Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oroxine 175 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Oroxine 175 microgram contains 194.7 microgram of levothyroxine sodium pentahydrate equivalent to 175 microgram of levothyroxine sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Levothyroxine sodium 175 microgram tablets are round, 6.5mm in diameter, white coloured, flat, bevelled tablets debossed with '175' on the one side and 'L20' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levothyroxine 25 – 200 micrograms
- Hypothyroidism,
- Prophylaxis against goitre recurrence following resection of euthyroid goitre,
- Benign, euthyroid goitre,
- Suppression and replacement therapy in thyroid malignancy, especially post thyroidectomy.

Levothyroxine 25 – 100 micrograms
- Co-therapy in the antithyroid treatment of hyperthyroidism, once euthyroid status has been achieved.

Levothyroxine 100/150/200 micrograms
- Thyroid suppression test.

4.2 Posology and method of administration

Thyroid hormone therapy/replacement
Posology
The dosing information serves as a guideline. The individual daily dose should be determined by laboratory diagnostic tests and clinical examinations. If any residual thyroid function remains, a lower replacement dose may be sufficient.

In elderly patients, patients with coronary heart disease and patients with severe or chronic hypothyroidism, thyroid hormone treatment must be initiated with particular caution, i.e. by selecting a low initial dose and increasing it slowly and at longer intervals, with frequent thyroid hormone monitoring. Experience has shown that a lower dose is also sufficient in patients with a low body weight and in patients with large goitres. As the Levothyroxine 25 microgram tablets can be divided into equal halves, a starting dose of 12.5 micrograms can be used.

As T_4 or fT_4 levels may be increased in some patients, determination of the serum TSH concentration is better suited for monitoring the treatment regimen.

<u>Paediatric patients</u>
The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area.
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.

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.

Infants should be given the total daily dose at least half an hour before the first meal of the day.

Method of administration
The total daily dose is taken in the morning on an empty stomach at least half an hour before breakfast. The tablets are swallowed whole, without chewing, with some liquid.

Infants are given the total daily dose at least half an hour before their first meal of the day. Tablets are to be disintegrated in some water (10-15 ml) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5-10 ml).

Indication		**Dose (Micrograms of levothyroxine sodium/day)**
Hypothyroidism:		
Adults initially		25-50
followed by		100-200
(increased at 2 to 4 week intervals in increments of 25-50 micrograms)		
Prophylaxis against goitre recurrence:		75-200
Benign euthyroid goitre:		75-200
Co-therapy in the antithyroid treatment of hyperthyroidism:		50-100
Post thyroidectomy due to thyroid malignancy:		150-300
Thyroid suppression scintigraphy:	Levothyroxine 100 microgram tablets	200 micrograms (equivalent to 2 tablets)/day (for 14 days until the scintigram is performed)
	Levothyroxine 150 microgram tablets	150 micrograms (equivalent to 1 tablet)/day (for 14 days until the scintigram is performed)
	Levothyroxine 200 microgram tablets	200 micrograms (equivalent to 1 tablet)/day (for 14 days until the scintigram is performed)

Duration of administration
In most cases, treatment is lifelong when used in hypothyroidism and thyroidectomy due to thyroid malignancy, several months or years and even lifelong when used for euthyroid goitre and prophylaxis against goitre recurrence, or is dependent on the duration of the antithyroid medicinal product when used as co-therapy in the treatment of hyperthyroidism.

For the treatment of euthyroid goitre, a treatment period of 6 months up to 2 years is necessary. If treatment with Levothyroxine sodium has failed to achieve the desired success within this time, other therapeutic options should be considered.

Thyroid suppression test

For performing thyroid suppression tests, 150 - 200 micrograms of levothyroxine sodium is taken daily for 14 days.

Elderly patients
In individual cases, e.g. in the presence of cardiac problems, slow up titration of the levothyroxine sodium dose should be preferred in elderly patients, together with regular monitoring of the TSH level.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- Untreated hyperthyroidism,
- Untreated subclinical (suppressed serum TSH level with normal T_3 and T_4 levels of any aetiology) or overt thyrotoxicosis,
- Untreated adrenal insufficiency,

- Untreated pituitary insufficiency,
- Acute myocardial infarction,
- Acute myocarditis,
- Acute pancarditis.

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

For use during pregnancy and lactation, see section 4.6.

4.4 Special warnings and precautions for use

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.

In combination with certain weight-reduction agents such as orlistat reduced control of hypothyroidism may occur. This could be due to a decreased absorption of iodine salts and/or levothyroxine.To avoid this levothyroxine and weight reduction agents such as orlistat should be administered at least 4 hours apart. Regular monitoring for changes in thyroid function is required.

