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Public Assessment Report

Scientific discussion

Levothyroxine Abdi 25 micrograms tablets
Levothyroxine Abdi 50 micrograms tablets
Levothyroxine Abdi 75 micrograms tablets
Levothyroxine Abdi 100 micrograms tablets
Levothyroxine Abdi 125 micrograms tablets
Levothyroxine Abdi 150 micrograms tablets
Levothyroxine Abdi 175 micrograms tablets
Levothyroxine Abdi 200 micrograms tablets

levothyroxine sodium

CZ/H/0840/001-008/DC

Date: 20.5.2020

This module reflects the scientific discussion for the approval of Levothyroxine Abdi. The procedure was finalised on 6.11.2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levothyroxine Abdi 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg, 175 µg, 200 µg, tablets, from Abdi Farma Unipessoal Lda.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.
The concerned member states involved in this procedure were Netherlands and Poland.

The original and reference medicinal product is Euthyrox 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg, 175 µg, 200 µg tablets from Merck Serono GmbH, Germany, authorized since 2000-03-01.

The product is indicated for:

Levothyroxine Abdi 25 – 200 micrograms:

– Treatment of benign goiter (thyroid enlargement) with euthyroid function
– Prophylaxis of recurrent goiter after resection of the goiter with euthyroid function, depending on the postoperative hormonal status
– Thyroid hormone replacement in hypothyroidism
– Suppression treatment in thyroid malignancy

Levothyroxine Abdi 25 – 100 micrograms:

– Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism

Levothyroxine Abdi 100/150/200 micrograms:

– Diagnostic use for thyroid suppression test

A comprehensive description of the indications and posology is given in the SmPC.

The active substance levothyroxine sodium that is not considered as a new active substance

The synthetic levothyroxine contained in Levothyroxine Abdi is identical to the naturally occurring thyroid hormone predominantly produced by the thyroid gland in terms of its action. It is transformed into T3 in the peripheral organs, and like the natural hormone, shows its characteristic effects at the T3 receptors. The body cannot distinguish between endogenous and exogenous levothyroxine.

A bioequivalence study was conducted between the Levothyroxine Abdi 200 µg tablets and the reference product Euthyrox 200 µg tablets from Merck Sereno GmbH, Germany. A biowaiver was proposed for 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg and 175 µg strengths.

The RMS was assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for this product.

No scientific advice was given to the Applicant for this medicinal product.

II. QUALITY ASPECTS

II.1 Introduction

Levothyroxine Abdi 25 micrograms tablets are round white tablets with debossed on one side with “25” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 50 micrograms tablets are round white tablets with debossed on one side with “50” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 75 micrograms tablets are round white tablets with debossed on one side with “75” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 100 micrograms tablets are round white tablets with debossed on one side with “100” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 125 micrograms tablets are round white tablets with debossed on one side with “125” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 150 micrograms tablets are round white tablets with debossed on one side with “150” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 175 micrograms tablets are round white tablets with debossed on one side with “175” and scored in the shape of “+” sign on the other side.
Levothyroxine Abdi 200 micrograms tablets are round white tablets with debossed on one side with “200” and scored in the shape of “+” sign on the other side.

The tablet can be divided into equal doses.

The tablets contain 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 175 mcg or 200 mcg of levothyroxine sodium. The tablets are packaged in PVC/PE/PVDC-Al blisters.

The excipients are: lactose monohydrate, maize starch, gelatin, croscarmellose sodium and magnesium stearate.

II.2 Drug Substance

The drug substance levothyroxine sodium is described in Ph.Eur. One source of drug substance is proposed using Certificate of suitability. The re-test period of the substance stated on CEP is 24 months. The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance. Control of the drug substance has been provided by the finished drug product manufacturer.

