

**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION  
(PL 20249/0004)**

**EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION  
(PL 20249/0007)**

**EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION  
(PL 20249/0005)**

## **UK Public Assessment Report**

**The marketing authorisations for Evotrox 25, 50 and 100 microgram/5ml Oral Solutions were revoked on 23 January 2013.**

**This Public Assessment Report has been updated accordingly to explain the reasons for revocation.**

**The original Public Assessment report (03 July 2006) is appended to this report.**

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**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0004)  
EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0007)  
EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0005)**

**Public Assessment Report: Revocation of a Marketing Authorisation**

On 23 January 2013, the MHRA revoked marketing authorisations (“product licence”) for the medicinal products, Evotrox 25 microgram/5ml Oral Solution (PL 20249/0004), Evotrox 50 microgram/5ml Oral Solution (PL 20249/0007) and Evotrox 100 microgram/5ml Oral Solution (PL 20249/0005) meaning that these products could no longer be supplied to the market. These licences had been granted to Kappin Limited on 03 July 2006.

Information presented in the licence application supported the shelf-life and storage conditions that were approved. However, a Good Manufacturing Practice inspection performed by the MHRA in November 2011 cast doubt upon the reliability of this information. Subsequent monitoring identified significant quality concerns with product stability and manufacture.

Product remaining in pharmacies and wholesalers was recalled on 28 August 2012.

The MHRA asked advice from the Commission on Human Medicines (an independent panel of experts with whom the licensing authority consults regarding the safety, quality and efficacy of medicines). Having examined the evidence, the advice of the Commission in January 2012 was that the marketing authorisations for Evotrox 25 microgram/5ml Oral Solution (PL 20249/0004), Evotrox 50 microgram/5ml Oral Solution (PL 20249/0007) and Evotrox 100 microgram/5ml Oral Solution (PL 20249/0005) should be revoked.

## **Background to Licence Revocation**

Evotrox 25 microgram/5ml Oral Solution (PL 20249/0004), Evotrox 50 microgram/5ml Oral Solution (PL 20249/0007) and Evotrox 100 microgram/5ml Oral Solution (PL 20249/0005) were granted marketing authorisations on 03 July 2006 with a 24 month shelf-life when stored below 25°C. At that time, these products represented the sole, licensed, oral liquid presentation of levothyroxine sodium.

Stability data reviewed in April 2012 identified a number of results for assay (content of drug substance) that did not comply with their specified control limits. Concerns were also raised that the manufacturing process was not assured and may not be sufficiently robust.

In light of a lack of assurance of stability performance and process performance, Kappin Limited complied with the MHRA's request to cease to market this product on 28 August 2012. This was accompanied by a pharmacy-level recall.

The licence was revoked by the MHRA on 23 January 2013.

## **REVISION HISTORY**

Issue of UKPAR: Update 02	31 Jan 2014
Issue of UKPAR: Update 01	08 Feb 2013
Initial issue	03 July 2006

## **Annex 1 - UKPAR for initial grant of Marketing Authorisation:**

**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0004)  
EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0007)  
EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0005)**

### **UKPAR**

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**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0004)**  
**EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0007)**  
**EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0005)**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency granted Kappin Limited Marketing Authorisations (licences) for the medicinal products Evotrox 25, 50 and 100 microgram /5ml Oral Solution (PL 20249/0004, 7 & 5) on 3 July 2006. These products are prescription only medicines.

Evotrox 25, 50 and 100 microgram /5ml Oral Solution contains a synthetic version of the naturally-occurring hormone thyroxine, which is made by the thyroid gland. Evotrox Oral Solution is used to treat hypothyroidism, a condition in which the thyroid gland is underactive and does not make enough thyroxine. It is also used to treat some conditions in which the thyroid gland becomes enlarged, causing swelling of the neck. This product has been developed for use in children and in the elderly who cannot swallow tablets and is sugar-free, alcohol-free and colour-free.

Evotrox 25, 50 and 100 microgram /5ml Oral Solution raised no clinically significant safety concerns and it was judged, therefore, that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0004)**  
**EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0007)**  
**EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0005)**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Evotrox 25, 50 and 100 microgram /5ml Oral Solution (PL 20249/0004, 7 & 5) to Kappin Limited on 3 July 2006. These oral solutions have been granted prescription only status.

These applications were submitted as abridged applications according to article 10a of Directive 2001/83/EC and were submitted with a complete bibliography in support of well-established use.

Evotrox Oral Solution contains the active ingredient levothyroxine sodium and is indicated for hypothyroidism (congenital or acquired) and also for diffuse, non toxic goitre or Hashimoto's thyroiditis and thyroid carcinoma.



# **PHARMACEUTICAL ASSESSMENT**

## **1. INTRODUCTION**

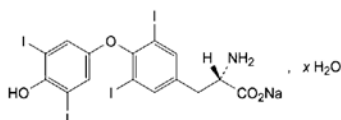
These are abridged standard applications for Marketing Authorisation in the UK submitted under Article 10a of Directive 2001/83 (as amended), as so-called 'bibliographic applications'.

## **2. ACTIVE SUBSTANCE**

### **General information**

The active substance, Levothyroxine sodium, is supplied by a manufacturer that has a Certificate of Suitability (R1-CEP 1998-048) granted 01 February 2004, Revision 01 has been supplied.

Structure:



Description: An almost white or slightly brownish-yellow powder or a fine, crystalline powder.

Molecular formula:  $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$

### **Manufacture**

#### **Manufacturing process**

The manufacturing process is referenced to the certificate of suitability.

#### **Impurities**

Appropriate limits have been applied to impurities.

#### **Control of active substance**

#### **Specification**

The specification used by the finished product manufacturer is that in the European Pharmacopoeia as supplemented by the certificate of suitability.

#### **Analytical test methods**

The test methods used are those described in the European Pharmacopoeia and are supplemented by the certificate of suitability.

## Batch analyses

Analytical data for three production batches demonstrate compliance to the specifications and inter-batch conformity.

## Container closure system

Relevant specifications and certificates of analysis have been provided for the packaging components. Suitable documentation has also been provided to demonstrate compliance of the primary packaging components with the food contact requirements of Directive 2002/72/EC.

## Stability

Stability data for storage under ICH conditions are presented for three validation batches and remained within specifications up to 48 months.

A commitment to put the first three commercial scale batches through stability testing has been provided.

A shelf-life of five years with a re-test period of 2 years is applied by the product manufacturer. This is accepted.