If a switch to another levothyroxine-containing product is required, there is a need to undertake a close monitoring including a clinical and biological monitoring during the transition period due to a potential risk of thyroid imbalance. In some patients, a dose adjustment could be necessary. The values of TSH and T_4 should be measured after four to six weeks. It is recommended that the dose should be adjusted according to the patient's clinical response and the laboratory values.

Caution in the following circumstances is required to maintain thyroid balance, namely:

-Women who are pregnant or are planning conception (see section 4.6);
- Hypothyroidism, congenital or acquired in childhood;
- Suppressive therapy in patients with previous thyroid cancer , especially if frail or elderly;
- Patients with central hypothyroidism;

- Patients with cardiac symptoms, or diabetes mellitus or insipidus. Before starting thyroid hormone therapy, the following diseases or conditions must be excluded or treated:

- Coronary heart disease;
- Angina pectoris;
- Hypertension;
- Pituitary and/or adrenocortical insufficiency;
- Thyroid autonomy.

Prior to performing thyroid suppression tests, these diseases or conditions must likewise be excluded or treated, with the exception of thyroid autonomy, which may be the reason for performing the suppression test.

Even relatively mild, medicinal product induced hyperthyroid function must be strictly avoided in cases of coronary heart disease, heart failure, tachyarrhythmias, chronic hypothyroidism or in patients with a history of myocardial infarction. The initial dose and any dose increments should be carefully chosen, too high initial dose or too rapid increase may cause or aggravate symptoms of angina, arrhythmias, myocardial infarction, cardiac failure or a sudden raise in blood pressure. In thyroid hormone therapy, more frequent monitoring of thyroid hormone parameters must be performed in these patients (see section 4.2).

In secondary hypothyroidism or panhypopituitarism, it must be established whether adrenocortical insufficiency is also present. Treatment with levothyroxine in patients with adrenal insufficiency may cause reactions, including dizziness, weakness, malaise,

weight loss, hypotension and adrenal crisis. In case of adrenocortical dysfunction, this should be treated before starting the therapy with levothyroxine by adequate replacement treatment to prevent acute adrenal insufficiency (See section 4.3). It is advisable to initiate corticosteroid therapy before giving levothyroxine sodium in these cases.

If thyroid autonomy is suspected, it is recommended that a TRH test or suppression scintigram be performed.

In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density. When administering levothyroxine therapy to postmenopausal women, who are at increased risk of osteoporosis, thyroid function should be monitored more frequently to avoid supraphysiological blood levels of levothyroxine and the dosage of levothyroxine should be titrated to the lowest possible level.

Thyroid replacement therapy may cause an increase in dosage requirements of insulin or other anti-diabetic therapy (see section 4.5). Care is needed for patients with diabetes mellitus and diabetes insipidus.

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.

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.

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 hormones on seizure threshold.

For patients on anticoagulant therapy, see section 4.5.

Patients with myxoedema have an increased sensitivity to thyroid hormones; in these patients the starting dose should be low with slow dosing increments.

Levothyroxine absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective levothyroxine treatment with regular levothyroxine dose.

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)

4.5 Interaction with other medicinal products and other forms of interaction

Interactions decreasing levothyroxine absorption
Ion exchange resins:
Cholestyramine, calcium, aluminium, magnesium, iron supplements, polystyrene sulfonates, sucralfate, lanthanum, bile acid sequestrants (e.g. colestipol), anion/cation exchange resins (e.g. kayexelate, sevelamer).

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.

Separate the dosages of levothyroxine and the above-mentioned medicines as much as possible to avoid interaction in the stomach or the small bowel.

Ciprofloxacin:
Ciprofloxacin may decrease the serum concentration of levothyroxine.

Soya productsand high-fibre diets
Soya productsand high-fibre dietscan reduce the intestinal absorption of levothyroxine. In children, there have been reports of a rise in the serum TSH level when they were given a diet containing soya and treatment with levothyroxine for congenital hypothyroidism. Unusually high doses of levothyroxine may be required to achieve normal serum levels of T4 und TSH. During and upon termination of a diet containing soya, close monitoring of serum T4 and TSH levels is necessary; a dose adjustment of levothyroxine may be required.

Weight loss agents (including orlistat):
In combination with certain weight-reduction agents, such as orlistat, reduced control of hypothyroidism may occur. This may be due to a decreased absorption of iodine salts and/or levothyroxine. To avoid this levothyroxine and weight reduction agents such as orlistat should be administered at least 4 hours apart. Regular monitoring for changes in thyroid function is required.

