IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Oroxine 200 microgram tablets
Levothyroxine
PA1691/013/008

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number NL/H/2700/001-008 with NL as RMS. The responsibility of RMS was transferred to Ireland on 26 April 2022 under procedure number IE/H/1225/001-008
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1691/013/001-008
Marketing Authorisation Holder: Aspen Pharma Trading Limited

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The NL public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 100 mcg,
125 mcg, 150 mcg, 175 mcg and 200 mcg tablets. The Marketing Authorisation Holder (MAH) is Vale Pharmaceuticals Limited.

Levothyroxine Natrium 25-200 micrograms is indicated for:

- Hypothyroidism
- Prophylaxis against goitre recurrence following resection of euthyroid goitre
- Benign, euthyroid goitre
- Suppression and replacement therapy in thyroid malignancy, especially post thyroidectomy.

Levothyroxine Natrium 25-200 micrograms is indicated for:

- Co-therapy in the antithyroid treatment of hyperthyroidism, once euthyroid status has been achieved.

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

- Thyroid suppression test.

Levothyroxine Natrium Vale tablets, contain synthetic crystalline L-,3,3',5,5'-tetraiodothyronine sodium salt (levothyroxine (T4) sodium). Synthetic T4 is identical to that produced in the human thyroid gland.

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, 100 mcg, 125 mcg, 150 mcg, 175 mcg and 200 mcg tablets (NL License RVG 11718, 11344, 21494, 101391, 09009, 101393, 15468, 101394, 11345, 26173, 26174). In the Netherlands, the first marketing authorisation was granted in 1982, for Euthyrox 100 mcg tablets.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Slovenia, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Levothyroxine Natrium Vale tablets are:
25 mcg: white to off-white, round, tablets imprinted with 25 on one side and bisected on the other side to allow sub-division to achieve a 12.5 mcg dose.
50 - 200 mcg: white to off-white, round, flat, bevelled tablets imprinted with "L01, L02, L07, L10, L11, L12, L15, L17, L20 or L21" on one side and "50, 75, 88, 100, 112, 125, 137, 150, 175 or 200" on the other side.

The tablets are packed in high density polyethylene (HDPE) bottles, closed with white polypropylene (PP) screw caps with foil heat induction seals, and with a 1.0 g white polypropylene canister containing oxygen absorber. The canister (oxygen absorber) should remain inside the bottle during the in-use period.

The excipients are: microcrystalline cellulose PH101 (E460), pregelatinised maize starch, talc (E553b), colloidal anhydrous silica (E551), magnesium stearate (E470b).

These Levothyroxine tablets are in principle similar to the innovator Eltroxin tablets. In addition supplementary strengths are introduced. The current 50 mcg tablet has a tablet weight of 75.0 mg. The MAH introduced a new formulation with a weight of 75.0 mg instead of 150.0 mg for all other strengths i.e. all strengths across the range now have a tablet weight of 75.0 mg. The MAH conducted a bioequivalence study to compare the 75.0 mg formulation with the 150.0 formulation, using the 100 mcg strength. In addition, as Euthyrox is the innovator product in some CMS and Eltroxin is not, a bioequivalence study is submitted using Euthyrox as comparator. Next to these 2 studies a dose proportionality/bioavailability study was carried out using the 50, 100 and 200 µg Eltroxin tablets. The results of these studies are discussed under section IV.2 ´Pharmacokinetics´.

All strengths were formulated with the same tablet mass 75.0 mg. Differences in the drug substance content between strengths were compensated for by slight mass changes in the microcrystalline cellulose.

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 a white to pale brownish-yellow, hygroscopic amorphous or crystalline powder, which is soluble in alkali hydroxides, very slightly soluble in ethanol and practically insoluble in water, chloroform, ethyl ether and acetone. The drug substance has one chiral center, the active ingredient is levothyroxine. The product does not exhibit polymorphism.

The CEP procedure is used for both manufacturers of 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 European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the additional requirement of the CEPs. Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer on 8 batches of the drug substance obtained from one manufacturer and 1 batch of the other supplier. Additional batch analysis data have been provided
by this second manufacturer.

Stabilityof drug substance
The active substance from the first manufacturer is stable for 36 months when stored under the stated conditions. For the second supplier the active substance is stable for 24 months if stored at a temperature at 2-8 °C in the proposed package. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients justified and their functions have been explained. All excipients used are well known. The choices of the packaging and
manufacturing process are justified.

The aim of the product development was to extend the innovator formulation Eltroxin 50 µg and 100 µg tablets. The new range includes 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg tablet strengths.

The main bioequivalence study was performed on one batch (200 µg) with the same composition as the commercial batches. The reference product used for this bioequivalence study is Euthyrox 200 µg
(Merck Germany, DE/H/0284/008/MR). The second study was a single dose pharmacokinetic and dose proportionality study of Eltroxin 50, 100 and 200 µg tablets at a dose of 600 µg. A third biostudy was performed to compare the currently registered 100 µg Eltroxin product (with tablet mass 150 mg) to the proposed 100 µg product (with tablet mass 75 mg).