## 3. DRUG PRODUCT

### Composition

The qualitative composition of the products is summarised the following table. The product is a sugar free, colourless solution, packed in 100ml amber glass bottles.

#### Qualitative composition of Levothyroxine 25mcg/5ml, 100mcg/5ml and 50mcg/ml oral solution

Name	Function	Reference
<b>Dose</b>		
Levothyroxine sodium	API	Ph Eur
Citric acid monohydrate	Acidifying agent	Ph Eur
Glycerol	Viscosity	Ph Eur
Sodium methyl parahydroxybenzoate	Preservative	Ph Eur
Purified water	Solvent	Ph Eur

### Pharmaceutical Development

#### Formulation development

The aim was to develop three liquid formulations for use in children and in the elderly who cannot swallow tablets that is sugar-free, alcohol-free and colour-free.

#### Clinical manufacture

Three batches were manufactured for stability trials.

### **Manufacturing development**

A flow chart of the manufacturing process was provided, which is commonly used in the manufacture of oral solutions.

### **Container closure system**

The product will be packed in 100ml amber type III glass medical bottles sealed with 28mm child resistant, tamper evident screw caps. A polyethylene double measuring spoon is also provided.

### **Manufacture**

#### **Manufacturer**

Manufacture, packaging, QC and batch release is carried out at a suitable site.

#### **Batch formula**

A suitable maximum batch size has been set for all strengths.

### **Manufacturing process and process controls**

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A satisfactory written summary of the process has been included.

#### **Control of critical steps (in-process controls)**

The in-process controls cover finished product and manufacturing specifications and are satisfactory.

### **Process validation or evaluation**

Satisfactory validation data presented is on three batches.

The critical steps for validation have been identified and the relevant sampling schedule provided. The limits for the critical steps have been confirmed across the three validation batches.

A maximum overall processing time from initial manufacture to filling and packaging of 72 hours is proposed, which will be validated on the manufacture of the first three full scale batches.

### **Control of excipients**

### **Specification**

Citric acid monohydrate, glycerol, sodium methyl parahydroxybenzoate and purified water are controlled to the Ph. Eur. monographs. Satisfactory certificates of analysis are provided by the suppliers.

The manufacturer declared that there are no excipients of animal or human origin in the product.

## **Control of drug product**

### **Specification**

The finished product specifications are satisfactory, with appropriate tests and limits listed.

### **Analytical procedures**

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods. The assay and identification methods and related substances methods for the active substance are all HPLC methods.

### **Validation**

The HPLC assay for the active ingredient and preservative has been validated satisfactorily for system suitability, precision, linearity and accuracy. Validation data for the microbiological tests have also been provided.

### **Reference standards**

Certificates of analysis on the reference standards for levothyroxine and methyl parahydroxybenzoate are provided by the manufacturer.

### **Batch analyses**

Batch analyses have been provided for three pilot scale batches of the 25mcg/5ml and 100mcg/5ml strengths. These are all within specification and show a reasonable degree of comparability. Satisfactory certificates of analysis have been supplied.

### **Container closure system**

The product will be packed in 100ml amber type III glass medical bottles sealed with 28mm child resistant, tamper evident screw caps. Specifications for the primary packaging components are provided

Confirmation has been provided that the materials used in the assembly of the container closure system conform to the food contact requirements in 2002/72/EC and are controlled to the Ph Eur monograph.

A polyethylene double measuring spoon is also provided which is CE marked. Specifications and a certificate of CE marking are provided. Confirmation is provided

that the polyethylene spoon conforms to the food contact requirements in 2002/72/EC and is controlled to the Ph Eur monograph.

Assurance has been provided that no adsorption of active or preservative occurs on the plastic components of the container closure system. This is accepted.

### **Stability**

Stability tests are carried out for three pilot batches of the 25mcg/5ml and 100mcg/5ml strengths. The storage conditions are 25°C/60%RH (up to 36 months), 30°C/60%RH (up to 12 months) and 40°C/75%RH (up to 6 months). The solutions are packed in 100ml amber type III glass bottle.

Stability is assessed according to the finished product specification.

There are no changes in the product specifications during the storage period of up to 6 months. Based on these data, the applicant is proposing a shelf life of 24 months.

Stability data, stability in-use data and preservative efficacy testing data on commercial batches have been provided to support the proposed shelf-life.

## **4. CONCLUSIONS AND ADVICE**

Marketing authorisations can be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none is required for an application of this type.

# **CLINICAL ASSESSMENT**

## **1. Introduction**

These are national generic applications for UK marketing authorisations and it is not known at present whether they are intended for subsequent mutual recognition by other Member States.

The applicant has submitted the current applications under Article 10a of Directive 2001/83/EC – the so-called bibliographical applications.

The proposed Summary of Product Characteristics is essentially identical to that of one of the index products under assessment and to one of the generic products approved by MHRA in the UK.

## **2. Bibliographic evidence**

The Applicant has provided a Clinical Overview (13 pages) which references 50 citations to justify the claims in the proposed SPC. This includes MHRA Drug Analysis publications on adverse drug reactions to thyroxine and review articles on safety and efficacy.

## **3. Assessment**

The following is a comparison of the Summaries of Product Characteristics of the index generic products under assessment and the Summary of Product Characteristics of a generic product approved by MHRA in the UK. This latter SPC was approved in October 2001 and revised in June 2004:

### **3.1. Therapeutic indications**

Identical.

### **3.2. Posology and method of administration**

Identical.

### **3.3. Contraindications**

Identical.

### **3.4. Special warnings and precautions for use**

Identical.

### 3.5. Interactions with other medicinal products and other forms of interaction

Identical.

### 3.6. Pregnancy and lactation

Identical.

### 3.7. Effects on ability to drive and use machines

Identical.

### 3.8. Undesirable effects

Identical.

### 3.9. Overdose

Identical.

### 3.10. Pharmacodynamic properties

Identical.

### 3.11 Pharmacokinetic properties

Identical.

## **4. Bioequivalence Study**

The Applicant has not provided a bioequivalence study.

The issue of bioequivalence of various thyroxine preparations has been addressed in a number of published studies. A number of these studies have included thyroxine solutions and the consensus is that there are no bioavailability/bioequivalence problems associated with solutions.