Interactions affecting levothyroxine
Propylthiouracil, glucocorticoids, propranolol, lithium, iodide, oral contrast agents and beta receptor blockers:
These substances inhibit conversion of T_4 to T_3 and therefore also lower the therapeutic effect.

Amiodarone and iodinated contrast media:
Due to their high iodine content the media can initiate both hyperthyroidism and hypothyroidism. Particular caution should be exercised in patients with nodular goitres with possibly undetected autonomy. As a result of this effect of amiodarone on thyroid function, a dose adjustment of Levothyroxine sodium may be required.

Salicylates, furosemide, clofibrate,:
Levothyroxine may be displaced from plasma protein binding by salicylates, , high doses (250 mg) of furosemide, clofibrate, and other substances. This leads to an increase in the plasma level of free thyroxine (fT_4).

Anticonvulsants:
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 levothyroxine sodium dose requirements.

Oestrogen based contraceptives, medications used in postmenopausal hormone replacement:
Levothyroxine requirements may increase during intake of oestrogen based contraceptives or during postmenopausal hormone replacement therapy.

Statins:
Reports indicate that some HMG-CoA reductase inhibitors (statins), such as simvastatin and lovastatin, may increase thyroid hormone requirements in patients receiving levothyroxine therapy. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate levothyroxine dose adjustments may be necessary when levothyroxine and statins are co-prescribed.

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

Tyrosine kinase inhibitors:
Treatment with tyrosine kinase inhibitors (e.g. imatinib and sunitinib) was associated with increased levothyroxine dosage requirements in hypothyroid patients.

Enzyme inducing medications:
Effects of drugs inducing cytochrome P-450: Enzyme-inducing drugs such as barbiturates, rifampicin, and other medicinal products containing St John's Wort (Hypericum perforatum L.) may increase hepatic clearance of levothyroxine, 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.

Protease inhibitors:
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.

Methadone, and 5-fluorouracil may increase serum concentration of thyroxine-binding globulin, and therefore increase levothyroxine dosage requirements.

Interactions affecting other drugs
Antidiabetic agents:
Levothyroxine may reduce the antihyperglycaemic effect of antidiabetics. Blood glucose levels must therefore be regularly monitored in patients with diabetes, particularly at the start of thyroid hormone therapy. The antihyperglycaemic dosage should be adjusted as necessary. Lowering the dose of levothyroxine can cause hypoglycaemia if the insulin or oral antidiabetics dose remains unchanged.

Coumarin derivatives:
Levothyroxine may potentiate the effect of coumarin derivatives due to plasma protein binding displacement. With concomitant treatment, regular monitoring of blood coagulation is therefore required and the anticoagulant dosage must be adjusted as necessary (dose reduction).

Digitalis preparations
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.

Tricyclic antidepressants
Levothyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants (e.g. amitriptyline, imipramine).

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

Phenytoin
Phenytoin levels may be increased by levothyroxine.

Interferences with laboratory test:
A number of drugs may decrease serum concentration of thyroxine-binding globulin, and therefore decrease levothyroxine dosage requirements, including androgens and anabolic steroids.
False low plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy. Administration of acetylsalicylic acid together with levothyroxine results in an initial transient increase in serum free T4. Continued administration results in normal free T4 and TSH concentrations, and therefore, patients become clinically euthyroid.

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:
Levothyroxine 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.

Levothyroxine requirements may increase during pregnancy due to increased oestrogen levels. Thyroid function should therefore be monitored both during and after pregnancy and the thyroid hormone dose adjusted as appropriate. Since postpartum TSH serum levels are similar to preconception values, levothyroxine dosage can be reduced to the pre-pregnancy dose.

Very small amounts of levothyroxine cross the placenta and its administration using the appropriate doses lacks of fetal consequences.
The development of the child depends on the thyroid function of the mother. Thyroxine is necessary to ensure proper brain development of the child. Treatment with levothyroxine should be continued throughout pregnancy to provide the necessary maternal balance in order to have a good progress of pregnancy (and in particular to reduce the risk of fetal hypothyroidism). Clinical and biological monitoring should be started as early as possible, especially during the first half of pregnancy, in order to confirm that the maternal serum TSH values lie within the trimester-specific pregnancy reference range and to adjust the treatment if necessary.
In any case, it is recommended to have the thyroid hormone values of newborn and mother checked.
A maternal postpartum monitoring will adjust treatment as needed.

