Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

LEVOTHYROXINE 12.5 MICROGRAM TABLETS
LEVOTHYROXINE 25 MICROGRAM TABLETS
LEVOTHYROXINE 75 MICROGRAM TABLETS
(levothyroxine sodium)

UK Licence No: PL 00289/1971-73

TEVA UK Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Levothyroxine 12.5 microgram Tablets
Levothyroxine 25 microgram Tablets
Levothyroxine 75 microgram Tablets
(levothyroxine sodium)

This is a summary of the Public Assessment Report (PAR) for Levothyroxine 12.5 microgram Tablets, Levothyroxine 25 microgram Tablets and Levothyroxine 75 microgram Tablets (PL 00289/1971-73). It explains how the applications for these products were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Levothyroxine 12.5, 25 and 75 microgram Tablets.

For practical information about using Levothyroxine 12.5, 25 and 75 microgram Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Levothyroxine 12.5, 25 and 75 microgram Tablets and what are they used for?
The applications for Levothyroxine 12.5 and 75 microgram Tablets were submitted as hybrid applications. This means that Levothyroxine 12.5 and 75 microgram Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Eltroxin 100 microgram Tablets (PL 10972/0032).

Levothyroxine 25 microgram Tablets are a 'generic medicine'. This means that Levothyroxine 25 microgram Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Eltroxin 25 microgram Tablets (PL 12762/0016).

These medicines are used to treat hypothyroidism (an under-active thyroid gland).

How do Levothyroxine 12.5, 25 and 75 microgram Tablets work?
These medicines contain the active substance levothyroxine sodium. Thyroxine is a hormone which is produced naturally in the body by the thyroid gland. Levothyroxine sodium is a synthetic version of this hormone.

Thyroxine controls how much energy your body uses. When the thyroid gland does not produce enough thyroxine (in a condition known as hypothyroidism) many of the body's functions slow down. Some of the most common symptoms of hypothyroidism are tiredness, weight gain and feeling depressed.

Levothyroxine 12.5, 25 and 75 microgram Tablets are used to replace the thyroxine that the thyroid gland cannot produce and prevent the symptoms of hypothyroidism.

How are Levothyroxine 12.5, 25 and 75 microgram Tablets used?
The tablets should be swallowed, with a drink of water, in the morning at least 30 minutes and preferably one hour before breakfast.

In adults up to 50 years old, the usual starting dose is 50 to 100 micrograms daily. A doctor may gradually increase the dose by 50 micrograms every three to four weeks until thyroid deficiency is corrected, usually at a dosage of 100 - 200 micrograms daily.

In adults over 50 years old the starting dose should be no more than 50 micrograms per day.
In patients with heart disease, the starting dose should be no more than 25 micrograms per day or 50 micrograms on alternate days. A doctor may gradually increase the dose by 25 micrograms every four weeks until thyroid deficiency is corrected.

The dose for children depends on their age, weight and the condition being treated. The child will be

monitored to make sure he/she gets the right dose. The child should be given this medicine at least half an hour before the first meal of the day.

For the treatment of congenital hypothyroidism in infants, the initial dose should be 10 to 15 micrograms/kg body weight a day for the first 3 months. The dose will then be adjusted depending on response to treatment.

For the treatment of acquired hypothyroidism in children, the initial dose should be 12.5 to 50 micrograms a day. The dose should be increased gradually every 2 to 4 weeks depending on response to treatment.

For the treatment of juvenile myxoedema, the initial recommended dose is 25 micrograms daily. The daily dose may be increased by 25 micrograms every 2 - 4 weeks, until mild symptoms of hyperthyroidism (a condition where the thyroid gland produces too much thyroxine) are seen. The dose will then be reduced slightly.

In children under 5 years of age, the administration of whole tablets is not recommended. Therefore, for young children, the doctor is likely to prescribe a levothyroxine product in a liquid formulation.

These medicines can only be obtained with a prescription.

What benefits of Levothyroxine 12.5, 25 and 75 microgram Tablets have been shown in studies?
Studies in patients have been conducted to determine that a higher strength of the product, Levothyroxine 100 microgram Tablets, is bioequivalent to the reference medicine, Eltroxin 100 microgram Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

A further study in patients (a dosage form proportionality study) assessed the levels of the active substance found in the body when Levothyroxine 25 microgram Tablets and Levothyroxine 100 microgram Tablets were given as a single 600 microgram dose. This study concluded that a 600 microgram dose of Levothyroxine 25 microgram Tablets is bioequivalent to a 600 microgram dose of Levothyroxine 100 microgram Tablets. As Levothyroxine 100 microgram Tablets have demonstrated bioequivalence to Eltroxin 100 microgram Tablets (Mercury Pharma Limited) it was deduced from these studies that Levothyroxine 25 microgram Tablets can be considered bioequivalent to Eltroxin 25 microgram Tablets.

The Marketing Authorisation Holder has also presented pharmaceutical data to demonstrate similarity and similar dissolution between five different strengths of levothyroxine tablets (12.5, 25, 50, 75 and 100 micrograms). From these data it was deduced that Levothyroxine 12.5 microgram Tablets and Levothyroxine 75 microgram Tablets can also be considered bioequivalent to equivalent strengths of the reference product and that clinical studies on these strengths were not required.

Because Levothyroxine 12.5, 25 and 75 microgram Tablets are considered to be equivalent to the reference medicines, Eltroxin 100 microgram Tablets and Eltroxin 25 microgram Tablets, their benefits and risks are taken as being the same as those of the reference medicines.

What are the possible side effects of Levothyroxine 12.5, 25 and 75 microgram Tablets?
Like all medicines, Levothyroxine 12.5, 25 and 75 microgram Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Levothyroxine 12.5, 25 and 75 microgram Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why were Levothyroxine 12.5, 25 and 75 microgram Tablets approved?
It was concluded that, in accordance with EU requirements, Levothyroxine 12.5, 25 and 75 microgram Tablets have been shown to have comparable quality and to be bioequivalent to Eltroxin 100 microgram Tablets and Eltroxin 25 microgram Tablets. Therefore, the MHRA decided that, as for Eltroxin 100 microgram Tablets and Eltroxin 25 microgram Tablets, the benefits outweigh the identified risks and recommended that Levothyroxine 12.5, 25 and 75 microgram Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Levothyroxine 12.5, 25 and 75 microgram Tablets?
A risk management plan (RMP) has been developed to ensure that Levothyroxine 12.5, 25 and 75 microgram Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Levothyroxine 12.5, 25 and 75 microgram Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Levothyroxine 12.5, 25 and 75 microgram Tablets
Marketing Authorisations were granted in the UK on 15 September 2016.