II.3 Medicinal Product

The pharmaceutical dosage form of the drug product is tablet. The drug product composition has been adequately described. The different product strengths are visually distinguishable.
The development of the drug product has been described, the choice of excipients has been justified and their functions have been explained. The objective was to obtain levothyroxine sodium tablets achieving pharmaceutical equivalence and bioequivalence with the reference product. A study to evaluate the dosage form proportionality of three different strengths of levothyroxine has been provided. Comparative dissolution data between the proposed and reference products have been provided including the bio-batches. A biowaiver for additional strengths could be approved as it fulfills criteria given by an appropriate EU guideline. Discriminative power of the selected dissolution method has been proved.
The manufacturing process can be considered as a non-standard due to very low content of the drug substance in the drug product. The manufacturing process was well described and validated.
All used excipients are widely used and comply with the requirements of the Ph. Eur.

The drug product release and shelf-life specifications cover appropriate parameters for this dosage form. Certificates of analysis have been provided.
The packaging material has been specified in sufficient manner and materials used comply with the Ph. Eur. and EU directives.
The stability of the drug products was tested and evaluated in several stability studies in accordance with the predefined individual stability protocols. Based on the data proposed shelf life of 18 years and the storage conditions "Do not store above 25 °C" are acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier and updates provided during the procedure, the member states consider that Levothyroxine Abdi 25 micrograms, 50 micrograms, 75 micrograms, 100 micrograms, 125 micrograms, 175 micrograms and 200 micrograms tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been done for the active substances and finished products.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of levothyroxine sodium are well known. As levothyroxine sodium is a widely used, well-known synthetic levo isomer of the thyroid hormone thyroxine, the Applicant did not provide additional studies and further studies were not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Levothyroxine Abda 25 micrograms, 50 micrograms, 75 micrograms, 100 micrograms, 125 micrograms, 150 micrograms, 175 micrograms, 200 micrograms tablets are intended for generic substitution, this would not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Justification for omission of performing full ERA was provided and was acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

The basis of the BE study is justified. The SmPC is in line with the innovator's SmPC.

IV.2 Pharmacokinetics

To support the application, the Applicant submitted as report one bioequivalence study and further study to evaluate the dosage form proportionality of three different strengths of levothyroxine.

Bioequivalence study - I
This was an open label, balanced, randomized, two-treatment, two-period, two sequences, single oral dose, crossover bioequivalence study of two products of levothyroxine sodium

tablets 200 µg (3 tablets x 200 µg) in normal, healthy, adult, human subjects under fasting conditions.

Results

Table 1. Pharmacokinetic parameters for levothyroxine [baseline corrected data] (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	3581.52 ± 853.57	*Not calculated*	97.11 ± 20.20	3.17 (1.50 – 5.00)
Reference	3805.30 ± 850.75	*Not calculated*	94.45 ± 17.72	3.51 (1.50 – 10.00)
***Ratio (90% CI)**	95.30% (89.73%, 101.25%)	*Not calculated*	102.80% (98.99%, 106.77%)	

AUC_{0-72} Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters for levothyroxine [baseline uncorrected data] (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	10417.25 ± 1978.33	*Not calculated*	192.06 ± 35.42	3.17 (1.50 – 5.00)
Reference	10560.18 ± 1780.04	*Not calculated*	188.42 ± 31.69	3.51 (1.50 – 10.00)
***Ratio (90% CI)**	98.90% (96.55%, 101.35%)	*Not calculated*	101.90% (99.57%, 104.34%)	

AUC_{0-72} Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

The Applicant applied for biowaiver for Levothyroxine sodium 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg and 175 µg tablets.

Study - II

A dose-proportionality study was performed to evaluate the dosage form proportionality of three different strengths of levothyroxine, representing low, medium and high strengths (50 µg, 100 µg and 200 µg) administered as a single oral dose of 600 µg.
This was a comparative, randomized, three -period, three-treatment, six-sequence, single dose, open-label, crossover study evaluating the dosage form proportionality of (3 x 200 µg Levothyroxine Sodium Tablet (dose: 600 µg) versus (6 x 100 µg Levothyroxine Sodium Tablet (dose: 600 µg) versus (12 x 50 µg Levothyroxine Sodium Tablet (dose: 600 µg) in healthy subjects under fasting conditions.