Particularly during pregnancy and lactation, treatment with thyroid hormones must be consistently administered.

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy. In fact, only very small amounts of levothyroxine cross the placenta, while large amounts of anti-thyroid agents pass from mother to child. This can result in fetal hypothyroidism. See section 4.3 for information on concomitant intake of levothyroxine and antithyroid agents during pregnancy.

Breastfeeding
Even during high dose therapy with levothyroxine, the amount of thyroid hormone secreted into breast milk during breastfeeding is insufficient to induce the development of hyperthyroidism or suppression of TSH secretion in the infant. However, it may be sufficient to interfere with neonatal screening for hypothyroidism.

Suppression tests must not be performed during pregnancy and breastfeeding.

4.7 Effects on ability to drive and use machines

There are no available studies on the effects on the ability to drive and use machines. As levothyroxine is identical to the naturally occurring thyroid hormone, Levothyroxine sodium is not expected to have any influence on the ability to drive and use machines.

4.8 Undesirable effects

All adverse reactions are listed by system organ class and frequency; rare (≥1/10,000 to <1/1,000) and not known (cannot be estimated from the available data).

System Organ class	Frequency	Adverse event term
Immune system disorders	Not known	Hypersensitivity reactions including rash, pruritus and oedema In the case of hypersensitivity to levothyroxine or any of the excipients of levothyroxine sodium tablets, allergic reactions of the skin **(erythema)** and respiratory tract region **(dyspnoea)** may occur.
Endocrine disorders	Not known	Hyperthyroidism (see section 4.9)
Metabolism and nutrition disorders	Not known	Increased appetite, osteoporosis at suppressive doses of levothyroxine, especially in postmenopausal women, mainly when treated for a long period (see section 4.9)
Psychiatric disorders	Not known	Agitation, insomnia, restlessness

Nervous system disorders	Rare Not known	Benign intracranial hypertension in children Tremor, convulsion, headache
Cardiac disorders	Not known	Angina pectoris, arrhythmia, palpitations, tachycardia, heart failure, myocardial infarction
Vascular disorders	Not known	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Gastrointestinal disorders	Not known	Abdominal pain, nausea, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Not known	Alopecia in children,hyperhidrosis, angioedema, rash, urticaria
Musculoskeletal and connective tissue disorders	Not known	Muscle spasms, muscular weakness, premature closure of epiphysis in children
Reproductive system and breast disorders	Not known	Menstruation irregular
Congenital, familial and genetic disorders	Not known	Craniostenosis in infants
General disorders and administration site conditions	Not known	Pyrexia , temperature intolerance in children
Investigations	Not known	Weight decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allowscontinued 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

Symptoms:

Hyperthyroidism may result from treatment imbalance or levothyroxine overdose. An increased T_3 level is a more reliable sign of an overdose than elevated T_4 or fT_4 levels.

In addition to exaggeration of side effects the following symptoms may be seen: agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions. Psychiatric symptoms associated with hyperthyroidism may also occur, including affect lability, fatigue, anxiety and nervousness. The appearance of clinical hyperthyroidism may be delayed for up to five days.

Discontinuation of treatment and a follow up examination are recommended, depending on the extent of the overdose.

In cases of intoxication incidence (suicide attempts) in humans, doses of up to 10 mg levothyroxine have been tolerated without complications. Serious complications, such as a threat to vital functions (respiration and circulation), are not anticipated unless coronary heart disease is present. Nevertheless, cases of thyrotoxic crisishave been occasionally reported following massive or chronic intoxication, leading to seizures, cardiac arrhythmias, heart failure and coma. Individual cases of sudden cardiac death have been reported in patients with many years of levothyroxine abuse.

Exceptional cases of seizures have been reported in epileptic patients when levothyroxine therapy is initiated, particularly when the dose of levothyroxine is increased rapidly.

Excessive levothyroxine use may cause decreased bone mineral density, particularly in postmenopausal women.

Treatment:
Treatment is mostly symptomatic and supportive.

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

In the event of an acute overdose, gastrointestinal absorption can be reduced by administering medicinal charcoal. For severe beta sympathomimetic effects such as tachycardia, state of anxiety, agitation and hyperkinesia, symptoms can be alleviated with beta receptor blockers (propranolol), diazepam and/ or chlorpromazine. Antithyroid agents are not indicated, as the thyroid is already fully quiescent.

At extremely high doses (suicide attempt), plasmapheresis may be of assistance.