A biowaiver for the additional strengths was applied for. The MAH provided data to show similarity in dissolution profiles. The dissolution profiles were similar for most strengths and batches. For some strengths and under some of the test conditions, similarity of dissolution profiles was not demonstrated. However, some of these batches (50 µg and 200 µg strengths) were used in a dose proportionality bioequivalence study, which demonstrated bioequivalence. Further justification based on solubility characteristics was provided. In conclusion, dissolution similarity has been sufficiently demonstrated using an appropriate method, and a biowaiver for the additional strengths can be granted from a chemical-pharmaceutical point of view.

Breakability of the 25 µg tablet has been demonstrated according to the Ph. Eur. sub-division test for tablets. Overall, the pharmaceutical development has been described in sufficient detail.

Manufacturing process

The manufacturing process for levothyroxine sodium tablets includes preparation of a trituration of the drug substance with microcrystalline cellulose, mixing, sieving, blending and compressing. As the total amount of active substance present in the formulation is less than 2% the manufacturing process is considered as a non-standard process. The MAH applied a matrix approach and provided process validation data for the most critical 25 µg strength, for 2 inter-mediate strengths (88 µg and 100 µg), and the lowest & highest strengths (50 µg and 200 µg). For each of these strengths 3 batches were validated. This approach is considered acceptable and the provided validation data are considered satisfactory. In addition the MAH committed to validate the tablet strengths that have not been validated yet (75 µg, 112 µg, 125 µg, 137 µg, 150 µg and 175 µg) post authorisation.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, average mass, uniformity of mass, hardness, dimensions, friability, disintegration time, moisture content, HPLC assay, identification, related
substances, content uniformity, uniformity of dosage units, dissolution, residual solvents, microbiological tests and subdivision of tablets (25 µg). The specifications are in line with the Ph. Eur. or USP. The test methods which are used in both release and shelf-life specifications have the same specification limits except for hardness and related substances. The analytical methods have been adequately described and validated. The stability indicating properties of the assay and related substances method has been demonstrated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specifications.

Stability of drug product

Full stability data on the product has been provided for three full-scaled batches of each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months) for the 25-50-100-150-200 µg strengths. For the remaining strengths a matrix approach has been applied; however, at 12-18-24 months full stability data is available. The batches were stored in 40 cc white multilayer HDPE bottle; polypropylene closure with induction seals liner and 1.0 g oxygen absorber.
Stability results showed that at accelerated conditions out of specifications were observed. For some tablet strengths at various conditions deviating results were found, and this resulted in 3 different
storage conditions for the 11 tablet strengths. Nevertheless it is correct to base all storage conditions on actual stability data. Based on the available stability data above the proposed shelf-life of 2 years can be accepted.
The applicant provided in-use stability of limited in-use test periods: 67 days at 25°C/60% RH for the 25 µg strength (for tablets having been stored before for 24 months at 25°C/60% RH) and 30 days at 30°C/75% RH for 50 µg tablets (having been stored

before for 18 months at 30°C/75% RH). Test parameters for 25 µg tablets were appearance, assay, related substances, dissolution and microbiological testing. Test parameters for the 50 µg tablets were appearance, assay, related substances, average hardness, friability, disintegration time, water content, dissolution and microbiological testing.

In the 50 µg/30 days study no deviating results were observed. Results after 67 days for the 25 µg tablets also meet the set specifications, although some assay and dissolution decrease and increase for total impurities have been observed. The MAH committed to perform in-use stability studies on 28-, 50- and 100-tablet packs for the 25 µg and 200 µg validation batches. The following in-use stability claim is included in the SmPC: "After opening of the HDPE container the tablets should be used within 2 months". In view of the 112 tablet bottle as the maximum pack size, the minimum in use period would be 112 days. Additional in-use stability data in support of this period will be provided post authorisation.

Specific measures concerning the prevention of the transmission of anima lspongiform 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. The raw materials used for the production of magnesium stearate are not of animal origin and do not come into direct contact with such materials.

II.4 Discussion on chemical,pharmaceutical and biological aspects

CMD(h) referral

Grounds for referral
The procedure was referred to the CMD(h) due to a different point of view between RMS and CMS regarding the required dissolution specification limits for these generic levothyroxine products to ensure that batches will show a batch to batch consistency based on the dissolution profiles of the biobatches, and thus to ensure a satisfactory *in-vivo*behaviour for all future commercial batches.

Outcome
The CMD(h) requested the CHMP's Quality Working Party (QWP) to provide a scientific opinion on the dissolution specifications required for these products. As the MAH has amended the dissolution specifications in line with the feedback of the QWP, the issue is considered resolved and agreement has been reached.

