula: Soya-based infant formulas may impair absorption of ELTROXIN NEW FORMULATION, and frequent testing may be needed, particularly when there are changes in formula.

Simvastatin: Increased thyroid stimulating hormone concentrations, requiring increased doses of ELTROXIN NEW FORMULATION, can occur when simvastatin is used.

Furosemide: Furosemide in high doses (250 mg) can displace levothyroxine sodium as contained in ELTROXIN NEW FORMULATION from plasma proteins, resulting in an elevated free-thyroxine (T_4) fraction.

HUMAN REPRODUCTION

Pregnancy

ELTROXIN NEW FORMULATION has been taken by pregnant women and women of childbearing age without any form of definite disturbances in the reproductive process having been observed. Thyroid hypo- or hyperactivity in the mother may, however, unfavourably influence the foetal and postnatal development, therefore ELTROXIN NEW FORMULATION dosage may need to be adjusted during pregnancy.

Lactation

ELTROXIN NEW FORMULATION is excreted in breast milk and this may be sufficient to interfere with neonatal screening for hypothyroidism. It is very important to monitor thyroid function in the mother as well as in the infant regularly.

DOSAGE AND DIRECTIONS FOR USE

If the dose of ELTROXIN NEW FORMULATION 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.

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.

The dose of ELTROXIN NEW FORMULATION for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

Adults

Initially 50 µg to 100 µg 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 micrograms to 300 micrograms.

Elderly

As for patients aged over 50 years.

For patients over 50 years, initially, it is not advisable to exceed 50 micrograms daily. In this condition, the daily dose may be increased by 50 micrograms at intervals of every 3 to 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 micrograms to 200 micrograms.

Patients over 50 years with cardiac disease

Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In these conditions, 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 micrograms to 200 micrograms.

For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather than serum levels.

Paediatric dosing

The maintenance dose is generally 100 micrograms 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.

Congenital hypothyroidism in infants

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 micrograms to 15 micrograms per kg body weight 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.

Acquired hypothyroidism in children

For children with acquired hypothyroidism, the initial recommended dosage is 12,5 micrograms to 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.

Juvenile myxoedema in children

The initial recommended dosage is 25 micrograms daily. In such conditions, the daily dose may be increased by 25 micrograms at intervals of every 2 to 4 weeks, until mild symptoms of hyperthyroidism are seen. The dose will then be reduced slightly.

When applicable

Tablets are to be disintegrated in some water (10 ml to 15 ml) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 ml to 10 ml).

SIDE EFFECTS

The following effects are indicative of excessive dosage, and usually disappear on reduction of dosage or withdrawal of treatment for a few days.

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

Immune system disorders

Frequency unknown: Hypersensitivity reactions such as skin rash, pruritus, eosinophilia, fever and liver dysfunction

Endocrine disorders

Less frequent: Hyperthyroidism, hypothyroidism

Frequency unknown: Heat intolerance, flushing

Metabolism and nutrition disorders

Frequency unknown: Increased appetite

Psychiatric disorders

Frequency unknown: Excitability, restlessness, insomnia, confusion, agitation

Nervous system disorders

Frequency unknown: Headache, tremors, seizure, cephalalgia. Cases of pseudotumour cerebri (benign intracranial hypertension) have been reported, especially in children

Cardiac disorders

Frequency unknown: Anginal pain, cardiac-dysrhythmias, palpitations, tachycardia, heart failure, myocardial infarction

Vascular disorders

Frequency unknown: Increased blood pressure

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Dyspnoea

Gastrointestinal disorders

Frequency unknown: Abdominal cramps, nausea, vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Frequency unknown: Sweating, hair loss

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: 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

Frequency unknown: Menstrual irregularity, impaired fertility

General disorders and administrative site conditions

Frequency unknown: Fatigue, excessive loss of weight

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

In addition to exaggeration of side effects, the following symptoms may be seen: agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, dysrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions. In addition to all known side effects, thyroid storm (or thyrotoxic crisis) a medical emergency, may occur and require urgent medical attention as soon as possible. Some of the signs of thyrotoxicosis that have been reported include fever, dysrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications and coma.