Results

Baseline-unadjusted data results

Table 3. Pharmacokinetic parameters levothyroxine for baseline-unadjusted data (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
A = 3 x 200 µg (N=42)	6039.65 ± 811.63	107.63 ± 13.46	2.84 (1.00 – 36.00)
B = 6 x 100 µg (N=42)	5984.67 ± 742.81	106.29 ± 12.17	3.00 (1.50 – 34.13)
C = 12 x 50 µg (N=42)	6030.42 ± 825.38	107.75 ± 14.84	3.50 (1.00 – 36.00)

Table 4. Treatment comparison for levothyroxine for baseline-unadjusted data

Comparison*	AUC_{0-72} ratio (90% CI)	C_{max} ratio (90% CI)
A vs. B	100.79% (99.02%, 102.60%)	101.10% (98.67%, 103.59%)
A vs. C	100.18% (98.42%, 101.97%)	99.99% (97.58%, 102.45%)
B vs. C	99.39% (97.64%, 101.17%)	98.90% (96.52%, 101.33%)

**ratios and corresponding 90% confidence intervals are derived from ln-transformed data*

Baseline-adjusted data results

Table 5. Pharmacokinetic parameters levothyroxine for baseline-adjusted data (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
A = 3 x 200 µg (N=42)	1604.17 ± 391.78	46.52 ± 9.04	2.84 (1.00 – 36.00)
B = 6 x 100 µg (N=42)	1615.50 ± 363.82	45.94 ± 7.58	3.00 (1.50 – 34.13)
C = 12 x 50 µg (N=42)	1603.40 ± 422.59	47.25 ± 10.46	3.50 (1.00 – 36.00)

Table 6. Treatment comparison for levothyroxine for baseline-adjusted data

Comparison*	AUC_{0-72} ratio (90% CI)	C_{max} ratio (90% CI)
A vs. B	98.36% (92.25%, 104.88%)	100.55% (95.65%, 105.70%)
A vs. C	100.11% (93.89%, 106.74%)	98.70% (93.89%, 103.76%)
B vs. C	101.77% (95.44%, 108.51%)	98.15% (93.37%, 103.18%)

**ratios and corresponding 90% confidence intervals are derived from ln-transformed data*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study/ies Levothyroxine sodium 200 µg tablet is considered bioequivalent with Euthyrox 200 µg tablet.

The biowaiver for Levothyroxine sodium 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg and 175 µg tablets is considered adequately justified from clinical point of view.

IV.3 Risk Management Plan

The Applicant has submitted a risk management plan, 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 Abdi.

Summary table of safety concerns as approved in the RMP

Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance was suggested, and no additional pharmacovigilance activities were proposed by the Applicant, which was endorsed.

IV.4 Discussion on the clinical aspects

The application contained an adequate review of published non-clinical and clinical data. Bioequivalence between the test and the reference product was shown. The biowaiver for additional strengths has been justified.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the applications for Levothyroxine Abdi 25 – 200 micrograms, tablets, was considered positive.

The bioequivalence study for the highest strength between Levothyroxine sodium 200 µg tablet and reference drug product Euthyrox 200 µg tablet of Merck was demonstrated and is acceptable.
A dose-proportionality study was performed to evaluate the dosage form proportionality of three different strengths of levothyroxine, representing low, medium and high strengths (50 µg, 100 µg and 200 µg) administered as a single oral dose of 600 µg.
A biowaiver for the strengths 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg and 175 µg tablets has been applied and was accepted.

The SmPC, PIL and labelling are satisfactory.

Agreement between Member States was reached during the procedure. There was no discussion in the CMDh. The decentralised procedure was finalised with a positive outcome on 6th November 2019.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.