The full public assessment report (PAR) for Levothyroxine 12.5, 25 and 75 microgram Tablets follows this summary. For more information about treatment with Levothyroxine 12.5, 25 and 75 microgram Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited Marketing Authorisations for the medicinal products Levothyroxine 12.5, 25 & 75 microgram Tablets (PL 00289/1971-73) on 15 September 2016.

These products are prescription-only medicines (legal classification POM).

The applications for Levothyroxine 12.5 and 75 microgram Tablets were made under the National Procedure, according to Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference product is Eltroxin 100 microgram Tablets (PL 10972/0032), which was granted a Marketing Authorisation to Mercury Pharma Group Limited, in the UK, on 09 November 1993.

The application for Levothyroxine 25 microgram Tablets were made under the National Procedure and submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Eltroxin 25 microgram Tablets (PL 12762/0016), which was granted a Marketing Authorisation to Mercury Pharma Group Limited, in the UK, on 17 November 1999.

These applications are line extensions of the applicant's Levothyroxine 50 microgram and 100 microgram Tablets (PL 00289/0038-39). The rationale for the line extension to introduce these three new strengths is to aid adjustment of the daily dose of levothyroxine, without recourse to splitting tablets or giving different doses on alternate days.

Levothyroxine 12.5, 25 & 75 microgram Tablets are indicated for the control of hypothyroidism, congenital hypothyroidism in infants, acquired hypothyroidism in children and juvenile myxoedema.

These products contain the active substance levothyroxine sodium, which is a synthetic form of thyroid hormone. 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.

With the exception of the bioequivalence study and the dosage form proportionality study, no new clinical or non-clinical studies were conducted, which is acceptable given these are hybrid and generic applications cross-referring to originator products that have been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of a higher strength of the test product, Levothyroxine 100 microgram Tablets to those of the reference product, Eltroxin 100 microgram Tablets (PL 10972/0032; Mercury Pharma Limited).

A further study was performed to evaluate the dosage form proportionality of three different strengths of Levothyroxine Tablets (25 micrograms, 50 micrograms, and 100 micrograms) administered as a single oral dose of 600 micrograms. A biowaiver was requested for the 12.5 and 75 microgram strengths.

The studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory

During assessment of these applications, advice was sought from the Expert advisory Groups (EAGs) on the adequacy of the pharmaceutical development and on the acceptability of the comparative dissolution

data to support the biowaiver for the 12.5 and 75 microgram strengths. The applications were presented to the Expert Advisory Groups, including the Commission on Human Medicines (CHM). The advisory groups considered the evidence and the arguments presented by the applicant and advised the MHRA.

Further data were subsequently submitted by the applicant and these data were also considered by the Expert Advisory Groups. At the CHM Meeting in February 2016 the applications were considered to have satisfied the necessary requirements and therefore could be approved.

II QUALITY ASPECTS

II.1 Introduction

Each Levothyroxine 12.5 microgram Tablet contains 12.5 micrograms of the active substance levothyroxine sodium. The tablets are white, round and biconvex, with 12.5 marked on one side.

Each Levothyroxine 25 microgram Tablet contains 25 micrograms of the active substance levothyroxine sodium. The tablets are white, round and biconvex, with a break line on one side and 25 marked on the other side.

Each Levothyroxine 75 microgram Tablet contains 75 micrograms of the active substance levothyroxine sodium. The tablets are white, round and biconvex, with a break line on one side and 75 marked on the other side.

Other ingredients consist of the pharmaceutical excipients, namely maize starch, mannitol (E421), microcrystalline cellulose, sodium citrate, acacia and magnesium stearate

The finished product is packaged in polyvinyl chloride/polyethylene/polyvinylidene chloride/aluminium blisters in packs of 28, 56 and 112 tablets. Not all pack sizes may be marketed.

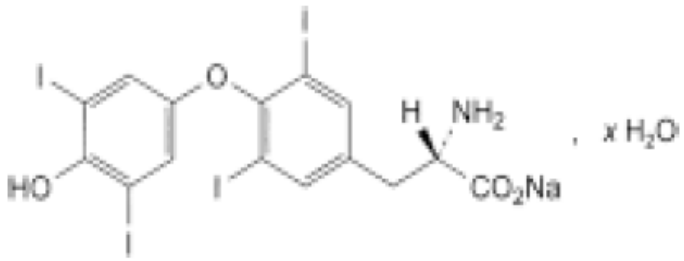
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Levothyroxine sodium

Chemical name(s): Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate

Structure:



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

Molecular weight: 799 (anhydrous)

Appearance: Almost white or slightly brownish-yellow, fine crystalline powder

Solubility: Very slightly soluble in water and slightly soluble in 96 % ethanol. Soluble in dilute solutions of alkali hydroxides.

All aspects of the manufacture and control of the active substance levothyroxine sodium from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. Particle size is also tested in line with additional in-house parameters. Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specifications.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a robust, stable formulation, comparable in performance to the reference products Eltroxin 100 microgram Tablets (PL 10972/0032; Mercury Pharma Group Limited) and Eltroxin 25 microgram Tablets (PL 12762/0016; Mercury Pharma Group Limited). Additionally, the objective was to design an appropriate formulation and manufacturing process that would deliver products of the specified quality in a reproducible manner.

A satisfactory account of the pharmaceutical development has been provided.

Comparative dissolution data and impurity profiles have been presented for the test and reference products.

In support of the biowaiver for the conduct of a dosage form proportionality study to investigate the 12.5 microgram and 75 microgram strengths, comparative dissolution profiles for levothyroxine 12.5, 25, 50, 75 and 100 microgram tablets have been provided.

All the excipients comply with their respective European Pharmacopoeia (Ph. Eur.) monographs. Sodium citrate, acacia, cellulose microcrystalline and magnesium stearate are also tested in line with additional in-house parameters.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on commercial scale batches of each strength of finished product. The results are satisfactory.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 18 months with the special storage conditions of "Do not store above 25°C" and "Store in the original package".