The appearance of clinical hyperthyroidism may be delayed for up to five days.

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.

Treatment is symptomatic and tachycardia has been controlled in an adult by a suitable beta blocking medicine and other symptoms by a suitable benzodiazepine as appropriate.

IDENTIFICATION

ELTROXIN NEW FORMULATION 25 µg: Round, white to off-white tablets debossed with '25' on the one side and a breakline on the other side.

ELTROXIN NEW FORMULATION 50 µg: Round, white to off-white flat, bevelled tablets debossed with '50' on the one side and 'L01' on the other side.

ELTROXIN NEW FORMULATION 75 µg: Round, white to off-white flat, bevelled tablets debossed with '75' on the one side and 'L02' on the other side.

ELTROXIN NEW FORMULATION 88 µg: Round, white to off-white flat, bevelled tablets debossed with '88' on the one side and 'L07' on the other side.

ELTROXIN NEW FORMULATION 100 µg: Round, white to off-white, flat, bevelled tablets debossed with '100' on the one side and 'L10' on the other side.

ELTROXIN NEW FORMULATION 112 µg: Round, white to off-white, flat, bevelled tablets debossed with '112' on the one side and 'L11' on the other side.

ELTROXIN NEW FORMULATION 125 µg: Round, white to off-white, flat, bevelled tablets

debossed with ‘125’ on the one side and ‘L12’ on the other side.

ELTROXIN NEW FORMULATION 137 µg: Round, white to off-white, flat, bevelled tablets debossed with ‘137’ on the one side and ‘L15’ on the other side.

ELTROXIN NEW FORMULATION 150 µg: Round, white to off-white flat, bevelled tablets debossed with ‘150’ on the one side and ‘L17’ on the other side.

ELTROXIN NEW FORMULATION 175 µg: Round, white to off-white, flat, bevelled tablets debossed with ‘175’ on the one side and ‘L20’ on the other side.

ELTROXIN NEW FORMULATION 200 µg: Round, white to off-white, flat, bevelled tablets debossed with ‘200’ on the one side and ‘L21’ on the other side.

PRESENTATION

The tablets are packed in 40 ml white multilayer HDPE bottles, closed with white polypropylene child-resistant caps with foil heat induction seals, and with a 1 g white polypropylene canister containing oxygen absorber. The bottles are packed into an outer cardboard carton in pack sizes of 30’s, 50’s and 100’s.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C and protect from light.

Keep container tightly closed.

Keep in the original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ELTROXIN NEW FORMULATION 25 µg:	47/21.3/0614
ELTROXIN NEW FORMULATION 50 µg:	47/21.3/0615
ELTROXIN NEW FORMULATION 75 µg:	47/21.3/0616
ELTROXIN NEW FORMULATION 88 µg:	47/21.3/0617
ELTROXIN NEW FORMULATION 100 µg:	47/21.3/0618
ELTROXIN NEW FORMULATION 112 µg:	47/21.3/0619
ELTROXIN NEW FORMULATION125 µg:	47/21.3/0620
ELTROXIN NEW FORMULATION 137 µg:	47/21.3/0621
ELTROXIN NEW FORMULATION 150 µg:	47/21.3/0622
ELTROXIN NEW FORMULATION 175 µg:	47/21.3/0623
ELTROXIN NEW FORMULATION 200 µg:	47/21.3/0624

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 30 September 2016

Date of the most recent amendment to the professional information as approved by the Authority: 30 September 2016

Namibia: NS2
25 µg 16/21.3/0096
50 µg 16/21.3/0097
75 µg 16/21.3/0098
88 µg 16/21.3/0099
100 µg 16/21.3/0100
112 µg 16/21.3/0101
125 µg 16/21.3/0102
137 µg 16/21.3/0103
150 µg 16/21.3/0104
175 µg 16/21.3/0105
200 µg 16/21.3/0106

Zimbabwe: P.P.10
50 µg 2017/17.8.1/5414
100 µg 2017/17.8.1/5413

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