Dong et al (1997) compared relative bioavailability of Synthroid, Levoxine, and two generic levothyroxine sodium preparations and found that there were no significant differences between the four products in terms of area under the curve or peak serum concentrations of total thyroxine, total triiodothyronine, or free thyroxine index. Although Synthroid produced a more rapid rise in total serum, triiodothyronine concentration and a higher total peak serum triiodothyronine concentration than the other products, these differences were not statistically significant ( $p = 0.08$ ). They concluded that the 4 generic and brand-name levothyroxine preparations studied were different but were bioequivalent by current criteria and were interchangeable in the majority of patients receiving thyroxine replacement therapy.

Koytchev and Lauschner (2004) evaluated the bioequivalence of three levothyroxine sodium formulations, i.e. a test and a reference tablet and an oral solution. No



significant differences were found of principal pharmacokinetic parameters between the studied formulations. The 90%-confidence interval for the primary target parameters, intra-individual ratios of AUC<sub>0-24</sub> and C<sub>max</sub> of levothyroxine were within the acceptance ranges for bioequivalence trials, i.e. AUC<sub>0-24</sub> 0.954-1.016 and 0.966-1.011 as well as C<sub>max</sub> 0.948-1.027 and 0.968-1.032 for test tablets versus reference tablets and the oral solution, respectively. Similar results were observed for triiodothyronine. It was concluded that the levothyroxine test tablet is bioequivalent to the reference formulation in respect of extent and rate of absorption. The results of this study can also be taken to mean that solutions are bioequivalent to solid formulations

Walter-Sack et al (2004) conducted an assessment of relative bioavailability of levothyroxine sodium from eight solid preparations, compared with a liquid formulation and reported equivalence of the tablets to the drinking solution

Grussendorf et al (2004) investigated therapeutic equivalence of L-thyroxine tablets and a new liquid solution in patients with hypothyroidism. Tablets and liquid solution were shown to be therapeutically equivalent. The use of liquid solutions was concluded to have advantages in the treatment of hypothyroid infants or elderly patients with disturbed swallowing, patients who need a differentiated titration of the dose as well as patients with an allergy against the inactive ingredients of L-thyroxine tablets.

The three excipients in the index products under assessment are glycerol, citric acid monohydrate and sodium methyl parahydroxybenzoate. There are no reports of any interaction between L-thyroxine and any of these excipients, which may interfere with the absorption of L-thyroxine.

Section 5.1.2 of the CPMP guideline on bioequivalence studies provides for exemption for oral solutions.

The products under assessment also meet the criteria for exemption from in vivo bioequivalence studies as described in section 5.1.1 of the above guideline.

Therefore, it is concluded by the assessor that there is no need for a bioequivalence study.

## **5. Patient Information Leaflet**

This is satisfactory and in compliance of the Directive 2001/83/EEC, as amended.

## **6. Recommendations**

There are no issues of clinical concern and the recommendation is to grant marketing authorisations for these preparations.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Evotrox Oral Solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

**EVOTROX 25 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0004)**  
**EVOTROX 50 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0007)**  
**EVOTROX 100 MICROGRAM /5ML ORAL SOLUTION (PL 20249/0005)**

**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 19 August 2005.
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 6 February 2006
3	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 18 May 2006
6	The application was determined on 3 July 2006

## **SUMMARY OF PRODUCT CHARACTERISTICS**

**Evotrox 25 microgram /5ml Oral Solution (PL 20249/0004) has the following product summary:**

### **1 NAME OF THE MEDICINAL PRODUCT**

Evotrox 25microgram /5ml Oral Solution

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 5ml contains Levothyroxine sodium 25micrograms

For full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Oral Solution

Clear solution

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Evotrox Oral Solution is indicated for:

- i) hypothyroidism (congenital or acquired)
- ii) diffuse non toxic goitre or Hashimoto's thyroiditis
- iii) thyroid carcinoma

#### **4.2 Posology and method of administration**

The treatment of any thyroid disorder should be determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring. A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. If too rapid an increase of metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

Levothyroxine is best taken as a single dose on an empty stomach, usually before breakfast.

Adults, children over 12 years

Initial dose:	50 - 100 micrograms daily before breakfast.
Usual maintenance dose:	100 - 200 micrograms daily.

The initial dose is adjusted by 25 to 50 microgram increments at 3 – 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose established.

Elderly patients (over 50 years of age), or those with cardiac insufficiency or in those with severe hypothyroidism

Initial dose:	25 micrograms daily before breakfast.
Usual maintenance dose:	50 to 200 micrograms daily.

The initial dose is adjusted by 25 microgram increments at 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose is established.

Children under 12 years

The initial dose for children up to 1 month is 5-10 micrograms/kg daily, and for children over 1 month is 5 micrograms/kg daily. This dose should be adjusted in steps of 25 micrograms every 2-4 weeks until mild toxic symptoms appear then the dose should be reduce slightly.

### **4.3 Contraindications**

Thyrotoxicosis, hypersensitivity to any component. In patients with adrenal insufficiency without adequate corticosteroid cover.

### **4.4 Special warnings and precautions for use**

Thyroid treatments should be used with caution in patients with cardiovascular disorders, including myocardial insufficiency and hypertension.

Thyroid replacement therapy should be introduced gradually in elderly patients, and those with severe long standing hypothyroidism.

Special care is needed when there are symptoms of myocardial insufficiency or ECG evidence of myocardial infarction and for similar reasons the treatment of hypothyroidism in the elderly should be initiated cautiously.

Patients with adrenal insufficiency 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 or digitalised patients.

Sub-clinical 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 re-growth usually occurs.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

- The effects of warfarin, dicoumarol, acenocoumarol, phenindione and probably other anticoagulants are increased by the concurrent use of thyroid compounds.
- The antidepressant response to imipramine, amitriptyline and possibly other tricyclic antidepressants can be accelerated by the concurrent use of levothyroxine.
- 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.
- The concurrent use of carbamazepine, phenytoin, phenobarbital, primadone or rifampicin with levothyroxine have been found to increase levothyroxine metabolism.
- 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 digoxin may require adjustment, hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds, because initially patients are relatively sensitive to digoxin.
- 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 thyroxine-binding globulins.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.

#### **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 mask 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**

The following side effects are usually due to excessive dosage, and correspond to symptoms of hyperthyroidism:

- arrhythmias, anginal pain, tachycardia, cramps in skeletal muscles, headache, restlessness, excitability, flushing, sweating, diarrhoea, excessive weight loss and muscular weakness, insomnia, tremor, fever, vomiting, palpitations and heat intolerance.

These reactions usually disappear after dose reduction or withdrawal of treatment.

