SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levothyroxine 50 microgram Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 microgram of Levothyroxine Sodium.

Excipient(s) with known effect:
This medicinal product contains 0.27 mmol (or 6.1 mg) sodium per tablet. To be taken into consideration by patients on a controlled sodium diet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round biconvex tablets with scoreline on one side and marking 50 on the other side of the tablet.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Recommended clinical indications: Control of hypothyroidism, congenital hypothyroidism in infants, acquired hypothyroidism in children and 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 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 50 to 100 micrograms daily, preferably taken on an empty stomach, at least 30 minutes and preferably 1 hour before food, ideally taken before breakfast or your 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. The dose may need to be increased during pregnancy.

Elderly: As for patients aged over 50 years.
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 dosage may be increased by 25 microgram increments 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 than 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 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.
Infants should be given the total daily dose at least half an hour before the first meal of the day.

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
For oral administration.

In children under 5 years of age, the administration of whole tablets is not recommended. It is also not recommended that levothyroxine 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.

4.3. Contraindications

Hypersensitivity to the active susbstance or to any of the excipients listed in section 6.1
In addition Levothyroxine is contra-indicated in:

- 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 pectoris, arteriosclerosis, coronary artery disease, hypertension, symptoms or ECG evidence of myocardial infarction and in older people who have a greater likelihood of occult cardiac disorders. A patient with prolonged myxoedema should be restored to normality only gradually.

There is a risk of atrial fibrillation, particularly in elderly patients.

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.

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.

<u>Paediatric population</u>
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 subsequently regrowth usually occurs.

4.5. Interactions 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.

Treatment with Levothyroxine may result in an increase in dosage requirements of insulin or oral hypoglycaemic agents.

As levothyroxine increases receptor sensitivity to catecholamines, the response to tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) may also be accelerated; concomitant use may precipitate cardiac arrhythmias.

The effects of sympathomimetic agents e.g. adrenaline or phenylephrine) are also enhanced.
The toxicity of digitalis is enhanced by levothyroxine, therefore, in digitalised patients the dose of digitalis may need adjusting (gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin) if levothyroxine therapy is required.

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 and propranolol may inhibit the de-iodination of levothyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine, therefore reducing the effects of thyroid hormones.

Metabolism of thyroid hormones may be enhanced by anticonvulsants such as phenytoin and carbamazepine. The levothyroxine dose may need adjustment after initiating or terminating anticonvulsant therapy which may also displace them from plasma proteins.

Effects of levothyroxine may be decreased by concomitant sertraline.

Absorption of levothyroxine 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).

Barbiturates, primidone and enzyme inducing drugs such as rifampicin enhance thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. (may increase requirements for levothyroxine (thyroxine) in hypothyroidism).
Imatinib: plasma concentration of levothyroxine possibly reduced by imatinib.

Beta blockers may decrease the peripheral conversion of levothyroxine to tri-iodothyronine. An increased dosage of levothyroxine may be required when co-administered with oral contraceptives, Oestrogen, oestrogen containing product (including hormone replacement therapy) Conversely, androgens and corticosteroids may decrease serum concentrations of levothyroxine-binding globulins.
Thyroid function tests may be affected by a number of drugs. This should be taken into account when monitoring a patient's response to levothyroxine therapy.

In an interaction study in healthy volunteers, colesevelam reduced the AUC and Cmax of levothyroxine when administered either concomitantly or after one hour. No interaction was observed when colesevelam was administered at least four hours after levothyroxine.

Rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur when levothyroxine is taken concomitantly with orlistat.

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 during pregnancy has not been established. Any possible risk of congenital abnormalities should be assessed against the possible consequences to the foetus of untreated hypothyroidism.

Breast-feeding
Levothyroxine is excreted into breast milk in low concentrations and screening for congenital hypothyroidism might be affected.

Fertility
The effects of levothyroxine on fertility have not been established.

4.7. Effects on ability to drive and use machines

Levothyroxine has no known influence on the ability to drive and use machines.

