Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine Clonmel 100 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 microgram tablet contains 100 microgram levothyroxine sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White or almost white, round biconvex tablet with a score line on one side , “100” engraved on the other side and with a diameter of 7 mm.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levothyroxine Clonmel 25 - 200 microgram:

- Treatment of benign euthyroid goitre.
- Prophylaxis of relapse after surgery for euthyroid goitre, depending on the post-operative hormone status.
- Substitution therapy in hypothyroidism.
- Suppression therapy in thyroid cancer.

Levothyroxine Clonmel 25 - 100 microgram:

- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

Levothyroxine Clonmel 100/150/200 microgram:

- Diagnostic use for thyroid suppression testing.

4.2 Posology and method of administration

In order to treat each patient according to his/her individual needs, tablets are available with a levothyroxine sodium content ranging from 25 to 200 microgram. Patients therefore usually need to take only one tablet per day.

The dosage recommendations given are only for guidance.

The individual daily dose should be determined on the basis of laboratory tests and clinical examinations. As a number of patients show elevated concentrations of T_4 and fT_4, basal serum concentration of thyroid- stimulating hormone provides a more reliable basis for following treatment course. Thyroid hormone therapy should be started at low dose and increased gradually every 2 to 4 weeks until the full replacement dose is reached.

Paediatric population
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.

In elderly patients, in patients with coronary heart disease, and in patients with severe or long-existing hypothyroidism, special caution is required when initiating therapy with thyroid hormones, that is, a low initial dose (for example 12.5 microgram/day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 microgram/day fortnightly) with frequent monitoring of thyroid hormones. A dosage, lower than optimal dosage giving complete replacement therapy, consequentially not resulting in a complete correction of TSH level, might therefore need to be considered.

Experience has shown that a lower dose is sufficient in low-weight patients and in patients with a large nodular goitre.

Indication	**Recommended dose** (microgram levothyroxine sodium/day)
Treatment of benign euthyroid goitre	75 - 200
Prophylaxis of relapse after surgery for euthyroid goitre	75 - 200
Substitution therapy in hypothyroidism in adults - initial dose - maintenance dose	 25 - 50 100 - 200
Substitution therapy in hypothyroidism in children - initial dose - maintenance dose	 12.5- 50 100 - 150 microgram/m^2 body surface
Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism	50 - 100
Suppression therapy in thyroid cancer	150 - 300

Diagnostic use for thyroid suppression testing	Week 4 prior to test	Week 3 prior to test	Week 2 prior to test	Week 1 prior to test
levothyroxine 200 microgram			1 Tabl/day	1 Tabl/day
levothyroxine 100 microgram			2 Tabl/day	2 Tabl/day
levothyroxine 150 microgram	½ Tabl/day	½ Tabl/day	1 Tabl/day	1 Tabl/day

The daily doses can be given in a single administration.
Ingestion: as a single daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with a little liquid, (for example, half a glass of water).

Infants receive the entire dose at once at least 30 minutes before the first meal of the day. Tablets are to be disintegrated in some water and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid.

Duration of treatment is usually for life in the case of substitution in hypothyroidism and after strumectomy or thyroidectomy and for relapse prophylaxis after euthyroid goitre removal. Concomitant therapy of hyperthyroidism after achieving euthyroid status is indicated for the period in which the anti-thyroid drug is given.

For benign euthyroid goitre, a treatment duration of 6 months up to 2 years is necessary. If the medical treatment was not sufficient within this time, surgery or radioiodine therapy of the goitre should be considered.

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, and untreated thyrotoxicosis.
- Treatment with levothyroxine 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 precautions for use

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.

When initiating levothyroxine therapy in patients at risk of psychotic disorders, it is recommended to start at a low levothyroxine dose and to slowly increase the dosage at the beginning of the therapy. Monitoring of the patient is advised. If signs of psychotic disorders occur, adjustment of the dose of levothyroxine should be considered

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 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 supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely.

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

Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9).

Once a levothyroxine treatment has been established, it is recommended to adjust the dosage following the patient's clinical response and laboratory test, in case of switching the brand.

Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered (see section 4.5). Patients taking levothyroxine should consult a doctor before starting treatment with orlistat, as orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted. Further, it is recommended to monitor the patient by checking the hormone levels in the serum.

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.

For diabetic patients and patients under anticoagulant therapy, see section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Coumarin derivates:
The effect of anti-coagulant therapy can be intensified as levothyroxine displaces anti-coagulative drugs from plasma proteins, which may increase the risk of haemorrhage, e.g. CNS or gastrointestinal bleeding, especially in elderly patients. Therefore it is necessary for coagulation parameters to be checked regularly at the start of and during concomitant therapy. If necessary, the dosage of the anti-coagulative drug has to be adapted.

Protease inhibitors:
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.

Phenytoin:
Phenytoin may influence the effect of levothyroxine by displacing levothyroxine from plasma proteins resulting in an elevated fT4 and fT3 fraction. On the other hand phenytoin increases the hepatic metabolisation of levothyroxine. Close monitoring of thyroid hormone parameters is recommended.

Colestyramine, Colestipol:
Ingestion of ion exchange resins such as cholestyramine and colestipol inhibits the absorption of levothyroxine sodium. Levothyroxine sodium should therefore be taken 4-5 hours before administration of such products.

Aluminium containing drugs, iron-containing drugs, calcium carbonate:
Aluminium-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 aluminium-containing drugs. Same is true for iron-containing drugs and calcium carbonate.