II.4 Discussion on chemical, pharmaceutical and biological aspects

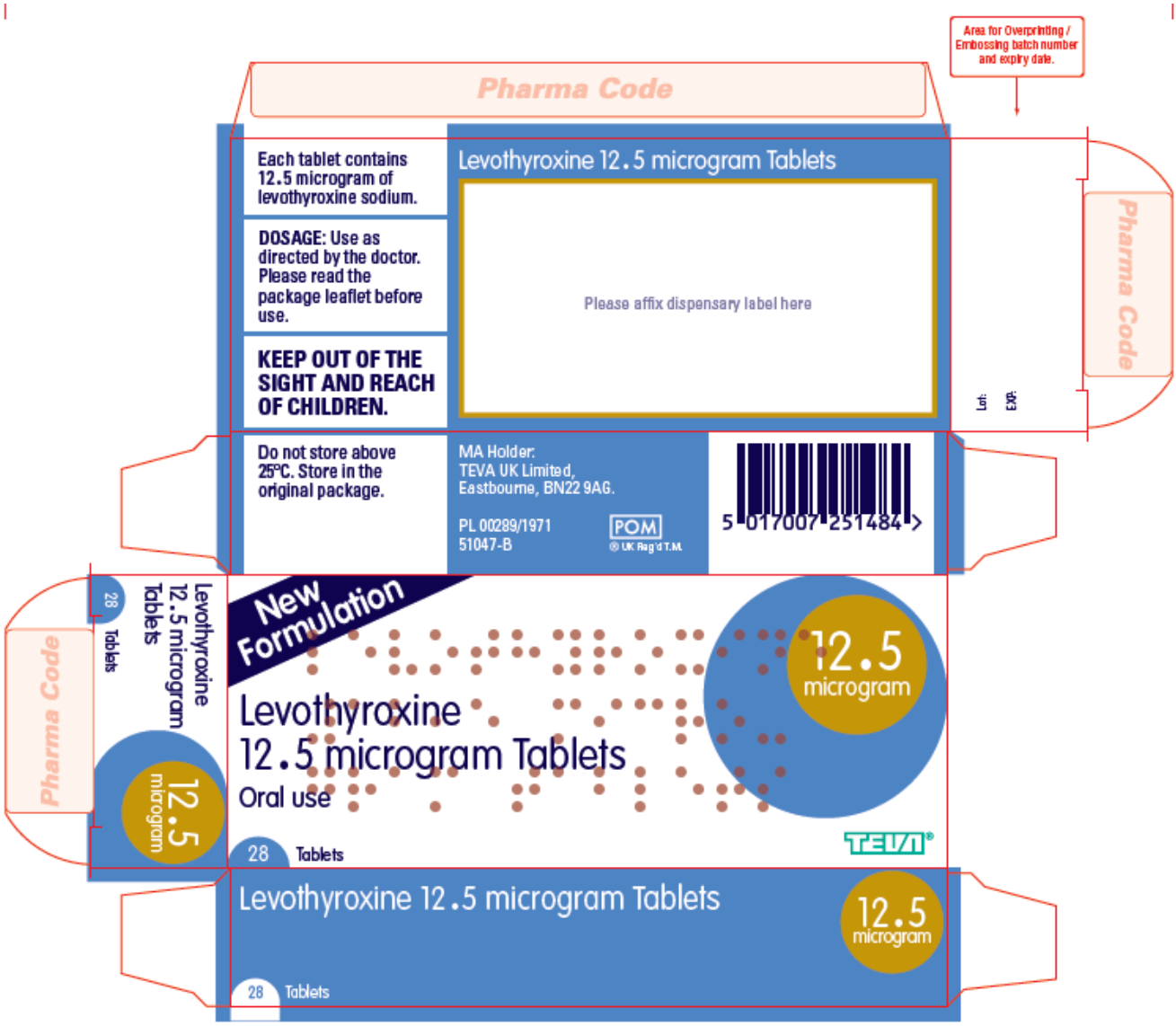
It is recommended that Marketing Authorisations are granted for Levothyroxine 12.5, 25 and 75 microgram Tablets.

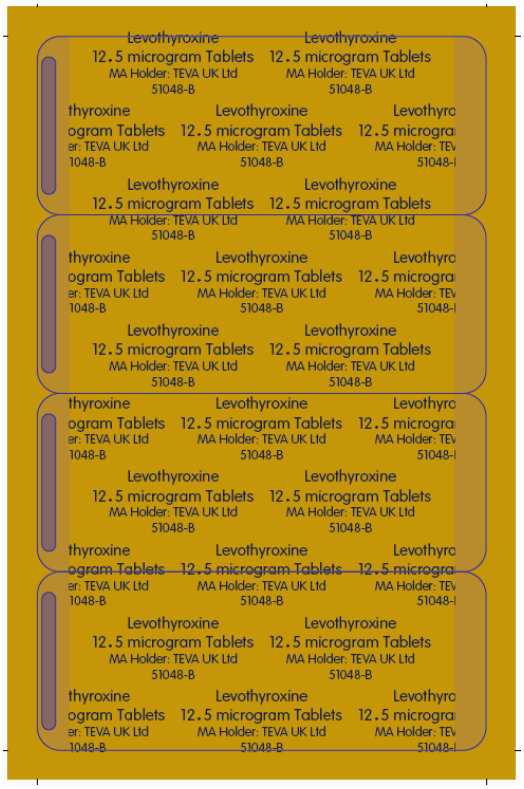
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

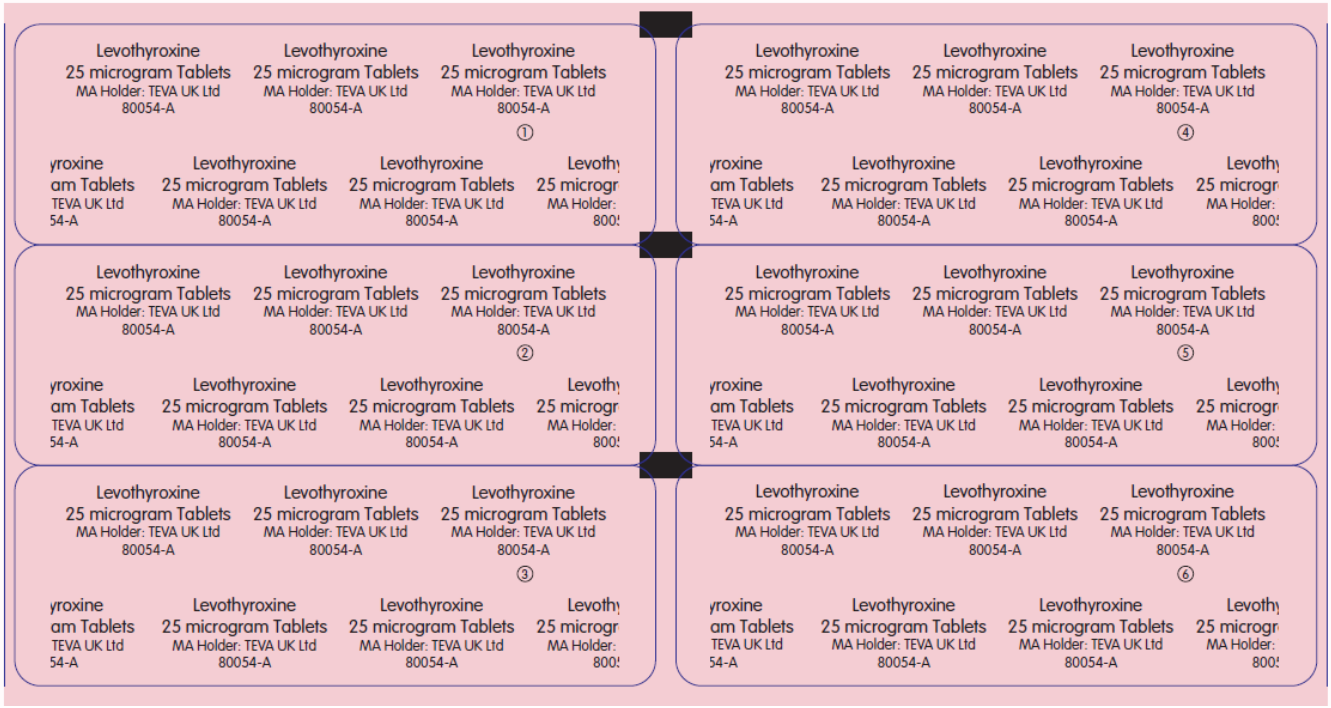
In accordance with Directive 2010/84/EU, the current versions of the SmPCs and PIL are available on the MHRA website.

