SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levothyroxine 50 micrograms Tablets (Thyroxine 50 micrograms Tablets).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 micrograms Levothyroxine Sodium anhydrous also known as thyroxine sodium anhydrous. Excipients with known effect
Lactose 31.88mg per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White uncoated biconvex tablets engraved on one face FW21 with a breakline on the other.

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 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: Initially 50 to 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: 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 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.

Paediatric population: The maintenance dose is generally 100 to 150 micrograms per m² 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 2-4 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
Oral

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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.

Levothyroxine sodium should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease and hypertension.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Levothyroxine should be introduced very gradually in elderly patients and those with long standing hypothyroidism to avoid any sudden increase in metabolic demands.

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.

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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting other drugs:

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

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

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

Sympathomimetics: 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:

Anti arrhythmics: Amiodarone may inhibit the de iodination of thyroxine to triiodothyronine resulting in a decreased concentration of triiodothyronine, thereby reducing the effects of thyroid hormones.

Anti-convulsants, such as carbamazepine, primidone and phenytoin, enhance the metabolism of thyroid hormones and increase requirement for thyroid hormones in hypothyroidism.

Effects of Levothyroxine may be decreased by concomitant sertraline.

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

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.

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

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

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).

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 foetal abnormalities should be weighed against the risk to the foetus 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.

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)

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

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

Levothyroxine 50 micrograms Tablets are tablets containing Levothyroxine sodium 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.

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 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

No further data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Citrate
Lactose
Maize starch
Powdered Acacia
Magnesium Stearate

6.2 Incompatibilities

None known.
6.3 Shelf life

36 months for polypropylene containers.
24 months for blister packs.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Polypropylene container with tamper-evident low density polyethylene lid, containing 28, 56, 100, 112 or 1000 Levothyroxine 50 micrograms tablets.

Blister packaging PVC/PVdC film (heat treated foil/heat seal lacquer) containing 28, 56 and 112 Levothyroxine tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Mercury Pharma (Generics) Ltd
Capital House, 85 King William Street,
London EC4N 7BL, UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 16201/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
Aug 2004

10 DATE OF REVISION OF THE TEXT

21/12/2016