SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine Aristo 100 micrograms tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Levothyroxine Aristo 100 micrograms tablet contains 100 micrograms levothyroxine sodium anhydrous.

Excipient(s) with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Levothyroxine Aristo tablets are white, round uncoated tablets with a score line on one side and "100" embossed on the other. The tablets have an approx. diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Recommended clinical indications:

- control of hypothyroidism
- congenital hypothyroidism *in infants*
- acquired hypothyroidism in children
- juvenile myxoedema.

4.2 Posology and method of administration

Posology

In younger patients and in the absence of heart disease, a serum Levothyroxine (T4) level of 70 to 160 nanomols per litre, or a serum thyrotropin level of less than 5 milli-units per litre should be targeted. A pre-therapy ECG is valuable because ECG changes due to hypothyroidism may be confused with ECG evidence of cardiac ischaemia. If too rapid an increase in metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors, and sometimes anginal pain where there is latent cardiac ischaemia,) dosage must be reduced, or withheld, for a day or two, and then re-started at a lower dose level.

Adults

Initially 100 micrograms daily, preferably taken before breakfast or the first meal of the day. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained. The final daily dose may be up to 100 to 200 micrograms.

Elderly

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 3-4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 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 this condition, the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

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

Paediatric population

The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated. Regular monitoring using serum TSH levels, as in adults, 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 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.

Acquired hypothyroidism in children

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.

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 - 4 weeks, until mild symptoms of hyperthyroidism are seen. The dose will then be reduced slightly.

Method of administration

The tablets should be taken orally at least 30 minutes before the first meal of the day. The tablets should not be subdivided to obtain the desired dose. The appropriate tablet strength or an oral solution formulation of levothyroxine should be administered.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Thyrotoxicosis
- Adrenal gland disorder or adrenal insufficiency

4.4 Special warnings and precautions for use

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

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

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

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

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.

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.

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

See note above regarding withdrawal of treatment.

Levothyroxine can precipitate or exacerbate a pre-existing myasthenic syndrome.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting other drugs

Levothyroxine increases the effect of anticoagulants (Warfarin) and it may be necessary to reduce the anticoagulation dosage if excessive, hypoprothrombinaemia and bleeding are to be avoided.

Blood sugar levels are raised and dosage of anti-diabetic agents may require adjustment.

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

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

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

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

Beta Blockers: levothyroxine (thyroxine) accelerates metabolism of propranolol, atenolol and sotalol.

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

Interactions affecting Levothyroxine
Amiodarone may inhibit the de iodination of thyroxine to tri iodothyronine resulting in a decreased concentration of tri iodothyronine, thereby reducing the effects of thyroid hormones.

Anti-convulsants, such as carbamazepine and phenytoin, enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Initiation or discontinuation of anti-convulsant therapy may alter levothyroxine dosage requirements.

Effects of Levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine (thyroxine) possibly reduced by antacids, proton pump inhibitors, calcium salts, cimetidine, oral iron, sucralfate, colestipol, polystyrene sulphonate resin and cholestyramine (administration should be separated by 4-5 hours).

Metabolism of levothyroxine (thyroxine) accelerated by rifampicin, barbiturates, and primidone. (may increase requirements for levothyroxine (thyroxine) in hypothyroidism)

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.

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

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

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

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

4.6 Fertility, Pregnancy and lactation

Pregnancy
The safety of Levothyroxine treatment during pregnancy is not known, but any possible risk of fetal abnormalities should be weighed against the risk to the fetus of

untreated hypothyroidism.

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

Fertility
The potential risk for humans is unknown. In animal studies with supratherapeutic doses effects on fertility were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Levothyroxine has no or negligible 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:
Very common (≤1/10)
Common (≤1/100 to <1/10)
Uncommon (≤1/1,000 to <1/100)
Rare (≤1/10,000 to <1/1,000)
Very rare (<1/10,000)
not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Immune system disorders	Not known	Hypersensitivity reaction
Endocrine disorders	Not known	Thyrotoxic crisis[1]
Psychiatric disorders	Not known	Restlessness, agitation, insomnia
Nervous system disorders	Not known	Tremor
Cardiac disorders	Not known	Angina pectoris, arrhythmia, palpitations, tachycardia
Vascular disorders	Not known	Flushing
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea
Gastrointestinal disorders	Not known	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Not known	Hyperhidrosis, rash, pruritus
Musculoskeletal and connective tissue disorder	Not known	Arthralgia, muscle spasm, muscular weakness
Reproductive system disorders	Not known	Menstruation irregular
General disorders and administration site	Not known	Headache, pyrexia, malaise, oedema

System organ class	Frequency	Undesirable effects
conditions		
Investigations	Not known	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
Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
In most cases there will be no features. Signs of an overdose may include: fever, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea, tremor, insomnia and hyperpyrexia. These signs can take up to 5 days to appear**.** Atrial fibrillation may develop. Convulsions occurred in one child. There may be increased toxicity in those with pre-existing heart disease.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid therapy, Thyroid hormones
ATC Code: H03AA01

Levothyroxine sodium is a synthetic thyroid hormone which used for the treatment of hypothyroidism. The thyroid gland is dependent upon 2 active principles for its main hormone activity. These are levothyroxine (tetraiodothyronine) and tri-iodothyronine (see Goodman and Gilman, 1985). These closely related iodine containing amino acids are incorporated into the glycoprotein thyroglobulin. The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form tri-iodothyronine which is thought to be active tissue form of thyroid hormone. Tri-iodothyronine is certainly more rapid acting and has shorter duration of action than Levothyroxine.

5.2 Pharmacokinetic properties

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. It is almost completely bound to plasma proteins and has a half-life in the circulation of about a week in healthy subjects, but longer during pregnancy in patients with myxoedema. A large portion of the Levothyroxine leaving the circulation is taken up by the liver. Part of a dose of Levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine as free drug, deiodinated metabolites and conjugates. Some Levothyroxine is excreted in the faeces. There is limited placental transfer of Levothyroxine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Effects reported in literature reproductive toxicity studies in rats were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
2 years

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 28 tablets.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 40546/0159

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08/07/2019

10 DATE OF REVISION OF THE TEXT

04/02/2020