The approved labelling is shown below:


Area for Overprinting / Embossing batch number and expiry date.
Pharma Code
Each tablet contains 12.5 microgram of levothyroxine sodium.
DOSAGE: Use as directed by the doctor. Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not store above 25°C. Store in the original package.
Levothyroxine 12.5 microgram Tablets
Please affix dispensary label here
Lot:
EXP:
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1971
51047-B
POM
® UK Reg'd T.M.
5 017007 251484
New Formulation
Levothyroxine 12.5 microgram Tablets
Oral use
12.5 microgram
28 Tablets
TEVA
Levothyroxine 12.5 microgram Tablets
12.5 microgram
28 Tablets


Levothyroxine 12.5 microgram Tablets
MA Holder: TEVA UK Ltd
51048-B


Area for Overprinting / Embossing batch number and expiry date.
Each tablet contains 25 microgram of levothyroxine sodium.
DOSAGE:
Use as directed by the doctor. Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not store above 25ºC.
Store in the original package.
Levothyroxine 25 microgram Tablets
Please affix dispensary label here
2024
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1972
80053-C
POM
® UK Reg'd T.M.
5 017007 251583
New Formulation
Levothyroxine
25 microgram Tablets
Oral use
28 Tablets
25 microgram
TEVA
47 x 16 x 134mm