Quality conclusion
Overall, based on the submitted dossier, the member states consider that a proven chemical- pharmaceutical quality has been demonstrated for Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to validate the tablet strengths that have not been validated yet (75 µg, 112µg, 125 µg, 137 µg, 150 µg and 175 µg).
- The MAH committed to test homogeneity on the final blend on all process validation batches of all product strengths, thereafter on the first 10 commercial batches of all product strengths. Subsequently this will be performed once a year, if the specific product strength is manufactured.
- The MAH committed to perform in-use stability studies on 28-, 50- and 100-count containers for the 25 µg and 200 µg validation batches. In view of the maximum pack size of 112 tablets, the minimum in use stability period of 112 days should be covered.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)
Since Levothyroxine Natrium Vale is intended for generic 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 formulation of Euthyrox tablets, which are 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.1Introduction

Levothyroxine 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 three pharmacokinetic studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted the following studies:
A single dose bioequivalence study comparing Euthyrox 200 µg tablet (Merck Pharma GmbH, Germany) and Levothyroxine Natrium Vale 200 µg tablet, under fasting conditions.

A single dose pharmacokinetic and dose proportionality study of Levothyroxine Natrium Vale 50, 100 and 200 µg tablets at a dose of 600 µg, under fasting conditions.

A single dose bioequivalence study comparing the current Eltroxin 100 µg tablet (weight 150 mg) and the new 100 µg tablet formulation (tablet weight 75 mg), under fasting conditions.

The choice of the reference products in the bioequivalence studies is justified. As Eltroxin is not available as an innovator product in all of the CMS, a bioequivalence study is submitted using Euthyrox as comparator.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The studies under fasting conditions are justified as according the SmPC l-
thyroxine should be taken on an empty stomach at least half an hour before breakfast. Therefore no food interaction study is needed. In all studies a 600 µg dose has been used to ensure that adequate levothyroxine plasma levels can be measured. This is agreed. Pharmacokinetic, statistical and bio- analytical methods used in the studies are acceptable. Both corrected and uncorrected data on total T4 and on total T3 were measured. However with regard to the endogenous l-thyroxine levels the statistical analysis and bioequivalence evaluation of the pharmacokinetic parameters should be performed on baseline-corrected data of total T4 only. Only these data are reported in the PAR.

The MEB has been assured that the studies have 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).

<u>Pharmacokinetic studies</u>

Studyl– bioequivalencestudy -200µgtablet

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 76 healthy subjects, 68 males and 8 females, aged 20-44
years. Each subject received a single dose of 600 mcg (3 x 200 mcg) of one of the 2 levothyroxine formulations. The tablet was orally administered with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate.

Results
One subject was withdrawn in period I due to an adverse event (vomiting). One subject dropped out before dosing in period I and three subjects dropped out before check-in of period II for personal reasons. The remaining 71 subjects completed the study and were included in the analysis.

The statistical evaluation on baseline corrected total (free+bound) T4 of the 200 µg Euthyrox (Reference, B) and Levothyroxine Natrium Vale (Test, A) formulations is given below.

Table 1

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	189.401	209.849	90.2556	86.8626	93.7812
C_{max}	6.890	7.839	87.9000	84.9950	90.9043

Table 5: (A vs. B) Geometric Means and 90% Confidence Interval for Total (bound+free) T4 (N=71)
**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed d*

Conclusion on the bioequivalence study
The 90% confidence intervals based on the calculated data of baseline corrected total (free+bound) levothyroxine (T4), for AUC0-t and Cmax are within the bioequivalence acceptance range of 80 – 125%. Based on the submitted bioequivalence study Levothyroxine Natrium Vale 200 mcg is considered bioequivalent to Euthyrox 200 mcg tablets.

StudyII -50 ,100 and 200 mcg tablet dose proportionality study
A randomized, open label, balanced, three-treatment, three-period, three-sequence, single dose, crossover, pharmacokinetic and dose proportionality study under fasted conditions. Seventy-five healthy subjects, 63 males and 12 females, aged 19 – 44 years, were included in this study. Each subject received a single dose (total dose 600 µg) of the 50, 100 and 200 µg levothyroxine formulations. The doses were administered as 12 x 50 mcg, 6 x 100 mcg 3 x 200 mcg tablets. The formulations were taken with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. For each subject there were 3 dosing periods, separated by a washout period of 38 days.

Blood samples were taken at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate. The study under fasting conditions and the administration of a 600 mcg dose are justified.

Results
Four subjects dropped out and four subjects were withdrawn from the study:
- One subject in period I due to vomiting
- Three subjects before check-in at period II due to personal reasons
- One subject, in period II due to an adverse event (giddiness)
- One subject during check-in period III as the subject was positive in the drug abuse test (benzodiazepines)
- One subject before check-in at period III due to personal reasons
- One subject in period III due to vomiting.