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

Thyroid crisis 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 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.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Thyroid hormones  
ATC Code: H03AA01

Thyroxine (T4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T3) in the peripheral tissues. Receptors for T3 are found on cell membranes, mitochondria and cell nuclei. Thyroid hormones are required for normal growth and development of the body, especially the nervous system. They increase the basal metabolic rate of the whole body and have stimulatory effects on the heart, skeletal muscle, liver and kidney.

### **5.2 Pharmacokinetic properties**

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. Levothyroxine is extensively metabolised in the thyroid, liver, kidney and anterior pituitary. Some enterohepatic re-circulation occurs. Part of the levothyroxine is metabolised to triiodothyronine. Levothyroxine is



excreted in the urine and faeces, partly as free drug and partly as conjugates and de-iodinated metabolites.

It has a half life of 7 days but this may be shortened or prolonged depending on the disease condition. Levothyroxine is almost completely bound to plasma protein, mainly thyroxine binding globulin, with approx. 0.03% of levothyroxine unbound. The unbound levothyroxine is converted to triiodothyronine.

There are four main pathways of metabolism:

1) Deiodination to triiodothyronine (active) - T3 or to reverse triiodothyronine (inactive). Further deiodination of T3 leads to the formation of thyroacetic acid.

2) Deamination to the tetrone.

3) Conjugation to the glucuronide or sulphate.

4) Ether bond cleavage to diiodotyrosines.

The most important metabolic pathway is deiodination. Between 30 - 55% of the levothyroxine dose is excreted in the urine and 20 - 40% in the faeces.

### **5.3 Preclinical safety data**

Not applicable since Levothyroxine has been used in clinical practice for many years and its effects in man are well known.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Glycerol  
Citric acid monohydrate  
Sodium methyl parahydroxybenzoate (E219)  
Purified water

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original container.

### **6.5 Nature and contents of containers**

Amber Type III Glass  
Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining  
5 ml polypropylene Spoon

Pack sizes available: 100 ml

#### **6.6 Special precautions for disposal**

No special requirements

### **7 MARKETING AUTHORISATION HOLDER**

Kappin Limited  
Unit 31, Northfields Industrial Estate  
Beresford Avenue  
Wembley, Middlesex  
HA0 1NW

### **8 MARKETING AUTHORISATION NUMBER**

PL 20249/0004

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/07/2006

### **10 DATE OF REVISION OF THE TEXT**

03/07/2006

**Evotrox 50 microgram /5ml Oral Solution (PL 20249/0007) has the following product summary:**

#### **1 NAME OF THE MEDICINAL PRODUCT**

Evotrox 50 micrograms/5ml Oral Solution

#### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 5ml contains Levothyroxine sodium 50 micrograms

For full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Oral Solution

Clear solution

## **4 CLINICAL PARTICULARS**

### **4.2 Therapeutic indications**

Evotrox Oral Solution is indicated for:

- i) Hypothyroidism (congenital or acquired)
- ii) Diffuse non toxic goitre or Hashimoto's thyroiditis
- iii) Thyroid carcinoma

### **4.3 Posology and method of administration**

The treatment of any thyroid disorder should be determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring. A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. If too rapid an increase of metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

Levothyroxine is best taken as a single dose on an empty stomach, usually before breakfast.

#### Adults, children over 12 years

Initial dose:	50 - 100 micrograms daily before breakfast.
Usual maintenance dose:	100 - 200 micrograms daily.

The initial dose is adjusted by 25 to 50 microgram increments at 3 – 4 week intervals until clinical

response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose established.

Elderly patients (over 50 years of age), or those with cardiac insufficiency or in those with severe hypothyroidism

Initial dose:	25 micrograms daily before breakfast.
Usual maintenance dose:	50 to 200 micrograms daily.

The initial dose is adjusted by 25 microgram increments at 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose is established.

Children under 12 years

The initial dose for children up to 1 month is 5-10 micrograms/kg daily, and for children over 1 month is 5 micrograms/kg daily. This dose should be adjusted in steps of 25 micrograms every 2-4 weeks until mild toxic symptoms appear then the dose should be reduce slightly.

### **4.3 Contraindications**

Thyrotoxicosis, hypersensitivity to any component. In patients with adrenal insufficiency without adequate corticosteroid cover.

### **4.4 Special warnings and precautions for use**

Thyroid treatments should be used with caution in patients with cardiovascular disorders, including myocardial insufficiency and hypertension.

Thyroid replacement therapy should be introduced gradually in elderly patients, and those with severe long standing hypothyroidism.

Special care is needed when there are symptoms of myocardial insufficiency or ECG evidence of myocardial infarction and for similar reasons the treatment of hypothyroidism in the elderly should be initiated cautiously.

Patients with adrenal insufficiency 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 or digitalised patients.

Sub-clinical 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 re-growth usually occurs.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

- The effects of warfarin, dicoumarol, acenocoumarol, phenindione and probably other anticoagulants are increased by the concurrent use of thyroid compounds.
- The antidepressant response to imipramine, amitriptyline and possibly other tricyclic antidepressants can be accelerated by the concurrent use of levothyroxine.
- 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.
- The concurrent use of carbamazepine, phenytoin, phenobarbital, primadone or rifampicin with levothyroxine have been found to increase levothyroxine metabolism.
- 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 digoxin may require adjustment, hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds, because initially patients are relatively sensitive to digoxin.
- 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 thyroxine-binding globulins.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.

#### **4.7 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 mask 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**

The following side effects are usually due to excessive dosage, and correspond to symptoms of hyperthyroidism:

- arrhythmias, anginal pain, tachycardia, cramps in skeletal muscles, headache, restlessness, excitability, flushing, sweating, diarrhoea, excessive weight loss and muscular weakness, insomnia, tremor, fever, vomiting, palpitations and heat intolerance.

These reactions usually disappear after dose reduction or withdrawal of treatment.

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

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

### **4.10 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 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Thyroid hormones  
ATC Code: H03AA01

Thyroxine (T4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T3) in the peripheral tissues. Receptors for T3 are found on cell membranes, mitochondria and cell nuclei. Thyroid hormones are required for normal growth and development of the body, especially the nervous system. They increase the basal metabolic rate of the whole body and have stimulatory effects on the heart, skeletal muscle, liver and kidney.

### **5.2 Pharmacokinetic properties**

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. Levothyroxine is extensively metabolised in the thyroid, liver, kidney and anterior pituitary. Some enterohepatic re-circulation occurs. Part of the levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine and faeces, partly as free drug and partly as conjugates and de-iodinated metabolites.