Levothyroxine 25 microgram Tablets
MA Holder: TEVA UK Ltd
80054-A
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④
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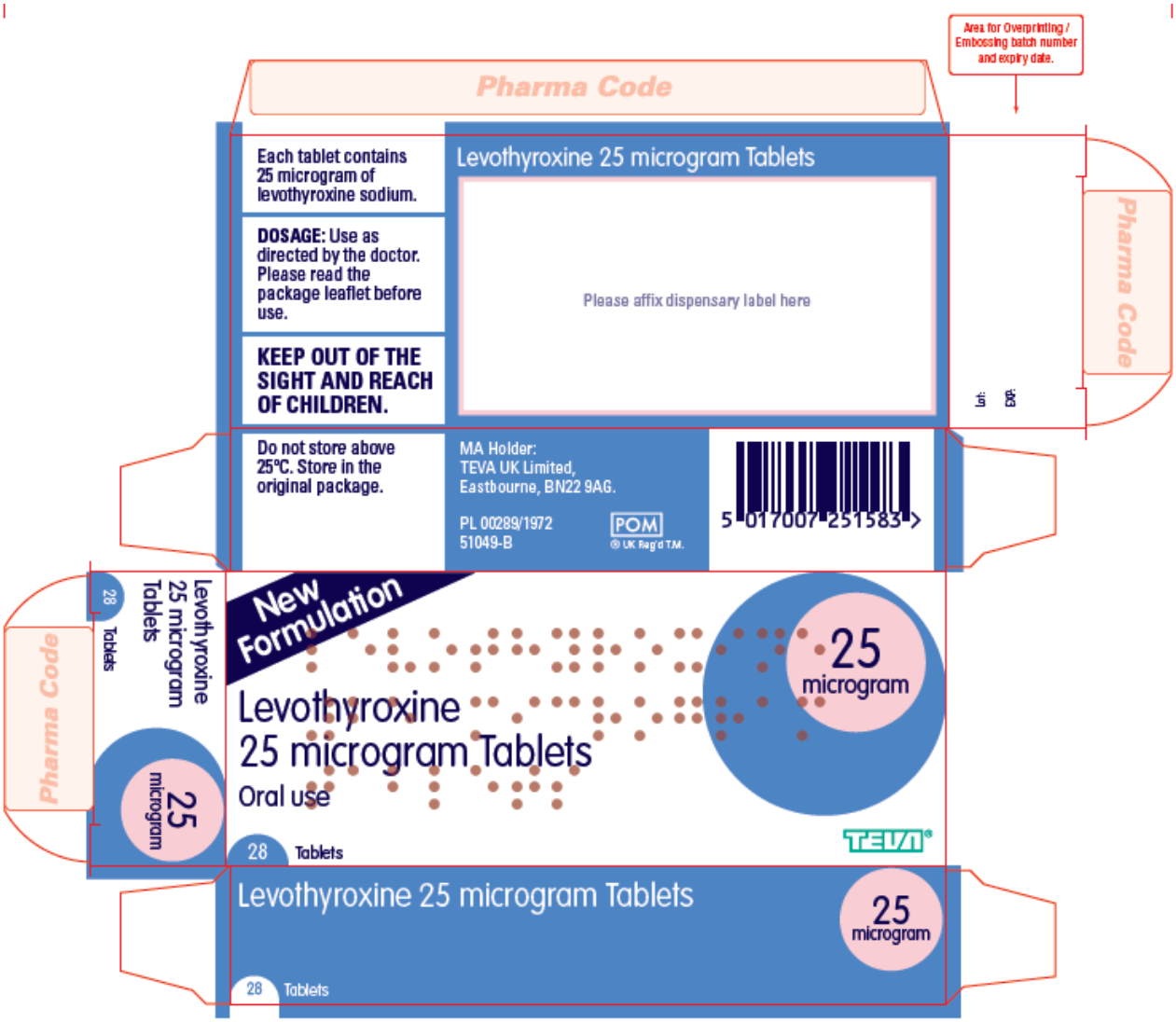
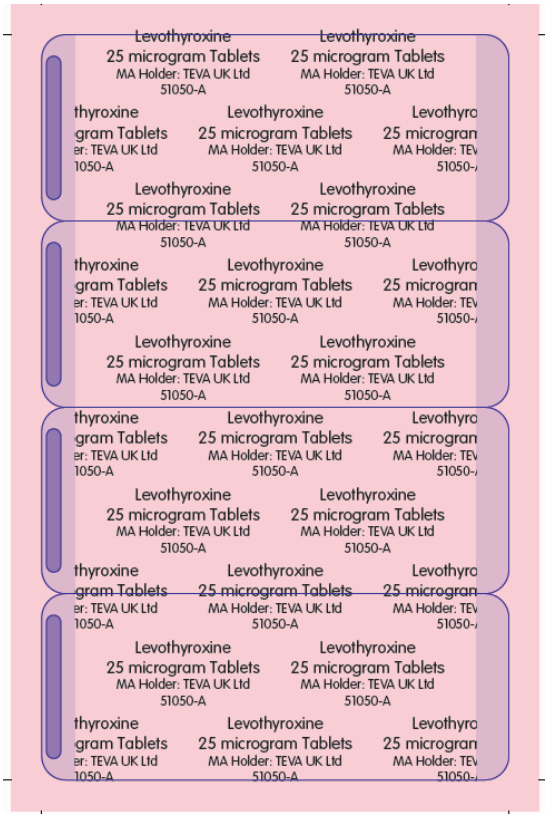
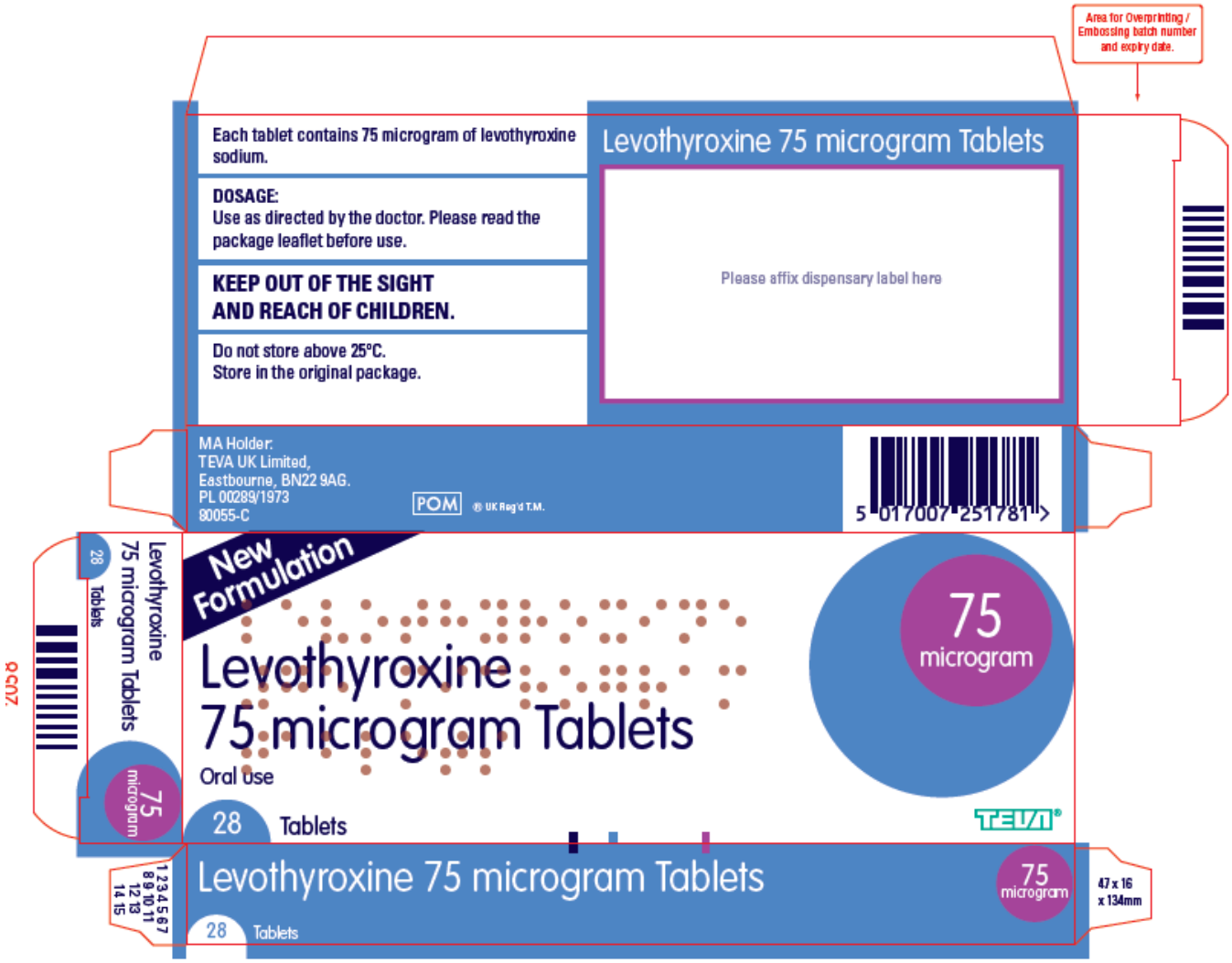
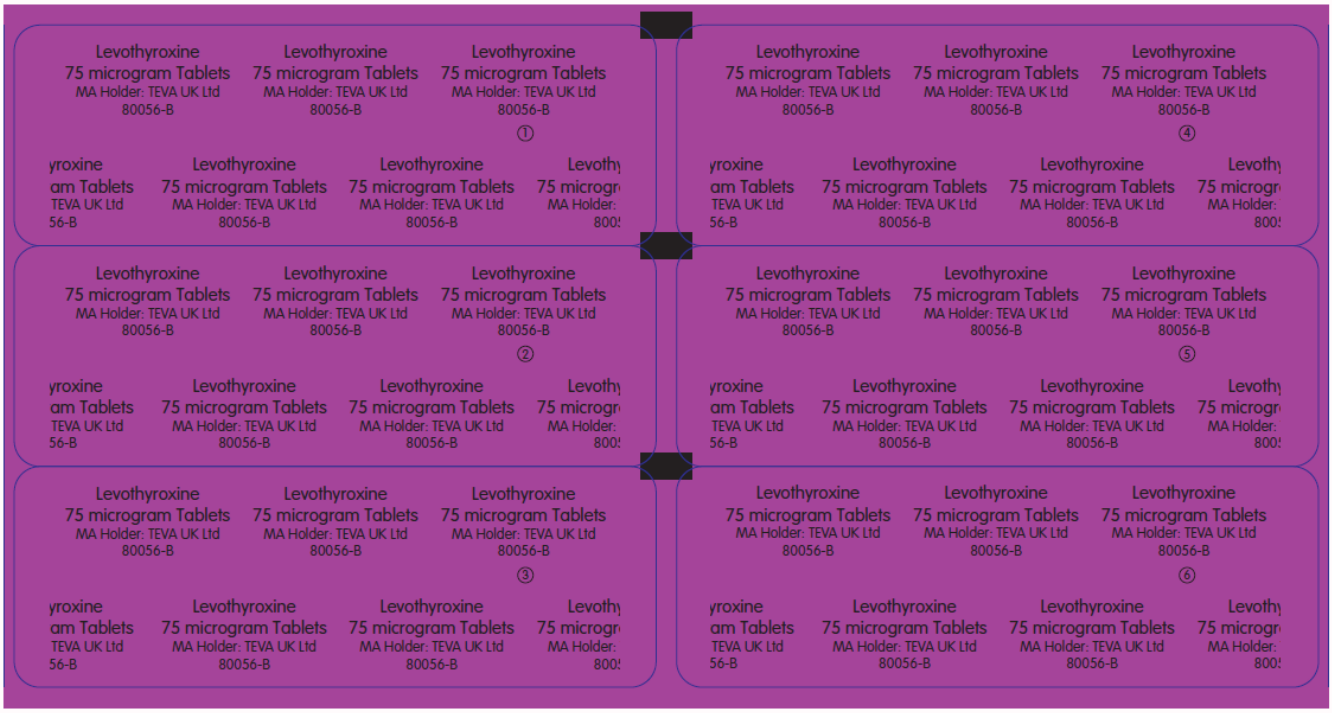

Area for Overprinting / Embossing batch number and expiry date.
Pharma Code
Each tablet contains 25 microgram of levothyroxine sodium.
DOSAGE: Use as directed by the doctor. Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Levothyroxine 25 microgram Tablets
Please affix dispensary label here
Do not store above 25°C. Store in the original package.
MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG.
PL 00289/1972
51049-B
POM
® UK Reg'd T.M.
5 017007 251583
Pharma Code
28 Tablets
Levothyroxine 25 microgram Tablets
New Formulation
Levothyroxine 25 microgram Tablets
Oral use
25 microgram
TEVA
28 Tablets
Levothyroxine 25 microgram Tablets
25 microgram
28 Tablets


Levothyroxine 25 microgram Tablets
MA Holder: TEVA UK Ltd
51050-A


Area for Overprinting / Embossing batch number and expiry date.
Each tablet contains 75 microgram of levothyroxine sodium.
DOSAGE:
Use as directed by the doctor. Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not store above 25°C.
Store in the original package.
Levothyroxine 75 microgram Tablets
Please affix dispensary label here
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1973
80055-C
POM
® UK Reg'd T.M.
5 017007 251781
New Formulation
Levothyroxine 75 microgram Tablets
Oral use
28 Tablets
75 microgram
TEVA
Levothyroxine 75 microgram Tablets
28 Tablets
47 x 16 x 134mm


Levothyroxine 75 microgram Tablets
MA Holder: TEVA UK Ltd
80056-B
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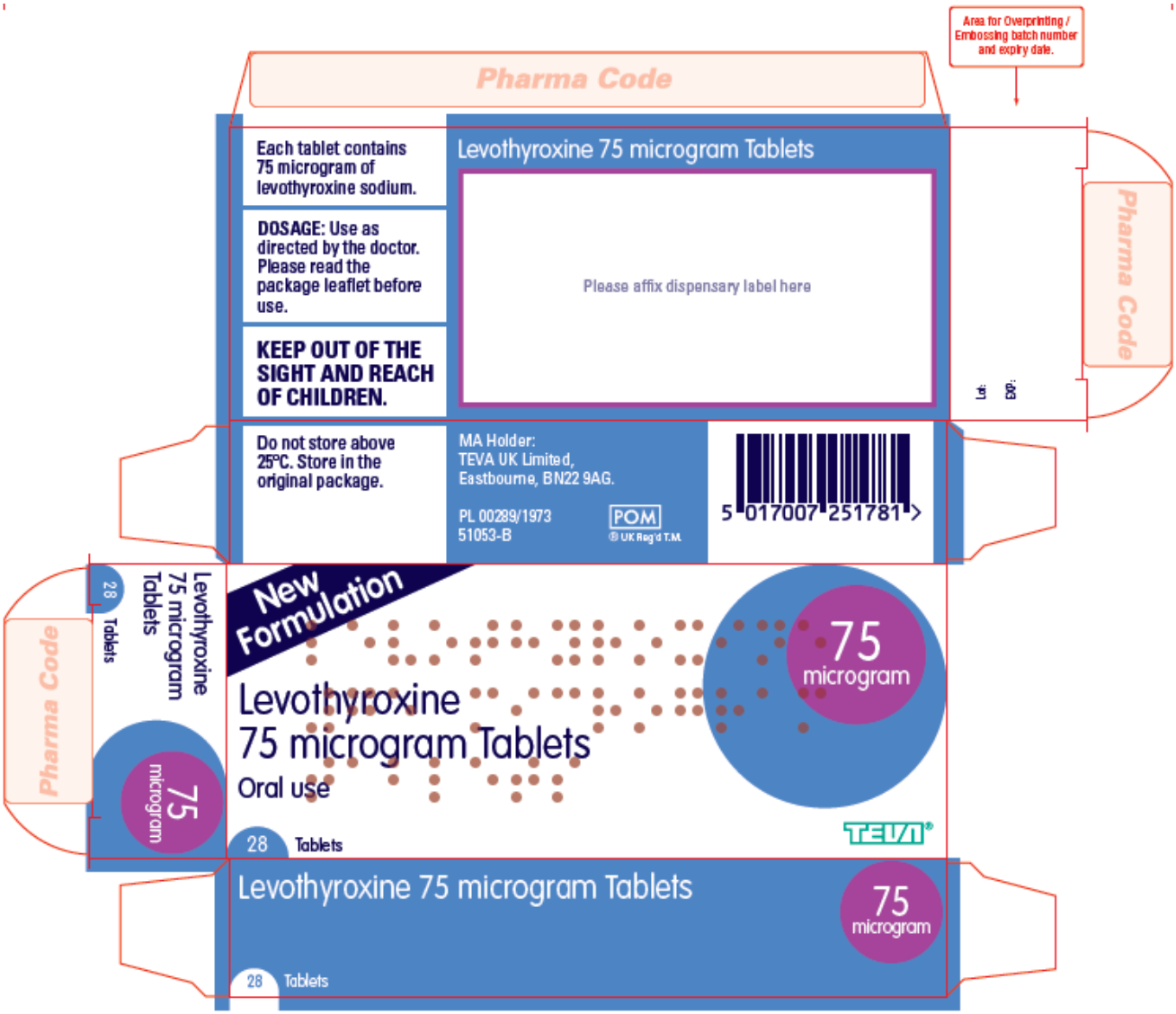
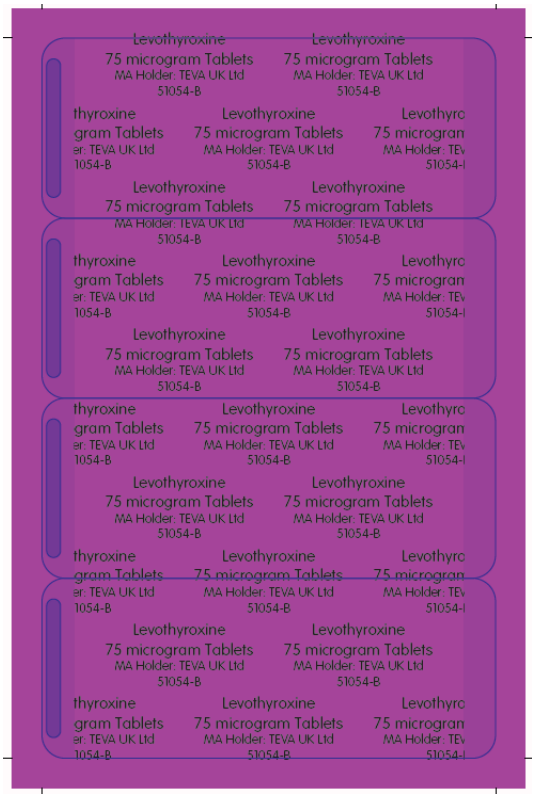

