COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levothyroxine Accord 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets

(levothyroxine sodium)

NL/H/4465/001-012/DC

Date: 15 April 2020

This module reflects the scientific discussion for the approval of Levothyroxine Accord tablets. The procedure was finalised at 14 February 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levothyroxine Accord 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets, from Accord Healthcare B.V.

Levothyroxine Accord 25 - 200 micrograms is indicated for:

- Treatment of benign euthyroid goitre
- Prophylaxis of relapse after surgery for euthyroid goitre, depending on the post-operative hormone status
- Substitution therapy in hypothyroidism
- Suppression therapy in thyroid cancer

Levothyroxine Accord 25 – 100 micrograms is indicated for:

- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism

Levothyroxine Accord 100/150/200 micrograms is indicated for:

- Diagnostic use for thyroid suppression testing

Levothyroxine Accord 12.5 micrograms is indicated for:

- In children as an initial dose for thyroid hormone replacement in cases of an underactive thyroid gland,
- In elderly patients, patients with coronary heart disease and patients with severe or chronic hypothyroidism as low initial dose which should then be increased slowly and at prolonged intervals (e.g. gradually increasing the dose by 12.5 mcg every 14 days) with frequent monitoring of thyroid hormone values,
- In any patient requiring gradual increase of levothyroxine dose

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Euthyrox 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets which has been registered in the Netherlands by Merck Sharp & Dohme Ltd since 1982 through a national procedure.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Czech Republic, Germany, Estonia, Finland, Greece, Italy, Latvia, Lithuania, Norway, Poland, Romania, Slovenia and the Slovak Republic.

Except for the 12.5 micrograms strengths, the marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The application for Marketing Authorisation of the Levothyroxine sodium Accord 12.5 micrograms tablets is made under Article 10(3) of Directive 2001/83/EC as amended, i.e. this application concerns a hybrid

medicinal product, since the strength of 12.5 micrograms tablets is not a registered strength of the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Levothyroxine Accord are round, standard flat tablets.

- 12.5 micrograms - white coloured, uncoated tablets, debossed with “P” and “13” on one side and plain on the other side. Each tablet contains 12.5 micrograms of levothyroxine sodium.
- 25 micrograms - orange coloured, uncoated tablets with a break line on both sides and debossed with "P" and "1" on one side and plain on the other side. The tablet can be divided into equal doses. Each tablet contains 25 micrograms of levothyroxine sodium.
- 50 micrograms - white coloured, uncoated tablets with a break line on both side and debossed with "P" and "2" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 50 micrograms of levothyroxine sodium
- 75 micrograms - violet coloured, uncoated tablets with a break line on both side and debossed with "P" and "3" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 75 micrograms of levothyroxine sodium.
- 88 micrograms - olive coloured, uncoated tablets with a break line on both side and debossed with "P" and "4" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 88 micrograms of levothyroxine sodium.
- 100 micrograms - yellow coloured, uncoated tablets with a break line on both side and debossed with "P" and "14" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 100 micrograms of levothyroxine sodium.
- 112 micrograms - rose coloured, uncoated tablets with a break line on both side and debossed with "P" and "6" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 112 micrograms of levothyroxine sodium.
- 125 micrograms - brown coloured, uncoated tablets with a break line on both side and debossed with "P" and "7" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 125 micrograms of levothyroxine sodium.
- 137 micrograms - turquoise coloured, uncoated tablets with a break line on both side and debossed with "P" and "8" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 137 micrograms of levothyroxine sodium.

- 150 micrograms - blue coloured, uncoated tablets with a break line on both side and debossed with "P" and "9" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 150 micrograms of levothyroxine sodium.
- 175 micrograms - lilac coloured, uncoated tablets with a break line on both side and debossed with "P" and "10" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 175 micrograms of levothyroxine sodium.
- 200 micrograms - pink coloured, uncoated tablets, break line on both side and debossed with "P" and "11" on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 200 micrograms of levothyroxine sodium.

The micrograms tablets are packed in PVC/EVOH/Aclar-Alu blisters.

The excipients are: microcrystalline cellulose, microcrystalline cellulose (PH 112), light magnesium oxide, sodium starch glycolate (Type A), sodium stearyl fumarate.
In addition, different colourants are used in the different tablet strengths:

- 25 micrograms - Lake Blend LB-530006 Orange containing sunset yellow FCF aluminium lake (E110)
- 75 micrograms - Lake Blend LB-505008 Purple containing indigo carmine aluminium lake (E132) and allura red AC aluminium lake (E129),
- 88 micrograms - Lake Blend LB-510028 Green containing tartrazine aluminium lake (E102) and indigo carmine aluminium lake (E132)
- 100 micrograms - Lake Blend LB-520044 Yellow containing tartrazine aluminium lake (E102) and sunset yellow FCF aluminium lake (E110)
- 112 micrograms - Lake Blend LB-540042 Pink containing carmine (E120) and allura red AC aluminium lake (E129)
- 125 micrograms - Lake Blend LB-575003 Brown containing sunset yellow FCF aluminium lake (E110), brilliant blue FCF aluminium lake (E133) and allura red AC aluminium lake (E129)
- 137 micrograms - Lake Blend LB-505013 Blue containing brilliant blue FCF aluminium lake (E133)
- 150 micrograms - Lake Blend LB-505010 Blue containing indigo carmine aluminium lake (E132)
- 175 micrograms - Lake Blend LB-500017 Purple containing carmine (E120) and brilliant blue FCF aluminium lake (E133)
- 200 micrograms - Lake Blend LB-540010 Maroon containing allura red AC aluminium lake (E129)

II.2 Drug Substance

The active substance is levothyroxine sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is an almost or slightly

brownish-yellow hydroscopic powder. Levothyroxine sodium is very slightly soluble in water. The active substance does not exhibit polymorphism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for ethanol content (in line with the CEP), particle size distribution and microbiological purity. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

A re-test period of 36 months is stated on the CEP. The CEP holder claims a re-test period of 36 months for the 'sieved' active substance and of 18 months for the 'milled' active substance. In both cases the storage condition is 'Store protected from light at a temperature between 2°C to 8°C', in line with the Ph. Eur. monograph for the substance. Stability data as generated by the CEP-holder is provided, which support the re-test period and storage condition stated in the CEP. Additional data about particle size distribution upon storage has been provided, which confirms compliance to the limits after storage.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Breakability of the tablets has been demonstrated according to the Ph. Eur. sub-division test for tablets.

Two bioequivalence studies have been performed with different test and reference batches. The manufacture/composition of the 200 micrograms test batches used in the studies is as currently proposed in the dossier. Comparative dissolution testing at 3 pHs and the QC medium has been performed with both biobatches and batches of test product of all proposed strengths in support of bioequivalence study and biowaiver of strength.

The *in-vitro* dissolution data supporting the results obtained in the bioequivalence study do not show similarity. However, the results obtained in the study prevail as per the EMA Guideline on Bioequivalence. The comparative dissolution studies to support the Biowaiver of Strength do show similarity between both 200 micrograms test batches and the other proposed tablet strengths. From a pharmaceutical point of view, the biowaiver of strengths can be granted. Overall, the pharmaceutical development is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The dry ingredients are mixed and sieved in several steps, followed by direct compression. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients microcrystalline cellulose, magnesium oxide, light, sodium starch glycolate, and sodium stearyl fumarate comply with the Ph. Eur. For some of these excipients critical functionality related characteristics are identified (particle size distribution, bulk density), which are adequately included in the excipient specification. The Lake Blends comply with in-house standards, their specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average weight, identity (for active substance and colourants), friability, resistance to crushing, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements/limits are identical, except for resistance to crushing, water content and impurities. The dissolution test limit is set in accordance with the results obtained with the second biobatch. Satisfactory validation data for the analytical methods have been provided. Forced degradation studies have been performed on one strength (25 micrograms) only, however it is adequately demonstrated that the degradation patterns are not impacted by the colourants present in the other strengths. The stability indicating nature of the method for related substances is adequately demonstrated. Batch analytical data for three full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full-scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions applied in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the products of all strengths are stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levothyroxine Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levothyroxine Accord is intended for generic and hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic and hybrid formulation of Euthyrox which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levothyroxine sodium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Levothyroxine Accord 200 mcg tablets (Accord Healthcare B.V., NL) is compared with the pharmacokinetic profile of the reference product Euthyrox 200 mcg tablets (Merck B.V., NL).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg and 175 mcg strengths. Dissolution similarity between strengths has been sufficiently demonstrated using an appropriate method. The justification for a biowaiver is acceptable in view of the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Bioequivalence studies

Bioequivalence study I – single dose under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 20-40 years. Each subject received a single dose (600 mcg; 3x 200 mcg) of one of the 2 levothyroxine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 49 days.

Blood samples were collected at -0.5 and -0.25 hours before dosing and at pre-dose and 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablet should be taken on an empty stomach. As such, the fasting conditions applied in the study are acceptable. Since a 600 mcg dose has been used, adequate levothyroxine plasma levels can be measured. The mean of -0.500, -0.250 and 0.000 hours pre-dose levels was to be used for the baseline adjustment of the post-dose levels of levothyroxine. The adjustment was to be performed by subtracting this mean baseline from every serum concentration for post dose samples (including pre-dose at 0.000 hour) prior to the calculation of the pharmacokinetic parameters for levothyroxine.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects were withdrawn from the study due to medical grounds and four subjects discontinued from the study on their own accord. Therefore, a total of 48 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of baseline corrected levothyroxine sodium under fasted conditions.

