Section 3 - Summary of Product Characteristics

Product Summary

1 Trade Name of the Medicinal Product

LEVOTHYROXINE TABLETS BP 50 micrograms

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 micrograms anhydrous Levothyroxine Sodium.

Excipient with known effect:
Each 50micrograms tablet contains 39.95mg lactose.

For the full list of excipients, see section 6.1.

3 Pharmaceutical Form

White uncoated tablets.
White, circular, biconvex uncoated tablets impressed “C” on one face and the identifying letters “T” and “A” on either side of a central division line on the reverse.

Clinical Particulars

4.1 Therapeutic Indications

Recommended clinical indications:
1. control of hypothyroidism,
2. congenital hypothyroidism in infants
3. acquired hypothyroidism in children
4. 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 thyrotrophin level of less that 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

Patients under 50 years age:
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.

Patients over 50 years age:
a. Without cardiac disease: 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.

b. With cardiac disease: Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In this conditions, the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms.

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

Elderly
Same as that for patients aged over 50 years

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 is seen. The dose will then be reduced slightly.

In children under 5 years of age, the administration of whole tablets is not recommended. It is also not recommended that tablets are crushed and dispersed in water or other liquids, owing to limited solubility which could lead to dosing inaccuracy. In this age group it is preferable to administer an approved oral solution of levothyroxine.

Method of Administration

For oral administration. To be taken preferably 30-60 minutes before breakfast, caffeine-containing liquids, (e.g. coffee, tea), or other medication.

4.3 Contraindications

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

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.

A small number of patients report adverse events on changing between different levothyroxine products. In some cases, symptoms are reported despite thyroid function tests within the reference range. If patients report side effects on switching between products, consider thyroid function testing. For patients who are persistently symptomatic after switching, whether they are biochemically euthyroid or have evidence of abnormal thyroid function, consider consistently prescribing a specific levothyroxine product that is well-tolerated by the patient. If symptoms or poor control of thyroid function persist despite adhering to a specific product, prescription of levothyroxine in an oral solution formulation should be considered.

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).

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.

Special care is needed for the elderly and for patients with symptoms of myocardial insufficiency, or ECG evidence of myocardial infarction.

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.

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.

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.

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.

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).

Paediatric population

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.

Levothyroxine Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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.

Cardiac 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.

NSAIDs: 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.

General anaesthetics: 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 triiodothyronine resulting in a decreased concentration of triiodothyronine, thereby reducing the effects of thyroid hormones.

Anticonvulsants, 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, 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).

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

Beta blockers may decrease the peripheral conversion of levothyroxine to triiodothyronine.

Lipid regulating drugs: Lovastatin has been reported to cause one case each of hypothyroidism and hyperthyroidism in two patients taking levothyroxine.

Sex Hormones: 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).

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.

Effects of drugs inducing cytochrome P-450: Enzyme-inducing drugs such as 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.

Interferences with laboratory test:

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Levothyroxine treatment during pregnancy is not known, but any possible risk of foetal abnormalities should be weighed against the risk to the foetus of untreated hypothyroidism.

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.
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.

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

Fertility
No data available

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:

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, alopecia, rash, pruritus, angioedema, urticaria.
Musculoskeletal and connective tissue disorder	Not known	Arthralgia, muscle spasm, muscular weakness
Reproductive system disorders	Not known	Menstruation irregular
General disorders and administration site conditions	Not known	Headache, pyrexia, malaise, oedema
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 Website: 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 hormones, ATC Code: H03AA01

Mechanism of action
Levothyroxine Tablets contain the hydrated form of Levothyroxine sodium which is 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 the active tissue form of thyroid hormone.

Pharmacodynamic effects
Tri-iodothyronine is certainly more rapid acting and has a shorter duration of action than Levothyroxine.

The chief action of Levothyroxine is to increase the rate of cell metabolism.

5.2 Pharmacokinetic properties

Absorption
Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract.

Distribution
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 and in patients with myxoedema.

Biotransformation
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.

Elimination
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

No further data of relevance.

Pharmaceutical Particulars

6.1 List of excipients

Also contains: lactose, magnesium stearate, maize starch, pregelatinised maize starch, stearic acid.

6.2 Incompatibilities

None known.

6.3 Shelf-life

Three years from the date of manufacture (polyethylene containers and amber glass bottles)
Two years from date of manufacture (blisters)
Two years from date of manufacture (polypropylene containers)

6.4 Special precautions for storage

Blister packs:
Do not store above 25ºC.
Store in the original package.
Keep container in the outer carton.

Polypropylene containers, polyethylene containers and amber glass bottles:
Do not store above 25ºC.
Store in the original container.
Keep the container tightly closed.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil.

Pack sizes: 7s, 14s, 28s, 56s, 84s, 100s, 250s, 500s, 1000s.

The product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.
Maximum size of bulk packs: 25,000

6.6 Instructions for use/handling

Not applicable.

Administrative Data

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 Marketing Authorisation Number

PL 0142/0104

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 June 1978
Date of latest renewal: 4 August 2002

10 DATE OF REVISION OF THE TEXT

02/02/2024