Area for Overprinting / Embossing batch number and expiry date.
Pharma Code
Each tablet contains 75 microgram of levothyroxine sodium.
DOSAGE: Use as directed by the doctor. Please read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Levothyroxine 75 microgram Tablets
Please affix dispensary label here
Lot:
EXP:
Do not store above 25°C. Store in the original package.
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1973
51053-B
POM
® UK Reg'd T.M.
5 017007 251781
New Formulation
Levothyroxine 75 microgram Tablets
Oral use
75 microgram
28 Tablets
TEVA
Levothyroxine 75 microgram Tablets
28 Tablets


Levothyroxine 75 microgram Tablets
MA Holder: TEVA UK Ltd
51054-B

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of levothyroxine sodium are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

No Environmental Risk Assessment has been conducted and an acceptable justification for its absence has been provided. Levothyroxine is similar to an endogenous thyroid hormone. In addition, the proposed products are intended for generic substitution of similar marketed products, and should therefore not lead to an increase in the total quantity of levothyroxine released into the environment. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Levothyroxine 12.5, 25 and 75 microgram Tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of levothyroxine sodium. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following studies:

1. An open label, two-period, two-sequence, cross-over, controlled, randomised, single administration, pivotal bioequivalence study comparing the bioavailability of the test product, Levothyroxine 100 microgram Tablets to those of the reference product, Eltroxin 100 microgram Tablets (Mercury Pharma Limited), in healthy human male and female volunteers, under fasting conditions.

Volunteers were given each treatment after an overnight fast. The treatment comprised of a single 600 microgram dose (6 tablets) of test or reference product. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each treatment was separated by a washout period of 35 days.

A summary of the main pharmacokinetic results is presented below:

Table 1. Pharmacokinetic parameters for levothyroxine (baseline-corrected values)

Pharmacokinetic parameter	Test		Reference	
	geometric mean	SD CV%	geometric mean	SD CV%
$AUC_{(0-72h)}$ (ng.h/ml)	2619.377	435.981 16.644	2493.42	619.115 24.83
$AUC_{(0-\infty)}$	N/R	N/R	N/R	N/R
C_{max} (ng/ml)	60.81	13.126 21.586	59.576	13.136 22.05
T_{max}*(hours)	2.403	1.268 52.749	4.435	12.583 283.687

<AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>
<AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)
N/R	Not reported

Table 2. Statistical analysis for levothyroxine (baseline-corrected values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Interval	
		Lower	Upper
$AUC_{(0-72h)}$	106.907	100.671	113.529
C_{max}	103.052	95.131	111.632

The 90 % confidence intervals for levothyroxine for the ratio of test/reference are within 80.00-125.00 % for Cmax and AUC_{0-72h}. Levothyroxine 100 microgram Tablets are, therefore, considered bioequivalent to Eltroxin 100 microgram Tablets (Mercury Pharma Limited).

2. A randomised, open- label, 3-way crossover study evaluating the dosage form proportionality of three different strengths of levothyroxine tablets (25, 50 and 100 micrograms), administered as a single oral dose of 600 micrograms in healthy human male and female volunteers, under fasting conditions

Volunteers were given each treatment after an overnight fast. The treatment comprised of a single 600 microgram dose of Levothyroxine 100 microgram Tablets (6 tablets), Levothyroxine 50 microgram Tablets (12 tablets) or Levothyroxine 25 microgram Tablets (24 tablets). Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each treatment was separated by a washout period of 35 days.

Table 1. Pharmacokinetic parameters for levothyroxine (baseline corrected values)

Pharmacokinetic parameter	Test1 100mcg tablets	Test2 50 mcg tablets	Test3 25 mcg tablets
$AUC_{(0\text{-}72h)}$ mean SD/CV%	2699.559 400.109/ 14.821	2757.777 496.129/ 17.99	2855.013 410.380/ 14.374
$AUC_{(0\text{-}\infty)}$	N/R	N/R	N/R
C_{max} Mean SD/CV%	65.46 10.756/ 16.431	64.943 11.509/ 17.722	67.333 12.417/ 18.422
T_{max}* Mean	2.346	2.643	4.607

Table 2. Statistical analysis for levothyroxine (baseline-corrected values)

Pharmacokinetic parameter	Geometric Mean Ratio Test2/Test1	Geometric Mean Ratio Test2/Test3	Geometric Mean Ratio Test3/Test1
$AUC_{(0\text{-}72h)}$	101.196	95.831	105.598
90% Confidence Interval	96.528, 106.090	91.524, 100.34	100.708, 110.726
C_{max}	99.476	96.573	103.006
90% Confidence Interval	93.38, 105.97	90.806, 102.706	96.670, 109.758

The results of this dose-proportionality study demonstrate that doses of the three strengths of levothyroxine (25 micrograms, 50 micrograms and 100 micrograms) administered as a 600 microgram dose, give equivalent bioavailability and therefore systemic exposure. As Levothyroxine 100 microgram Tablets has also demonstrated bioequivalence to Eltroxin 100 microgram Tablets (Mercury Pharma Limited) it can be concluded that the lower strengths of levothyroxine (25 micrograms and 50 micrograms) will give a systemic exposure proportional to that of Eltroxin 100 microgram Tablets. Therefore Levothyroxine 25 microgram Tablets can be considered bioequivalent to Eltroxin 25 microgram Tablets.

Biowaiver for 12.5 microgram and 75 microgram strengths

In accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) a biowaiver for the conduct of a bioequivalence or dosage form proportionality study for Levothyroxine 12.5 microgram Tablets and Levothyroxine 75 microgram Tablets was granted on the basis of satisfactory comparative dissolution data and profiles, obtained using discriminatory methods expected for levothyroxine, among the five strengths of tablets, in addition to fulfilment of general biowaiver requirements.