An overdose with levothyroxine demands a prolonged period of monitoring. Onset of symptoms may be delayed by up to 6 days, due to the gradual conversion of levothyroxine to liothyronine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid therapy; Thyroid hormones. *ATC: H03AA01*

Mechanism of action
The action of synthetic levothyroxine contained in Levothyroxine sodium is identical to that of the naturally occurring thyroid hormone, which is mainly produced by the thyroid gland. The body cannot differentiate between endogenously produced and exogenous levothyroxine.

Pharmacodynamic effects
Following partial conversion to liothyronine (T_3) particularly in the liver and kidney and after passage into bodily cells, the characteristic thyroid hormone effects on development, growth and metabolism are observed, mediated by activation of T_3 receptors.

Thyroid hormone replacement leads to normalisation of metabolic processes. Thus, for example, a rise in cholesterol due to hypothyroidism is significantly reduced by the administration of levothyroxine.

5.2 Pharmacokinetic properties

Absorption
Depending to a large extent on the type of galenic formulation, up to ≤ 80% of orally administered levothyroxine is absorbed when taken in the fasting state, mainly from the upper small intestine. Absorption is significantly reduced if the product is administered with food. Peak plasma levels are reached about 2 to 3 hours after ingestion.
At the start of oral therapy, onset of action occurs after 3 to 5 days.

Distribution
The volume of distribution is calculated to be about 10 to 12 l. Levothyroxine is approximately 99.97 % bound to specific transport proteins. As this protein hormone binding is not covalent, there is a constant and very rapid exchange between free and bound hormone.

Biotransformation
Metabolic clearance for levothyroxine is around 1.2 l plasma/day. It is mainly degraded in the liver, kidney, brain and muscle.

Elimination
The half-life of levothyroxine is about 7 days, although it is shorter in hyperthyroidism (3 to 4 days) and longer in hypothyroidism (about 9 to 10 days). In man, approximately 20 to 40% of levothyroxine is eliminated in the faeces and approximately 30 to 55% of a dose of levothyroxine is excreted in the urine.

Levothyroxine crosses the placenta only in small amounts. During normal dose therapy, only small amounts of levothyroxine are secreted into breast milk.

Due to its high protein binding, levothyroxine is not amenable to haemodialysis or haemoperfusion.

Special Patient Populations

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

Hepatic impairment
Due to impaired liver function the conversion into T3 may be decreased and the disposition of levothyroxine may be altered, depending on the severity of decreased hepatic function.

5.3 Preclinical safety data

Adverse effects observed in single and repeated dose toxicity studies only occurred at high doses.

Acute toxicity
Acute toxicity of levothyroxine is very low.

Chronic toxicity
Chronic toxicity studies were performed in different animal species (rats, dogs). At high doses, signs of hepatopathy, increased occurrence of spontaneous nephrosis and organ weight changes were seen in rats. No significant adverse reactions were observed in dogs.

Mutagenicity
There are no data available with regard to the mutagenic potential of levothyroxine. To date, there has been no suspicion or evidence of offspring damage due to genome changes caused by thyroid hormones.
Levothyroxine was not mutagenic in the mouse micronucleus test.

Carcinogenicity
Long term animal studies have not been performed to investigate the tumorigenic potential of levothyroxine.

Reproductive toxicity
Thyroid hormones cross the placenta in very small amounts.

Upon administration of levothyroxine during early pregnancy, in rats, adverse effects, including foetal and neonatal deaths, only occurred at very high doses. Some effects on limb formation in mice and effects on central nervous system development in chinchillas were reported but teratology studies in guinea pigs and rabbits did not reveal increases in congenital abnormalities.

Animal studies regarding effects on fertility are not known. There are no available data regarding impairment of male or female fertility. There is no suspicion or evidence that this might occur.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose PH101 (E460)
Pregelatinised maize starch
Talc (E553b)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years
For Oroxine 25 and 50 microgram tablets:
After opening of the HDPE container the tablets should be used within 2 months.

For Oroxine 75, 100, 125, 150, 175, 200 microgram tablets:
After opening of the HDPE container the tablets should be used within 112 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles, closed with white polypropylene (PP) screw caps with foil heat induction seals, and with a 1.0 g white polypropylene canister containing oxygen absorber. The canister (oxygen absorber) should remain inside the bottle during the in-use period.
Pack sizes:
For Oroxine 25 and 50 microgram tablets:
28, 50, 60 tablets.

For Oroxine 75, 100, 125, 150, 175, 200 microgram tablets:
28, 50, 60, 84, 90, 100, 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited

3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/013/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th September 2014
Date of last renewal: 10th April 2019

10 DATE OF REVISION OF THE TEXT

September 2024