It has a half life of 7 days but this may be shortened or prolonged depending on the disease condition. Levothyroxine is almost completely bound to plasma protein, mainly thyroxine binding globulin, with approx. 0.03% of levothyroxine unbound. The unbound levothyroxine is converted to triiodothyronine.

There are four main pathways of metabolism:

- 1) Deiodination to triiodothyronine (active) - T3 or to reverse triiodothyronine (inactive). Further deiodination of T3 leads to the formation of thyroacetic acid.
- 2) Deamination to the tetrone.
- 3) Conjugation to the glucuronide or sulphate.
- 4) Ether bond cleavage to diiodotyrosines.

The most important metabolic pathway is deiodination. Between 30 - 55% of the levothyroxine dose is excreted in the urine and 20 - 40% in the faeces.

### **5.4 Preclinical safety data**

Not applicable since Levothyroxine has been used in clinical practice for many years and its effects in man are well known.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.2 List of excipients**

Glycerol  
Citric acid monohydrate  
Sodium methyl parahydroxybenzoate (E219)  
Purified water

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original container.

### **6.5 Nature and contents of containers**

Amber Type III Glass  
Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining  
5 ml polypropylene Spoon

Pack sizes available: 100 ml

### **6.6 Special precautions for disposal**

No special requirements

## **7. MARKETING AUTHORISATION HOLDER**

Kappin Limited  
Unit 31, Northfields Industrial Estate  
Beresford Avenue  
Wembley, Middlesex  
HA0 1NW

## **8. MARKETING AUTHORISATION NUMBER**

PL 20249/0007

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**



03/07/2006

## **10 DATE OF REVISION OF THE TEXT**

03/07/2006

**Evotrox 100 microgram /5ml Oral Solution (PL 20249/0005) has the following product summary:**

### **1 NAME OF THE MEDICINAL PRODUCT**

Evotrox 100 micrograms/ 5ml Oral Solution

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 5ml contains Levothyroxine sodium 100 micrograms

For full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Oral Solution

Clear solution

### **4 CLINICAL PARTICULARS**

#### **4.3 Therapeutic indications**

Evotrox Oral Solution is indicated for:

- i) Hypothyroidism (congenital or acquired)
- ii) Diffuse non toxic goitre or Hashimoto's thyroiditis
- iii) Thyroid carcinoma

#### **4.4 Posology and method of administration**

The treatment of any thyroid disorder should be determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring. A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. If too rapid an increase of metabolism is produced (causing diarrhoea, nervousness, rapid

pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

Levothyroxine is best taken as a single dose on an empty stomach, usually before breakfast.

#### Adults, children over 12 years

Initial dose:	50 - 100 micrograms daily before breakfast.
Usual maintenance dose:	100 - 200 micrograms daily.

The initial dose is adjusted by 25 to 50 microgram increments at 3 – 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose established.

Elderly patients (over 50 years of age), or those with cardiac insufficiency or in those with severe hypothyroidism

Initial dose:	25 micrograms daily before breakfast.
Usual maintenance dose:	50 to 200 micrograms daily.

The initial dose is adjusted by 25 microgram increments at 4 week intervals until clinical response and measurements of plasma thyroxine and thyroid stimulating hormone indicate that the thyroid deficiency is corrected and a maintenance dose is established.

#### Children under 12 years

The initial dose for children up to 1 month is 5-10 micrograms/kg daily, and for children over 1 month is 5 micrograms/kg daily. This dose should be adjusted in steps of 25 micrograms every 2-4 weeks until mild toxic symptoms appear then the dose should be reduce slightly.

### **4.3 Contraindications**

Thyrotoxicosis, hypersensitivity to any component. In patients with adrenal insufficiency without adequate corticosteroid cover.

#### **4.4 Special warnings and precautions for use**

Thyroid treatments should be used with caution in patients with cardiovascular disorders, including myocardial insufficiency and hypertension.

Thyroid replacement therapy should be introduced gradually in elderly patients, and those with severe long standing hypothyroidism.

Special care is needed when there are symptoms of myocardial insufficiency or ECG evidence of myocardial infarction and for similar reasons the treatment of hypothyroidism in the elderly should be initiated cautiously.

Patients with adrenal insufficiency 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 or digitalised patients.

Sub-clinical 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 re-growth usually occurs.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

- The effects of warfarin, dicoumarol, acenocoumarol, phenindione and probably other anticoagulants are increased by the concurrent use of thyroid compounds.
- The antidepressant response to imipramine, amitriptyline and possibly other tricyclic antidepressants can be accelerated by the concurrent use of levothyroxine.
- 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.
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- If levothyroxine therapy is initiated in digitalised patients, the dose of digoxin may require adjustment, hyperthyroid patients may need their digoxin dosage gradually increased as treatment proceeds, because initially patients are relatively sensitive to digoxin.

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- 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 thyroxine-binding globulins.
- Amiodarone may reduce the effects of thyroid hormones used in the treatment of hypothyroidism.

## **4.8 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 mask 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.

## **4.9 Undesirable effects**

The following side effects are usually due to excessive dosage, and correspond to symptoms of hyperthyroidism:

- arrhythmias, anginal pain, tachycardia, cramps in skeletal muscles, headache, restlessness, excitability, flushing, sweating, diarrhoea, excessive weight loss and muscular weakness, insomnia, tremor, fever, vomiting, palpitations and heat intolerance.

These reactions usually disappear after dose reduction or withdrawal of treatment.

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

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

#### **4.11 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 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Thyroid hormones  
ATC Code: H03AA01

Thyroxine (T4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T3) in the peripheral tissues. Receptors for T3 are found on cell membranes, mitochondria and cell nuclei. Thyroid hormones are required for normal growth and development of the body, especially the nervous system. They increase the basal metabolic rate of the whole body and have stimulatory effects on the heart, skeletal muscle, liver and kidney.

#### **5.2 Pharmacokinetic properties**

Levothyroxine sodium is incompletely and variably absorbed from the gastrointestinal tract. Levothyroxine is extensively metabolised in the thyroid, liver, kidney and anterior pituitary. Some enterohepatic re-circulation occurs. Part of the levothyroxine is metabolised to triiodothyronine. Levothyroxine is excreted in the urine and faeces, partly as free drug and partly as conjugates and de-iodinated metabolites.

It has a half life of 7 days but this may be shortened or prolonged depending on the disease condition. Levothyroxine is almost completely bound to plasma protein, mainly thyroxine binding globulin, with approx. 0.03% of levothyroxine unbound. The unbound levothyroxine is converted to triiodothyronine.

There are four main pathways of metabolism:

1) Deiodination to triiodothyronine (active) - T3 or to reverse triiodothyronine (inactive). Further deiodination of T3 leads to the formation of thyroacetic acid.

2) Deamination to the tetrone.

3) Conjugation to the glucuronide or sulphate.

4) Ether bond cleavage to diiodotyrosines.

The most important metabolic pathway is deiodination. Between 30 - 55% of the levothyroxine dose is excreted in the urine and 20 - 40% in the faeces.

## **5.5 Preclinical safety data**

Not applicable since Levothyroxine has been used in clinical practice for many years and its effects in man are well known.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.3 List of excipients**

Glycerol

Citric acid monohydrate

Sodium methyl parahydroxybenzoate (E219)

Purified water

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original container.

### **6.5 Nature and contents of containers**

Amber Type III Glass

Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining

5 ml polypropylene Spoon

Pack sizes available: 100 ml

**6.7 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Kappin Limited  
Unit 31, Northfields Industrial Estate  
Beresford Avenue  
Wembley, Middlesex  
HA0 1NW

**8 MARKETING AUTHORISATION NUMBER**

PL 20249/0005

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/07/2006

**10 DATE OF REVISION OF THE TEXT**

03/07/2006

## **Patient Information Leaflet**

### **Evotrox Oral Solution**

3077/1

This leaflet contains important information about Evotrox Oral Solution. Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you have any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **1. What Evotrox Oral Solution is and what it is used for**

Evotrox Oral Solution is used to treat hypothyroidism, a condition in which the thyroid gland is underactive and so does not make enough thyroxine for the body's needs.

Evotrox Oral Solution is also used to treat thyroid cancer and diffuse non-toxic goitre or Hashimoto's thyroiditis, conditions in which the thyroid gland becomes enlarged causing a swelling in the front of the neck.

#### **2. Before you take Evotrox Oral Solution**

Please tell your doctor before you start to take your medicine if you:

- have ever had a bad reaction to any of the ingredients listed in the 'What Evotrox Oral Solution is and what it is used for' section
- have heart disease, problems with your circulation or high blood pressure
- are suffering from an overactive thyroid gland (hyperthyroidism), an underactive adrenal gland, diabetes, or have had an underactive thyroid gland for sometime

##### *Pregnancy and Breast-feeding*

Are you pregnant or are you breast feeding a baby? If so, tell your doctor.

##### *Driving and using machines*

- Your medicine is unlikely to affect your ability to drive or to operate machinery.

##### *Important information about some of the ingredients of Evotrox Oral Solution*

- Sodium methyl parahydroxybenzoate (E219): May cause allergic reactions (possibly delayed).

##### *Taking other medicines*

Are you taking any other medicines? If so, tell your doctor.

Levothyroxine can interfere with the action of some other drugs and some drugs can have an effect on Levothyroxine. Tell your doctor or pharmacist if you take the following drugs:

- medication to stop your blood clotting (for example Warfarin)
- medication for depression (for example Imipramine, Amitriptyline)
- medication for epilepsy (for example Phenytoin, Phenobarbital, Carbamazepine) or
- medication for diabetes

- Rifampicin (for infections, particularly tuberculosis),
- Digoxin or Amiodarone (for your heart),
- Propranolol (for high blood pressure), Lovastatin (for high cholesterol levels) or Phenylbutazone or Aspirin (anti-inflammatory drugs)
- oestrogen, oestrogen containing products and oral contraceptives, androgens or corticosteroids
- other medicines including ones that you have bought for yourself without a prescription

If you are taking:

- sucralfate, Cimetidine or aluminium hydroxide for a stomach ulcer or
- Colestyramine to lower your cholesterol levels, or calcium carbonate or iron supplements.

Let your doctor or pharmacist know. Evotrox Oral Solution can be taken with these medicines but not at the same time.

If you go into hospital to have an operation, tell the anaesthetist or the medical staff that you are taking Evotrox Oral Solution. It may react with an anaesthetic (Ketamine) which you may be given before an operation.

#### **3. How to take Evotrox Oral Solution**

Evotrox Oral Solution should be swallowed. Follow your doctor's instructions about when and how to take your medicine. Also read the label. Your pharmacist can also help if you are not sure.

Your doctor will have decided what dose you should take each day depending on your condition. Your doctor will take blood samples at regular intervals to monitor your response to treatment.

The usual daily dosages are:

##### *Adults and children over 12 years:*

The starting dose is 50 to 100 micrograms (mcg) a day, increasing by 25 to 50 mcg every 3-4 weeks, until you are taking the right amount for your condition. The usual maintenance dose is 100 to 200 mcg daily.

##### *Older patients (over 50 years of age):*

The starting dose is 25 mcg a day, increasing by 25 mcg every 4 weeks until the correct dose is obtained. The usual final dose is between 50 and 200 mcg daily. This dose also applies to patients with severe hypothyroidism, and to those with heart disease.



#### Children under 12 years:

The dose for children depends on their age or weight. They will be monitored to make sure they get the right dose. The following is a guide:

Age	mcg per kg bodyweight
Up to 1 month	5-10 micrograms
Over 1 month	5 micrograms

You should take your Evotrox Oral Solution on an empty stomach, usually before breakfast.

#### *If you take more Evotrox Oral Solution than you should*

If you accidentally take an overdose of your medicine, either call your doctor straight away, or go to your nearest hospital casualty department. Always take any remaining medicine, the container and the label with you, so that the medicine can be identified.

#### *If you forget to take Evotrox Oral Solution*

If you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Don't take two doses at the same time. If you have forgotten several doses tell your doctor when you have your next check-up or blood test. It can be dangerous to stop taking your tablets without your doctor's advice. If you are worried, ask your doctor or pharmacist for advice.

#### 4. Possible side effects

Like all medicines, Evotrox Oral Solution can have side effects. These usually only happen if the dose you are taking is too high.

If any of the following happen, stop taking Evotrox Oral Solution and tell your doctor immediately or go to the casualty department at your nearest hospital

- Swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing
- Hives
- Fainting
- Yellowing of the skin and eyes also called jaundice

These are all very serious side effects. If you have them, you may have a serious allergic reaction to Evotrox Oral Solution. You may need urgent medical attention or hospitalisation. All of these very serious side effects are very rare.

Tell your doctor if you notice any of the following:

Fast or irregular heart beats, palpitations, chest pain, muscle cramps or weakness, headache, restlessness, excitability, flushing, sweating, diarrhoea, vomiting, fever, tremor, sleeplessness, heat intolerance and excessive weight loss. Rash, itching and puffiness may also occur.

Very rarely, if far too much Evotrox Oral Solution has been taken in one go or over many years, the heart may fail and coma and death have been reported.

If you feel unwell in any other way, tell your doctor as soon as you can.

Children may have some hair loss at the beginning of treatment, however this is usually temporary and the hair returns.

Do not be alarmed by this list of possible events. You may not have any of them.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

#### 5. Storing Evotrox Oral Solution

As with all medicines, it is important to keep Evotrox Oral Solution out of the reach and sight of children.

Do not store above 25°C. Store in the original container.

Do not use Evotrox Oral Solution after the expiry date printed on the carton or the bottle.

Do not keep outdated medicine or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.

Always keep the medicine in the bottle in which it was originally given to you.

You may wish to read the leaflet again. Do not throw it away until you have finished your medicine.

#### 6. Further Information

Evotrox Oral Solution is a clear colourless solution.

Each 5 ml of Evotrox Oral Solution contains Levothyroxine sodium Ph.Eur. equivalent to Levothyroxine sodium anhydrous 25 micrograms (mcg)(PL 20249/0004), 50 mcg(PL 20249/0007) or 100 mcg(PL 20249/0005) (active ingredient).

It also contains the following inactive ingredients: Glycerol, citric acid monohydrate, sodium methyl parahydroxybenzoate (E219) and purified water.

Each bottle contains 100ml of oral solution. A double ended 5ml and 2.5ml polypropylene spoon is also included to help measure the dose.

The Marketing Authorisations for Evotrox Oral Solution are held by Kappin Ltd., Northfield Industrial Estate, Middlesex HA0 1NW. Evotrox Oral Solution is manufactured and distributed by Orbis Consumer Products Ltd Northfield Industrial Estate, Middlesex HA0 1NW

#### REMEMBER

This medicine is for you. Only a doctor can prescribe it for you. Never give it to anybody else, even if their symptoms are the same as yours.

This leaflet does not tell you all about your medicine. If you have any questions or are not sure about anything then ask your doctor or pharmacist.

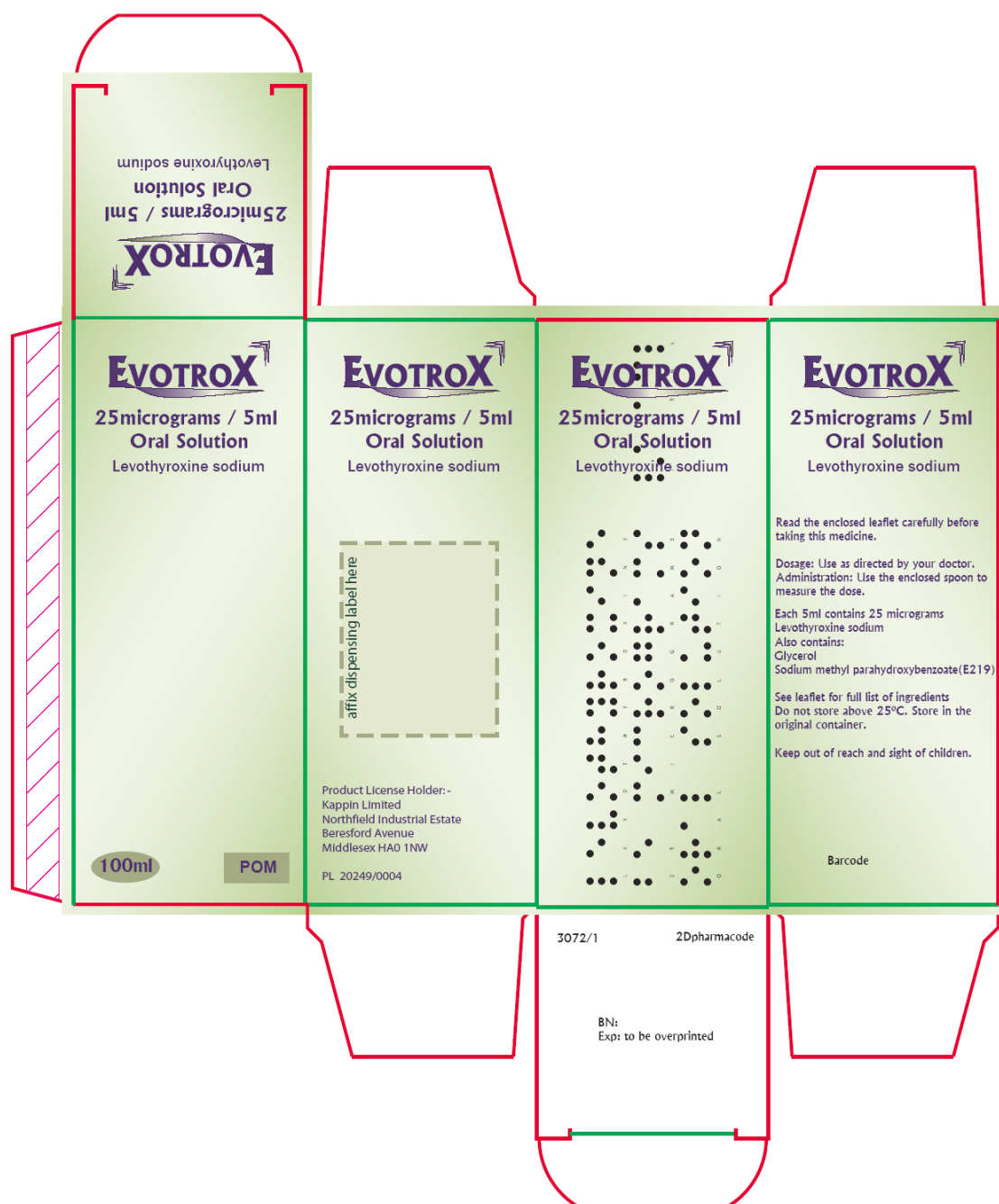
The information in this leaflet only applies to Evotrox Oral Solution.