Salicylates, dicoumarol, furosemide, clofibrate:
Salicylates, dicoumarol, furosemide in high doses (250 mg), clofibrate and other substances can displace levothyroxine sodium from plasma proteins, resulting in an elevated fT4 fraction.

Orlistat:
Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of iodine salts and/or levothyroxine.

Sevelamer:
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.

Tyrosine kinase inhibitors:
Tyrosine kinase inhibitors (e.g. imatinib, sunitinib) may decrease the efficacy of levothyroxine. 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.

Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone and iodine containing contrast media:
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.

Sertraline, chloroquine/proguanil:
These substances decrease the efficacy of levothyroxine and increase the serum TSH level.

Tricyclic anti-depressants:
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 also enhanced.

Digitalis glycosides
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.

Enzyme inducing medicinal products:
Enzyme inducing medicinal products such as barbiturates or carbamazepine can increase hepatic clearance of levothyroxine.

Oestrogens:
Women using oestrogen-containing contraceptives or postmenopausal women under hormone-replacement therapy may have an increased need for levothyroxine.

Soy-containing compounds:
Soy-containing compounds can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of levothyroxine may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

4.6 Fertility, pregnancy and lactation

Treatment with levothyroxine should be given consistently during pregnancy and breast-feeding in particular. Dosage requirements may even increase during pregnancy.

Experience has shown that there is no evidence of drug-induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose level. Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on foetal and postnatal development.

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.

Thyroid suppression diagnostic tests should not be carried out during pregnancy, as the application of radioactive substances in pregnant women is contraindicated.

Levothyroxine is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, since levothyroxine is identical to the naturally occurring thyroid hormone, it is not expected that levothyroxine has any influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are usually indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a few days. Such effects include:

General disorders and administration site conditions: flushing, fever and sweating

Immune system disorders: hypersensitivity reactions including rash, pruritus, dyspnoea, joint pain, malaise and oedema. Cases of angioedema have been reported.

Metabolism and nutrition disorders: weight loss

Nervous system disorders: tremor, restlessness, excitability, insomnia, headache. Rarely, benign intracranial hypertension in children.

Cardiac disorders: anginal pain, cardiac arrhythmias, palpitations, tachycardia

Gastrointestinal disorders: diarrhoea, vomiting

Musculoskeletal and connective tissue disorders: muscle cramps, muscle weakness, craniostenosis in infants and premature closure of epiphysis in children.

Reproductive system and breast disorders: menstrual irregularities

Heat intolerance, transient hair loss in children also reported.

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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

An elevated T3 level is a reliable indicator of overdose, more than elevated T4 or fT4 levels. After overdose the symptoms of a sharp increase in the metabolic rate occur (see section 4.8). Depending on the extent of the overdose it is recommended that treatment with the tablets is interrupted and that tests are carried out.

Symptoms consisting of intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia can be relieved by betablockers. After extreme doses plasmapheresis may be of help.

In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded.

Overdose of levothyroxine may result in hyperthyroidism and could lead to symptoms of acute psychosis, especially in patients at risk of psychotic disorders.

Several cases of sudden cardiac death have been reported in patients with long years of levothyroxine abuse.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones
ATC-Code: H03A A01

The synthetic levothyroxine contained in this medicine is identical in effect with the naturally occurring major hormone secreted by the thyroid. It is converted to T3 in peripheral organs and, like the endogenous hormone, develops its specific effects at the T3 receptors. The body is not able to differentiate between endogenous and exogenous levothyroxine.

5.2 Pharmacokinetic properties

Orally given levothyroxine is absorbed almost exclusively in the upper small intestine. Depending on the galenical formulation absorption amounts up to 80 %. t_{max} is approximately 5 to 6 hours.

Following oral administration the onset of action is seen after 3-5 days. Levothyroxine exhibits an extremely high binding to specific transport proteins of about 99.97 %. This protein hormone binding is not covalent and so the bound hormone in plasma is in continuous and very rapid exchange with the fraction of the free hormone.

Due to its high protein binding levothyroxine undergoes neither haemodialysis nor haemoperfusion.

The half-life of levothyroxine is on average 7 days. In hyperthyroidism it is shorter (3-4 days) and in hypothyroidism it is longer (approx. 9-10 days). The volume of distribution amounts to about 10-12 l. The liver contains 1/3 of the entire extra-thyroidal levothyroxine, which is rapidly exchangeable with the levothyroxine in serum. Thyroid hormones are metabolized mainly in the liver, kidneys, brain and muscles. The metabolites are excreted with urine and faeces. The overall metabolic clearance for levothyroxine is about 1.2 l plasma/day.

5.3 Preclinical safety data

Acute toxicity:
Levothyroxine has a very slight acute toxicity.

Chronic toxicity:
The chronic toxicity of levothyroxine was studied in various animal species (rat, dog). At high doses, signs of hepatopathy, increased occurrence of spontaneous nephroses as well as changes in organ weights were observed in rats.

Reproduction toxicity:
Reproductive toxicity studies in animals have not been performed.

Mutagenicity:
No information is available on this subject. So far no indications of any kind have become known suggesting damage to the progeny due to changes in the genome caused by thyroid hormones.

Carcinogenicity:
No long-term animal studies have been carried out with levothyroxine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Hypromellose
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/PVDC/aluminium blisters

Package size(s):

28, 30, 50, 90, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/257/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2015

10 DATE OF REVISION OF THE TEXT