Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine sodium Aristo 200 micrograms tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 microgram anhydrous levothyroxine sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Levothyroxine sodium Aristo tablets are white, round uncoated vaulted tablets (snap tab) with a break mark on one side and the numeric strength (200) embossed on the other. The tablets have an approximate diameter of 7 mm and approximate height of 3 mm.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypothyroidism
- Prophylaxis against goitre recurrence following resection of euthyroid goitre
- Benign, euthyroid goitre
- Suppression and replacement therapy in thyroid malignancy, especially post thyroidectomy
- 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, 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. Experience has shown that a lower dose is also sufficient in patients with a low body weight and in patients with a large goitre.

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.

Paediatric population

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.

The maintenance dose is generally 100 to 150 microgram per m^2 body surface area.

Congenital hypothyroidism in neonates and infants

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.

Indication		**Recommended dose** (microgram levothyroxine sodium/day)
Hypothyroidism in adults • initial dose • maintenance dose (increased at 2 to 4 week intervals in increments of 25–50 microgram)		 25–50 100–200
Hypothyroidism in children • initial dose • maintenance dose (increased at 2 to 4 week intervals)		 12.5–50 100–150/m^2 body surface
Hypothyroidism in newborns and infants • initial dose for the first 3 months • maintenance dose		 10–15 microgram per kg Individual adjustment according to the clinical findings and thyroid hormone and TSH values
Prophylaxis against goitre recurrence		75–200
Benign euthyroid goitre		75–200
Suppression and replacement therapy in thyroid cancer		150–300
Co-therapy in the antithyroid treatment of hyperthyroidism		50–100
Thyroid suppression scintigraphy	Levothyroxine sodium Aristo 200 microgram tablets	200 microgram (equivalent to 1 tablet)/day (for 14 days until the scintigram is performed)

Method of administration

The tablets should be taken orally as a single daily dose in the morning on an empty stomach, at least 30 minutes before the first meal of the day, preferably with a little liquid (for example, half a glass of water).

Infants are given the total daily dose at least half an hour before their first meal of the day, preferably with some water to facilitate swallowing. If necessary the tablet can be divided.

It is not recommended that tablets are crushed and dispersed in water or other liquids, which could lead to dosing inaccuracy.

Notice on divisibility

Place the tablet with the score line facing up on a hard flat surface. To divide the tablet push with your thumb straight in the middle of the tablet.

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 has failed to achieve the desired success within this time, other therapeutic options should be considered.

For performing thyroid suppression tests, 150 or 200 microgram of levothyroxine is taken daily for 14 days.

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
- Treatment with Levothyroxine sodium Aristo 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

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 (such as symptoms of hyperthyroidism, see section 4.9), particularly in combination with certain substances for weight reduction, and especially with sympathomimetic amines (see section 4.5).

In combination with certain weight-reduction agents such as orlistat reduced control of hypothyroidism may occur (see section 4.5). 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 close monitoring including 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.

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,
- patients with diabetes mellitus or insipidus, as well as for patients on anticoagulation therapy (see section 4.5).

Before starting thyroid hormone therapy, the following diseases or conditions must be excluded or treated:

- coronary heart disease,
- angina pectoris,

- arteriosclerosis,
- 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.

In case of adrenocortical dysfunction, this should be treated before starting therapy with levothyroxine by adequate replacement treatment to prevent acute adrenal insufficiency (see section 4.3). Treatment with levothyroxine in patients with adrenal insufficiency may cause reactions, including dizziness, weakness, malaise, weight loss, hypotension and adrenal crisis. It is advisable to initiate corticosteroid therapy before giving levothyroxine in these cases.

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

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

Even mild drug-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. More frequent monitoring of thyroid hormone parameters must be performed in these patients (see section 4.2).

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.

Long-term levothyroxine 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 (see section 4.8).

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 therapy, or when the dose of levothyroxine is increased rapidly and may be related to the effect of thyroid hormones on seizure threshold.

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.

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.

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.

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.

Interference with laboratory tests:
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).

Levothyroxine sodium Aristo tablets contain sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'

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), cimetidine and proton pump inhibitors decrease the absorption of levothyroxine. Separate the dosages of levothyroxine and the above mentioned medicines as much as possible, i.e. at least 4–5 hours, to avoid interaction in the stomach or the small bowel.

Soya products and high-fibre diets
Soya products and high-fibre diets can 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 T_4 und TSH. During and upon termination of a diet containing soya, close monitoring of serum T_4 and TSH levels is necessary; a dose adjustment of levothyroxine may be required.

Anti-obesity drugs (including orlistat)
Hypothyroidism and/or reduced control of hypothyroidism may occur when levothyroxine and orlistat are taken at the same time. This could be due to a decreased absorption of levothyroxine and/or iodine salts. See also section 4.4.

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.

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 both hyperthyroidism and hypothyroidism can be initiated. Particular caution should be exercised in patients with nodular goitres with possibly undetected autonomy. As a result of the effect of amiodarone on thyroid function, a dose adjustment of levothyroxine may be required.