It could, therefore, also be concluded that Levothyroxine 12.5 microgram Tablets and Levothyroxine 75 microgram Tablets will give a systemic exposure proportional to that of Eltroxin 100 microgram Tablets.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required (see Section IV.2).

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none were required (see Section IV.2).

IV.5 Clinical Safety

No new data on safety have been submitted and none and none were required (see Section IV.2).

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levothyroxine 12.5, 25 and 75 microgram Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Hypersensitivity reactions	Proposed SmPC text: • In section 4.3 the product is contraindicated in patients with hypersensitivity to levothyroxine or to any of the excipients. • In section 4.8 it points out that hypersensitivity reactions including rash, pruritus, dyspnoea, joint pain, malaise and oedema may occur.	Not applicable

	Prescription only medicine	
Use in patients with thyrotoxicosis	Proposed SmPC text: • In section 4.3 the product is contraindicated in thyrotoxicosis. • In section 4.5 it points out that thyroid function tests may be affected by a number of drugs. This should be taken into account when monitoring a patient's response to levothyroxine therapy. • In section 4.8 adverse effects of thyroid hormones which are generally associated with excessive doses and correspond to the symptoms of hyperthyroidism are listed. Prescription only medicine	Not applicable
Use in patients with adrenal gland disorder or adrenal insufficiency	Proposed SmPC text: • In section 4.3 the product is contraindicated in adrenal gland disorder or adrenal insufficiency. • In section 4.4 it points out that 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 Prescription only medicine	Not applicable
Use in patients over the age of 50 years and patients with a long term history of hypothyroidism	Proposed SmPC text: • In section 4.2 there are dosage recommendations for patients over the age of 50 years. • In section 4.4 it points out that levothyroxine should be introduced very gradually in patients aged over 50 years and those with long standing hypothyroidism to avoid any sudden increase in metabolic demands. Prescription only medicine	Not applicable
Use in patients with cardiovascular disorders	Proposed SmPC text: • In section 4.2 it highlights that in patients with heart disease, a clinical response is probably a more acceptable criteria of dosage rather that serum levels. • In section 4.2 it points out that it is valuable to obtain an ECG prior to therapy, as changes induced by hypothyroidism	Not applicable

	may be confused with ECG evidence of cardiac ischaemia. • In section 4.4: It highlights that levothyroxine sodium should be used with caution in patients with cardiovascular disorders including angina pectoris, arteriosclerosis, coronary artery disease, hypertension, symptoms or ECG evidence of myocardial infarction and in older people who have a greater likelihood of occult cardiac disorders. • In section 4.5: Beta blockers may decrease the peripheral conversion of levothyroxine to tri-iodothyronine. The toxicity of digitalis is enhanced by levothyroxine, therefore, in digitalised patients the dose of digitalis may need adjusting (gradually increased as treatment proceeds because initially patients are relatively sensitive to digoxin) if levothyroxine therapy is required. • In section 4.8: Cardiac disease may be exacerbated by the administration of thyroid hormones resulting in severe angina pectoris, myocardial infarction or sudden cardiac death. Prescription only medicine	
Use in patients with diabetes	Proposed SmPC text: • In section 4.4 it points out that 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. • In section 4.5 it highlights that treatment with Levothyroxine may result in an increase in dosage requirements of insulin or oral hypoglycaemic agents. Prescription only medicine	Not applicable
Sub-clinical hyperthyroidism associated with bone loss	Proposed SmPC text: • In section 4.4 it points out that to minimise the risk of osteoporosis, dosage of levothyroxine sodium should be titrated to the lowest possible effective level. Prescription only medicine	Not applicable

Hair loss in children	Proposed SmPC text: • In section 4.4 it points out that parents of children receiving thyroid agent should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequently regrowth usually occurs. • In section 4.8 it points out that transient hair loss in children has been reported. Prescription only medicine	Not applicable
Excessive dosage of levothyroxine	Proposed SmPC text: • In section 4.8 it points out that gross over dosage has been reported to result in a clinical state resembling thyroid storm, and in collapse and coma. Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a "thyroid crisis" with any of the following symptoms: Hyperpyrexia, tachycardia, arrhythmia, hypotension, cardiac failure, jaundice, confusion, seizure and coma Prescription only medicine	Not applicable
Myocardial ischaemia and arrhythmias	Proposed SmPC text: • In section 4.2 it highlights that 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. • In section 4.4 it highlights that an ECG before starting treatment with levothyroxine is advised, as changes induced by hypothyroidism may be confused with evidence of ischaemia. • In section 4.5 it highlights that levothyroxine increases receptor sensitivity to catecholamines, the response to tricyclic anti-depressants (e.g. amitriptyline, imipramine, dosulepin) may also be	Not applicable

	accelerated; concomitant use may precipitate cardiac arrhythmias. Prescription only medicine	
Important potential risks		
Use during lactation	Proposed SmPC text: • In section 4.6 it highlights that levothyroxine is excreted into breast milk in low concentrations and screening for congenital hypothyroidism might be affected. Prescription only medicine	Not applicable
Medication errors including unintentional overdose	• The strength of levothyroxine sodium appears on the outer packaging of each product and in the package leaflet. Proposed SmPC text: • In section 4.2 it highlights: Adults: Initially 50 to 100 micrograms daily. The final daily dose may be up to 100 to 200 micrograms. Older people: As for patients aged over 50 years For patients over 50 years, initially, it is not advisable to exceed 50 micrograms daily. The final daily dose may be up to 50 to 200 micrograms. Patients over 50 years with cardiac disease: Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In this condition, the daily dosage may be increased by 25 microgram increments at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 to 200 micrograms. For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather that serum levels. Paediatric patients: The maintenance dose is generally 100 to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated. Congenital hypothyroidism in infants: For neonates and infants with congenital hypothyroidism, where rapid replacement is	Not applicable

	important, the initial recommended dosage is 10 to 15 micrograms per kg BW per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values. Acquired hypothyroidism in children: For children with acquired hypothyroidism, the initial recommended dosage is 12.5-50 micrograms per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached. Juvenile myxoedema in children: The initial recommended dosage is 25 micrograms daily. In such conditions, the daily dose may be increased by 25 micrograms at intervals of every 2 - 4 weeks, until mild symptoms of hyperthyroidism is seen. The dose will then be reduced slightly. • In section 3 of PIL it highlights Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The dosage recommendations for patients are also present in section 3. Prescription only medicine	
Missing information		
Use in pregnancy	Proposed SmPC text: • In section 4.6 it highlights that the safety of levothyroxine during pregnancy has not been established. Any possible risk of congenital abnormalities should be assessed against the possible consequences to the foetus of untreated hypothyroidism. Prescription only medicine	Not applicable

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Levothyroxine 12.5, 25 and 75 microgram Tablets.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levothyroxine sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)