The remaining 67 subjects completed the study and were included in the analysis.

The geometric mean and 90% confidence interval based for the pharmacokinetic parameters Cmax and AUC0-t for baseline corrected total (bound+free) T4 for all 3 tablet strengths are presented below.

Data are given as A vs. B, C vs. B, A vs. C where: A = Levothyroxine sodium) 50 mcg
B= Levothyroxine sodium) 100 mcg
C = Levothyroxine sodium) 200 mcg

Table2a

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	179.369	160.330	111.8747	106.2184	117.8322
C_{max}	6.607	5.720	115.5029	109.8357	121.4624

Table 1: (A vs. B) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67).
**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Table 2b

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (C)	Reference (B)	C/B	Lower Limit	Upper Limit
AUC_{0-t}	172.094	160.330	107.3372	101.9104	113.0531
C_{max}	6.275	5.720	109.7080	104.3252	115.3686

Table 2: (C vs. B) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67).
**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Table 2c

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (C)	A/C	Lower Limit	Upper Limit
AUC_{0-t}	179.369	172.094	104.2273	98.9576	109.7775
C_{max}	6.607	6.275	105.2821	100.1164	110.7143

Table 3: (A vs. C) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67)
**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Conclusion on study II
Based on the statistical analysis of baseline corrected total (bound and free) T4, it is concluded that dose proportionality is demonstrated between Levothyroxine Natrium Vale 50 mcg tablets and 100 mcg tablets, between Levothyroxine Natrium Vale 200 mcg tablets and 100 mcg tablets and between Levothyroxine Natrium Vale 50 mcg tablets and 200 mcg tablets under fasting conditions.

StudyIII–Eltroxin 100 mcg current formulation vs. new Levothyroxine Natrium Vale 100mcg formulation
A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the Eltroxin 100 mcg tablet with the new 100 mcg levothyroxine sodium tablet formulation of Vale Pharmaceuticals Limited. The new formulation was developed with a tablet weight of 75.0 mg instead of the150.0 mg current Eltroxin tablet.

Seventy-six healthy subjects, 52 males and 24 females, aged 20–44 years, were included in this study. Each subject received a single dose (total dose 600 mcg) of the 100 mcg levothyroxine
formulations. The tablets were administered in solid form with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were taken at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate. The study under fasting conditions and the administration of a 600 mcg dose are justified.

Results
One subject dropped out before dosing of period I due to personal reasons. The remaining 75 subjects completed the study and were included in the analysis.

The statistical evaluation on baseline corrected total (free+bound) T4 of the current Eltroxin 100 mcg (Reference, B) and Levothyroxine Natrium Vale 100 mcg formulation applied for (Test, A) is given below.

Table 3

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	163.141	152.120	107.2450	100.1410	114.8529
C_{max}	5.710	5.463	104.5217	98.4222	110.9993

Table 4: (A vs. B) Geometric Means and 90% Confidence Interval for Total (bound+free) T4 (N=75)
**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Conclusion on study III
Based on the pharmacokinetic parameters of baseline corrected total (free+bound) levothyroxine (T4), the current Eltroxin 100 µg and the new levothyroxine Natrium Vale 100 µg tablets are bioequivalent.

Biowaiver
The MAH applied for a biowaiver for the 25 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.

IV.3 Risk Management Plan
The MAH has not submitted a risk management plan, which was acceptable at the time of submission of this application. The member states considered that the regulatory requirements for the pharmacovigilance system description were adequately fulfilled.

IV.4Discussion 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 the reference product. Dose proportionality of the Levothyroxine Natrium Vale 50, 100 and 200 µg tablets has been demonstrated at a dose of 600 µg. Bioequivalence has also been shown between the current Eltroxin 100 µg tablet and the new 100 µg tablet formulation. Based on the data submitted, the member states concluded that this generic formulation can be used instead of the reference product.

V. OVERALL CONCLUSIONS

Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 100 mcg, , 125 mcg, 150 mcg, 175 mcg and 200 mcg tablets have a proven chemical-pharmaceutical quality and are generic forms of Euthyrox 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.

This application was discussed with the chair of the Board on 8 January, 5 March, 16 April and 3 June 2014. The Board agrees with the QWP's opinion regarding the limits of the dissolution specification. The MEB maintained its positive position regarding this application.

Agreement between member states was reached during a CMD(h) referral. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levothyroxine Natrium Vale with the reference product, and have therefore granted a marketing authorisation. The CMD(h) referral procedure was finalised with a positive outcome on 20 June 2014. In the Netherlands the marketing authorisation was granted on 24 November 2015.

VI. REVISION DATE

24 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From NL/H/2700/001-008 to IE/H/1225/001-008	N/A	26 April 2022	N/A