4.8. Undesirable effects

Adverse effects of thyroid hormones are generally associated with excessive doses and correspond to the symptoms of hyperthyroidism. The effects may include:

System organ class	Not known (cannot be estimated from available data)
Immune system disorders	hypersensitivity reactions including rash, pruritus, dyspnoea, joint pain, malaise, oedema and angioedema

System organ class	Not known (cannot be estimated from available data)
Metabolism and Nutrition disorders	loss of weight
Nervous system disorders	tremors, restlessness, excitability, insomnia. Rarely, benign intracranial hypertension in children
Cardiac disorders	angina pain, cardiac arrhythmias, palpitations, tachycardia
Gastro- intestinal disorders	diarrhoea, vomiting
Musculoskeletal and Connective tissue disorders	muscle cramps, muscular weakness, craniostenosis in infants and premature closure of epiphysis in children
Reproductive system disorders	menstrual irregularities
General disorders and administration site conditions	Headache, flushing, fever and sweating

Intolerance to heat, transient hair loss in children, also reported.

Symptoms may not appear until several days after the administration of levothyroxine. All these reactions usually disappear on reduction of the dosage or temporary withdrawal of treatment.

Cardiac disease may be exacerbated by the administration of thyroid hormones resulting in severe angina pectoris, myocardial infarction or sudden cardiac death.

Gross over dosage has been reported to result in a clinical state resembling thyroid storm, and in collapse and coma.

Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a “thyroid crisis” with any of the following symptoms:

- Hyperpyrexia, tachycardia, arrhythmia, hypotension, cardiac failure, jaundice, confusion, seizure and coma

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Consumers are advised to report adverse events related to the use of medicines and medical product to the nearest NAFDAC office, NAFDAC PRASCOR (20543 TOLL FREE from all networks), pharmacovigilance@nafdac.gov.ng or via the eReporting platform available on the NAFDAC Website; https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=NG

4.9. Overdose

Symptoms:

In most cases there will be no features. Symptoms of over dosage include exaggeration of its side-effects, chest pain (angina), racing or irregular heartbeat, muscle cramps, headache, restlessness, flushing, diarrhoea, tremor, insomnia and hyperpyrexia, agitation, confusion, hyperactivity, irritability, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements. Convulsions occurred in one child. The appearance of clinical hyperthyroidism may be delayed for up to five days. Atrial fibrillation may develop. There may be increased toxicity in those with pre-existing heart disease.

Treatment:

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. Further treatment is symptomatic. Tachycardia has been controlled in an adult by administering beta-blockers (e.g. propranolol) every six hours and other symptoms by diazepam and chlorpromazine as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Levothyroxine sodium is used for the treatment of hypothyroidism. Levothyroxine is deiodinated in peripheral tissues to form triiodothyronine which is thought to be the active tissue form of thyroid hormone. Triiodothyronine has a rapid action but a shorter duration of activity than Levothyroxine.

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

ATC Code: H03A A01 (Thyroid preparations, thyroid hormones).

5.2. Pharmacokinetic properties

Absorption
Levothyroxine sodium is incompletely and variably absorbed from the gastro-intestinal tract. Absorption of orally administered levothyroxine from the gastrointestinal tract ranges from 40% to 80%. The majority of the dose is absorbed

from the jejunum and upper ileum. Levothyroxine absorption is increased by fasting, decreased in malabsorption syndrome, by certain foods and decreases also with age.

Distribution
Levothyroxine is almost completely bound to plasma-proteins and has a half-life in the circulation of about a week in healthy persons but longer in patients with myxoedema.

Biotransformation
The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating L-triiodothyronine is derived from peripheral levothyroxine by monodeiodination. The liver is the major site of degradation for both levothyroxine and L-triiodothyronine, with levothyroxine deiodination also occurring at a number of additional sites, including the kidney and other tissues. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination
Levothyroxine is primarily eliminated by the kidneys 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

There are no preclinical data of relevance to the prescriber, which are additional to that already described Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The tablet contains:
maize starch
mannitol (E421)
microcrystalline cellulose
sodium citrate
acacia
magnesium stearate.

6.2. Incompatibilities

None known.

6.3. Shelf life

Blisters packs: 18 months.

6.4. Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

PVC/PE/PVDC/PE/PVC//Al blister strips in packs of 28, 56 and 112 tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.