This leaflet was prepared in April 2006

3077/1

## Packaging

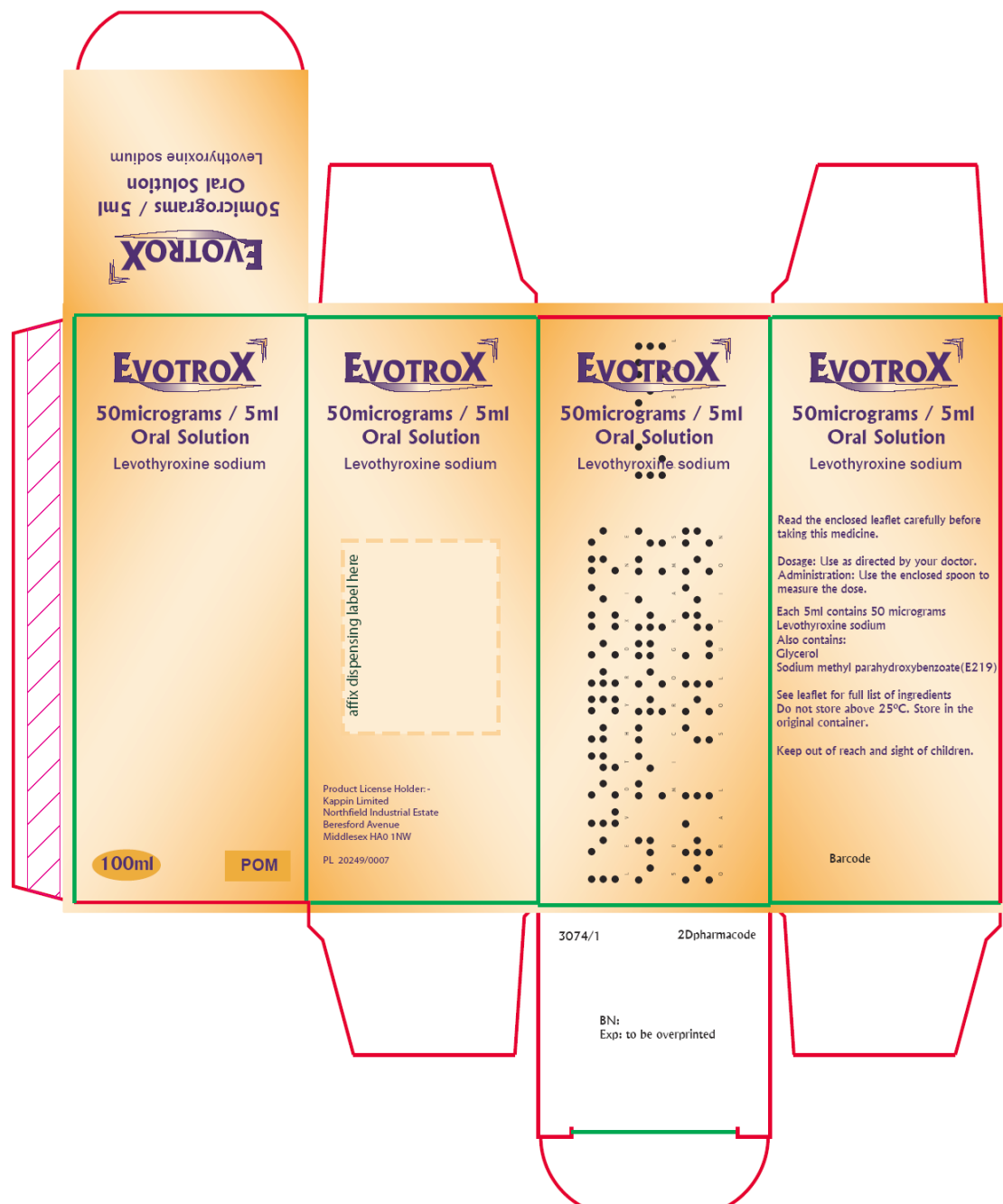
**Evotrox 25 microgram /5ml Oral Solution (PL 20249/0004) has the following packaging:**



<p>Each 5ml contains 25 micrograms of levothyroxine sodium</p> <p>Also contains: Glycerol Sodium methyl parahydroxybenzoate (E219) See leaflet for full list of ingredients</p> <p>Product License Holder:- Kappin Limited Northfield Industrial Estate Beresford Avenue Middlesex HA0 1NW</p> <p>PL 20249/0004</p>	 <p><b>EVOTROX</b></p> <p><b>25micrograms/5ml</b> <b>Oral Solution</b></p> <p>Levothyroxine sodium</p> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="border: 1px solid black; padding: 2px 5px;">POM</div> <div style="border: 1px solid black; border-radius: 15px; padding: 2px 10px;">100ml e</div> </div>	<p>Read the enclosed leaflet carefully before taking this medicine.</p> <p>Dosage: Use as directed by your doctor.</p> <p>Administration: Use the enclosed spoon to measure the dose.</p> <p>Do not store above 25°C. Store in the original container.</p> <p>Keep out of reach and sight of children.</p>
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3071/1

**Evotrox 100 microgram /5ml Oral Solution (PL 20249/0007) has the following packaging:**



Each 5ml contains 50 micrograms of  
levothyroxine sodium

Also contains:

Glycerol

Sodium methyl parahydroxybenzoate(E219)

See leaflet for full list of ingredients

Product License Holder:-  
Kappin Limited  
Northfield Industrial Estate  
Beresford Avenue  
Middlesex HA0 1NW

PL 20249/0007

**EVOTROX**

**50micrograms/5ml  
Oral Solution**

Levothyroxine sodium

POM

100ml €

Read the enclosed leaflet carefully before  
taking this medicine.

Dosage: Use as directed by your doctor.

Administration: Use the enclosed spoon  
to measure the dose.

Do not store above 25°C. Store in the  
original container.

Keep out of reach and sight of children.

3073/1

**Evotrox 100 microgram /5ml Oral Solution (PL 20249/0005) has the following packaging:**



<p>Each 5ml contains 100 micrograms of levothyroxine sodium</p> <p>Also contains: Glycerol Sodium methyl parahydroxybenzoate(E219)</p> <p>See leaflet for full list of ingredients</p> <p>Product License Holder:- Kappin Limited Northfield Industrial Estate Beresford Avenue Middlesex HA0 1NW</p> <p>PL 20249/0005</p>	<p><b>EVOTROX</b></p> <p><b>100micrograms/5ml</b> <b>Oral Solution</b> Levothyroxine sodium</p> <p>POM</p> <p>100ml e</p>	<p>Read the enclosed leaflet carefully before taking this medicine. Dosage: Use as directed by your doctor. Administration: Use the enclosed spoon to measure the dose.</p> <p>Do not store above 25°C. Store in the original container. Keep out of reach and sight of children.</p>
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