Treatment N=48	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**T_{max} (h)**
Test	2621 ± 473	72 ± 12	4.0 (1.25 – 8.0)
Reference	3125 ± 705	88 ± 18	3.0 (1.25 – 8.0)
***Ratio (90% CI)**	0.85 (0.80 – 0.89)	0.84 (0.81 – 0.87)	--
CV (%)	15.1	10.4	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of baseline uncorrected levothyroxine sodium under fasted conditions.

Treatment N=48	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**T_{max} (h)**
Test	8427 ± 1007	153 ± 19	4.0 (1.25 – 8.0)
Reference	9003 ± 1156	169 ± 24	3.0 (1.25 – 8.0)
***Ratio (90% CI)**	0.94 (0.92 – 0.95)	0.91 (0.89 – 0.93)	--
CV (%)	5.5	5.7	--

AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

Bioequivalence study II – single dose under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 80 healthy male subjects, aged 19-44 years. Each subject received a single dose (600 mcg; 3x 200 mcg) of one of the 2 levothyroxine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 49 days.

Blood samples were collected at -0.5 and -0.25 hours before dosing and at pre-dose and 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10, 12, 18, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablet should be taken on an empty stomach. As such, the fasting conditions applied in the study are acceptable. Since a 600 mcg dose has been used, adequate levothyroxine plasma levels can be measured. The mean of -0.500, -0.250 and 0.000 hours pre-dose levels was to be used for the baseline adjustment of the post-dose levels of levothyroxine. The adjustment was to be performed by subtracting this mean baseline from every serum concentration for post dose samples (including pre-dose at 0.000 hour) prior to the calculation of the pharmacokinetic parameters for levothyroxine.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects were withdrawn from the study due to medical grounds and three subjects discontinued from the study on their own accord. Therefore, a total of 75 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of baseline corrected levothyroxine sodium under fasted conditions.

Treatment N=75	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**T_{max} (h)**
Test	2484 ± 630	65 ± 15	3.0 (1.33 – 8.0)
Reference	2882 ± 546	74 ± 12	3.0 (1.33 – 7.0)

***Ratio (90% CI)**	0.85 (0.82 – 0.88)	0.86 (0.83 – 0.89)	--
CV (%)	13.9	12.0	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of baseline uncorrected levothyroxine sodium under fasted conditions.

Treatment N=75	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	7846 ± 1434	139 ± 26	3.0 (1.33 – 8.0)
Reference	8278 ± 1395	149 ± 23	3.0 (1.33 – 7.0)
***Ratio (90% CI)**	0.94 (0.93 – 0.96)	0.93 (0.91 – 0.94)	--
CV (%)	5.4	6.2	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

Pooling pharmacokinetic bioequivalence studies

To support the application, the MAH initially submitted bioequivalence study I. Based on this study, the Levothyroxine Accord 200 mcg tablet was considered not bioequivalent with the Euthyrox 200 mcg tablet, under fasting conditions. A new bioequivalence study (study II) was submitted and based on this study the Levothyroxine Accord 200 mcg tablet was considered bioequivalent with the Euthyrox 200 mcg tablet, under fasting conditions.
However, bioequivalence was not considered proven as two pivotal studies were available, of which one failing and one showing bioequivalence. As such, the MAH was requested to perform a pooled analysis of the results of both studies.

To pool the data of two studies, statistical analysis has been done considering ANOVA model with Study, Sequence, Study*Sequence, Subject (Study*Sequence), Formulation and Period (Study) as fixed effects.

Table 5. Results pooling of the data of bioequivalence studies I&II of levothyroxine (baseline corrected data)

Parameters	Geometric Least Squares Means (T/R) Ratio (%)	90% CI

C_{max}	84.6	82.40-86.79
AUC_{0-72}	84.2	81.60-86.95
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration		

Conclusion on bioequivalence studies

Based on the submitted bioequivalence studies and pooling Levothyroxine Accord is considered bioequivalent with Euthyrox.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH 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 Accord.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	- Adrenal crisis - Cardiovascular disorders - Hypersensitivity - Thyrotoxicosis - Substitution of a drug with greater or lesser potency (switching)
Important potential risks	- Off-label use for weight reduction - Osteoporosis - Seizures in patients with known history of epilepsy
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management

is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. For the content reference was made to Euthyrox 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets and for design, layout and style of writing to Mycophenolic acid 180mg and 360mg gastro-resistant tablets (ES/H/0183/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levothyroxine Accord 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets have a proven chemical-pharmaceutical quality and are generic (or hybrid for the 12.5 mcg strength) forms of product Euthyrox 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets. Euthyrox is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levothyroxine Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 February 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse