

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.

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

1) Hypothyroidism.

4.2 Posology and Method of Administration

Posology

It is recommended that the tablets should be administered before meals.

Adults: Initially 50-100 micrograms daily, then adjusted at 3-4 week intervals by 50 microgram increments until normal metabolism is steadily maintained. This may require doses of up to 150-300 micrograms daily.

Patients over 50 years: It is not advisable to exceed 50 micrograms a day initially, and 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 maybe 4 weeks.

In younger patients, and in the absence of heart disease, a serum levothyroxine (T4) level of approximately 70-160 nanomoles/litre or a serum thyrotrophin level of less than 5 milli-units/litre should be aimed at. In those aged over 50, and/or in the presence of heart disease, clinical response is probably a more acceptable criterion of dosage than serum levels.

A pre-therapy ECG is valuable, as changes induced by hypothyroidism may be confused with ECG evidence of ischaemia. If too rapid an increase of metabolism is produced, dosage should be reduced or withheld for a day or two, then recommenced at a lower level.

Congenital hypothyroidism and juvenile myxoedema: The largest dose consistent with freedom from toxic effects should be given. Clinically, normal pulse rate and absence of diarrhoea or constipation are the most useful indications. For congenitally hypothyroid infants, a suitable starting dose is 25 micrograms levothyroxine daily, with increments of 25 micrograms every 2-4 weeks until mild toxic symptoms appear. Dosage should then be slightly reduced. The same

applies to juvenile myxoedema, except that the starting dose for children older than one year may be 2.5-5 micrograms/kg bodyweight daily.

Method of Administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to levothyroxine or any other ingredients in the tablets.
- Thyrotoxicosis.
- Patients with adrenal insufficiency without adequate corticosteroid cover.

4.4 Special Warnings and Precautions for Use

Levothyroxine should be administered with caution where there are symptoms of myocardial insufficiency, ECG evidence of myocardial infarction and hypertension. A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. Thyroid replacement therapy should be introduced gradually in elderly patients, and those with severe long standing hypothyroidism.

Patients with adrenal insufficiency or other causes predisposing to it such as panhypopituitarism may react unfavourably to levothyroxine treatment so it is advisable to initiate corticosteroid therapy before giving levothyroxine. Caution should also be exercised when administering levothyroxine to diabetics (mellitus or insipidus) or digitalised patients.

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 a 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 Interactions with other Medicaments and other forms of Interaction

- A possible interaction occurs with hypoglycaemic agents, hence diabetic patients should be monitored for increased requirements of insulin or oral hypoglycaemic agents.
- 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.
- Levothyroxine may enhance the effects of anticoagulants (e.g. warfarin, dicoumarol, acenocoumarol and phenindione) and it may be necessary to reduce the dose of anticoagulant if excessive hypoprothrombinaemia and bleeding are to be avoided.
- Levothyroxine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants (e.g. amitriptyline).
- The effects of sympathomimetic agents (e.g. adrenaline (epinephrine)) are also enhanced.
- The absorption of levothyroxine is reduced by sucralfate, sodium polystyrene sulphonate or colestyramine binding within the gut. Cimetidine, aluminium hydroxide, calcium carbonate and ferrous sulphate also reduce absorption of levothyroxine from the G.I. tract. Dosages should be separated by an interval of several hours.
- Concurrent use of carbamazepine, phenytoin, phenobarbital, primidone or rifampicin have been found to increase levothyroxine metabolism.

- Isolated reports of marked hypertension and tachycardia has been reported with concurrent ketamine administration.
- Lovastatin has been reported to cause one case each of hypothyroidism and hyperthyroidism in two patients taking levothyroxine.
- False low total plasma concentrations have been observed with concurrent anti-inflammatory treatment such as phenylbutazone or acetylsalicylic acid and levothyroxine therapy.
- Levothyroxine accelerates the metabolism of propranolol.
- Oestrogen, oestrogen containing products and oral contraceptives may increase the requirement of thyroid therapy dosage. Conversely, androgens and corticosteroids may decrease serum concentrations of levothyroxine-binding globulins.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.
- 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 Pregnancy and Lactation

Pregnancy

Women on a maintenance dose for hypothyroidism, who become pregnant, must be monitored closely. Levothyroxine sodium does not readily cross the placenta in the second and third trimester but may do so in the first. Levothyroxine sodium is not known to have either carcinogenic or teratogenic effects.