Anti-inflammatory drugs, furosemide, clofibrate
Levothyroxine may be displaced from plasma protein binding by salicylates, phenylbutazone, 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 dosage 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.

Androgen
Androgens may decrease serum concentrations of thyroxine-binding globulins.

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
Barbiturates, rifampicin, primidone and other medicinal products with liver enzyme inducing properties can increase hepatic clearance of levothyroxine.

Effects of drugs inducing cytochrome P-450
Enzyme-inducing drugs such as barbiturates, rifampicin, primidone and 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, 5-fluorouracil
These substances 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 preparation
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
Tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) response may be accelerated because levothyroxine increases receptor sensitivity to catecholamines; concomitant use may precipitate cardiac arrhythmias.

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

Phenytoin
Phenytoin levels may be increased by levothyroxine.

Interference with laboratory tests
A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring a patient on levothyroxine therapy.

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 T_4. Continued administration results in normal free T_4 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
Treatment with levothyroxine should be given consistently during pregnancy.
Since elevations in serum TSH may occur as early as 4 weeks of gestation, pregnant women taking levothyroxine should have their TSH measured during each trimester, in order to confirm that the maternal serum TSH values lie within the trimester-specific pregnancy reference range. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine. Since postpartum TSH levels are similar to preconception values, the levothyroxine dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6 -8 weeks postpartum.

Experience has shown that there is no evidence of drug-induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose level. Thyroid hypo- or hyperactivity in the mother may, however, unfavourably influence the foetal outcome or well-being. 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 (see section 4.3). Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

Suppression tests must not be performed during pregnancy.

Breast-feeding
Treatment with levothyroxine should be given consistently during breast-feeding. 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. However, it may be sufficient to interfere with neonatal screening for hypothyroidism.

Suppression tests must not be performed during 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 is not expected to have any influence on the ability to drive and use machines.

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.
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:
Rare (≥1/10,000 to <1/1,000)
Not known (cannot be estimated from the available data)

The Frequency of the following undesirable effects is **not known**:

System organ class	Undesirable effects
Immune system disorders	Hypersensitivity reactions, including rash, pruritus and oedema: In the case of hypersensitivity to levothyroxine or any of the excipients, allergic reactions of the skin (erythema) and respiratory tract region (dyspnoea) may occur.
Endocrine disorders	Thyrotoxic crisis[1], hyperthyroidism (see section 4.9)
Metabolism and nutrition disorders	Increased appetite
Psychiatric disorders	Restlessness, agitation, insomnia
Nervous system disorders	Tremor, headache, convulsion
Cardiac disorders	Angina pectoris, arrhythmia, palpitations, tachycardia, heart failure, myocardial infarction
Vascular disorders	Hypertension, flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	Hyperhidrosis, angioedema, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorder	Arthralgia, muscle spasm, muscular weakness, osteoporosis at suppressive doses of levothyroxine (especially in postmenopausal women, mainly when treated for a long period)
Reproductive system and breast disorders	Menstruation irregular
General disorders and administration site conditions	Pyrexia, malaise, oedema
Investigations	Weight decreased

[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.

Paediatric population

System organ class	Frequency	Undesirable effects
Nervous system disorders	rare	benign intracranial hypertension
Skin and subcutaneous tissue disorders	not known	transient hair loss
Musculoskeletal and connective tissue disorder	not known	premature closure of epiphysis in children
Congenital, familial and genetic disorders	not known	craniostenosis in infants
General disorders and administration site conditions	not known	Temperature intolerance

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,
Website: www.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.
Signs of an overdose may include (in addition to exaggeration of side effects): agitation, confusion, irritability, fever, chest pain (angina), racing or irregular heartbeat, tachypnoea, muscle cramps, headache, restlessness, hyperactivity, flushing, sweating, mydriasis, diarrhoea, tremor, insomnia, hyperpyrexia, affect lability, fatigue, anxiety and nervousness. In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded.

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 crisis have 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.

The appearance of clinical hyperthyroidism may be delayed for up to 6 days.

Management
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.

After 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 Code: H03AA01

Mechanism of action
The action of synthetic levothyroxine 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 body 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). 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 population

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 T_3 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 repeat dose toxicity studies only occurred at high doses.

Acute toxicity

The acute toxicity of levothyroxine is very low.

Chronic toxicity

Chronic toxicity studies were performed on 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 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 the central nervous system development in chinchillas were reported but teratogenic studies in guinea pigs and rabbits did not reveal increases in congenital abnormalities.

Limited data on the effects on fertility are available. Animal studies with mice at high doses of levothyroxine have shown a reduction in male sexual activity and female lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- cellulose, microcrystalline
- maize starch
- magnesium oxide, heavy
- sodium starch glycolate (type A)
- vegetable magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

27 months

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

The tablets are packed in PVC/Aluminium blister in pack sizes of 15, 20, 25, 30, 50, 60, 84, 90 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Str. 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER

PA1983/004/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th January 2020

10 DATE OF REVISION OF THE TEXT

July 2023