Lactation

Minimal concentrations of levothyroxine are excreted in breast milk and may cause hypothyroidism in a newborn baby. It is considered that there is insufficient thyroid hormone in breast milk to meet the needs of a suckling infant with a non-functioning thyroid gland.

4.7 Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable Effects

Hypersensitivity reactions including rash, pruritus and oedema have also been reported.

The following side effects are usually due to excessive dosage and correspond to symptoms of hyperthyroidism. These reactions usually disappear after dose reduction or withdrawal of treatment. They include:

Effects on the heart: arrhythmias, anginal pain, tachycardia, palpitations.

Effects on the central nervous system (CNS): headache, restlessness, excitability, flushing, sweating, insomnia, tremor, fever, heat intolerance.

Effects on the gastrointestinal (G.I.) tract: diarrhoea, excessive weight loss, vomiting.

Musculoskeletal Effects: muscle cramps, muscle weakness.

Thyroid crises have occasionally been reported following massive or chronic intoxication and cardiac arrhythmias, heart failure, coma and death have occurred.

4.9 Overdose

Symptoms of mild to moderate overdose: fever, angina, tachycardia, arrhythmias, muscle cramps, headache, restlessness, flushing, sweating, diarrhoea. Reduction of dose or withdrawal of therapy reverses mild overdose effects.

Symptoms of severe overdose: this may resemble thyroid crisis with collapse and coma.

Signs and symptoms of hyperthyroidism may be delayed for up to 5 days due to the gradual peripheral conversion of levothyroxine to triiodothyronine. Overdosage following recent ingestion of tablets can be treated using gastric lavage/emesis.

Propranolol and other supportive measures are used to maintain the circulation. Antithyroid drugs such as propylthiouracil and lithium are unlikely to be of benefit to prevent thyrotoxic crisis due to delayed absorption/onset of action.

Pharmacological Properties

5.1 Pharmacodynamic properties

Levothyroxine sodium is employed in the treatment of thyroid deficiency states.

5.2 Pharmacokinetic properties

Levothyroxine sodium is incompletely and variably absorbed from the GI tract; it is almost completely bound to plasma proteins and has a half-life in the circulation of about a week in healthy persons and slightly longer during pregnancy and in patients with myxoedema.

Levothyroxine is excreted in the urine as free drug, deiodinated metabolites, and conjugates. Some levothyroxine is excreted in the faeces.

5.3 Preclinical safety data

Not applicable.

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

Shelf-life

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

Two years from date of manufacture (Blister)

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Blister packs:

Do not store above 25°C.

Store in the original package.

Keep container in the outer carton.

Polypropylene containers, polyethylene containers and amber glass bottles:

Do not store above 25°C.

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 with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

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

Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis UK Limited
(Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 Marketing Authorisation Number

PL 0142/0104

9 Date of First Authorisation/Renewal of Authorisation

8 June 1978
4 August 1997, 4 August 2002

10 DATE OF REVISION OF THE TEXT

February 2007

SUMMARY OF PRODUCT CHARACTERISTICS

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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3 PHARMACEUTICAL FORM

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4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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5.3 Preclinical safety data

Not applicable.

6 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

Shelf-life

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

Two years from date of manufacture (Blisters)

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

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Maximum size of bulk packs: 25,000

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis UK Limited
(Trading style: Actavis)
Whiddon Valley
Barnstaple
N Devon EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 June 1978
4 August 1997, 4 August 2002

10 DATE OF REVISION OF THE TEXT

April 2007

11 DOSIMETRY (IF APPLICABLE)

Not applicable.

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**

Not applicable.