Risk Management Plan

Active substance(s) (INN or common name):	**Levothyroxine sodium**
Pharmacotherapeutic group (ATC Code):	**H03AA01**
Name of Marketing Authorization Holder or Applicant:	**Merck KGaA** **Frankfurter Straße 250** **D-64293 Darmstadt** **Telephone +49 61 51-72-0** **Telefax +49 61 51-72 69 14** **e-mail: GlobalDrugSafety@merckgroup.com**
Products concerned (brand names):	**Euthyrox®, Levothyrox®, Eutirox®, Supratirox®, Euthyrox N®**
Data lock point for this RMP:	**05 Oct 2016**
Version number:	**5.0**
Date of final sign off:	**Document signed electronically, see date of e-signature at the end of the document**

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Table of Contents

Signatures 2
Table of Contents 3
Table of Tables 6
Table of Figures 7
List of Abbreviations 8
Part I: Product(s) Overview 12
Overview of Versions 14
Recent RMP Versions under Evaluation 15
Part II: Module SI - Epidemiology of the Indications and Target Population 18
SI.1.1 Epidemiology of the Disease Hypothyroidism 18
SI.1.2 Epidemiology of Thyroid Cancer 21
SI.1.3 Epidemiology of Euthyroid Goitre/Relapse of Euthyroid Goitre 25
SI.2 Concomitant Medication(s) in the Target Population 27
SI.3 Important Co-morbidities Found in the Target Population 27
Part II: Module SII - Non-clinical Part of the Safety Specification 29
SII Conclusions on Non-clinical Data 31
Part II: Module SIII - Clinical Trial Exposure 32
Part II: Module SIV - Populations not Studied in Clinical Trials 33
Part II: Module SV - Post-authorization Experience 34
SV.1 Action Taken by Regulatory Authorities and/or Marketing Authorization Holders for Safety Reasons 34
SV.2 Non-study Post-authorization Exposure 34
SV.2.1 Method Used to Calculate Exposure 35
SV.3 Post-authorization Use in Populations not studied in Clinical Trials 35
SV.4 Post-authorization Off-label Use 36
SV.5 Epidemiological Study Exposure 41
Part II: Module SVI - Additional EU Requirements for the Safety Specification 43
SVI.1 Potential for Harm from Overdose 43
SVI.2 Potential for Transmission of Infectious Agents 43
SVI.3 Potential for Misuse for Illegal Purposes 44

SVI.4 Potential for Medication Errors 45
SVI.4.1 Description of Medication Errors during the Clinical Trial Program....46
SVI.4.2 Preventive Measures for the Final Product Being Marketed....46
SVI.4.3 Effect of Device Failure....46
SVI.4.4 Reports of Medication Errors with the Marketed Product....46
SVI.5 Potential for Off-label Use....47
SVI.6 Specific Pediatric Issues 48
SVI.6.1 Issues Identified in Pediatric Investigation Plans 48
SVI.6.2 Potential for Pediatric Off-label Use 51
SVI.7 Conclusions....51
Part II: Module SVII - Identified and Potential Risks 52
SVII.1 Newly Identified Safety Concerns (Since this Module was last Submitted)....52
SVII.2 Recent Study Reports with Implications for Safety Concerns 53
SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)....53
SVII.4 Identified and Potential Interactions....66
SVII.4.1 Overview of Potential for Interactions 66
SVII.4.2 Important Identified and Potential InteractionsSVII.5 Pharmacological Class Effects 69
SVII.5.1 Pharmacological Class Risks Already Included as Important Identified or Potential Risks 69
SVII.5.2 Important Pharmacological Class Effects not Discussed Above....69
Part II: Module SVIII - Summary of the Safety Concerns 70
Part III: Pharmacovigilance Plan 71
III.1 Safety Concerns and Overview of Planned Pharmacovigilance Actions....71
III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimization Measures....72
III.3 Studies and Other Activities Completed Since last Update of Pharmacovigilance Plan....73
III.4 Details of Outstanding Additional Pharmacovigilance Activities....73
III.5 Summary of the Pharmacovigilance Plan....73

III.5.1 Table of On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan....73
III.5.2 Table of Completed Studies/Activities from the Pharmacovigilance Plan....73
Part IV: Plans for Post-authorization Efficacy Studies....74
IV.1 Applicability of Efficacy to all Patients in the Target Population....74
IV.2 Tables of Post-authorization Efficacy Studies....74
IV.3 Summary of Post authorization Efficacy Development Plan....74
IV.4 Summary of Completed Post Authorization Efficacy Studies....74
Part V: Risk Minimization Measures....75
V.1 Risk Minimization Measures by Safety Concern....75
V.2 Risk Minimization Measure Failure (if applicable)....79
V.2.1 Analysis of Risk Minimization Measure(s) Failure....79
V.2.2 Revised Proposal for Risk Minimization....79
V.3 Summary Table of Risk Minimization Measures....80
Part VI: Summary of Activities in the Risk Management Plan by Product....82
VI.1 Elements for Summary Tables in the EPAR....82
VI.1.1 Summary Table of Safety Concerns....82
VI.1.2 Table of On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan....82
VI.1.3 Summary of Post Authorization Efficacy Development Plan....82
VI.1.4 Summary Table of Risk Minimization Measures....83
VI.2 Elements for a Public Summary....85
VI.2.1 Overview of Disease Epidemiology....85
VI.2.2 Summary of Treatment Benefits....86
VI.2.3 Unknowns Relating to Treatment Benefits....87
VI.2.4 Summary of Safety Concerns....87
VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern....91
VI.2.6 Planned Post Authorization Development Plan....92
VI.2.7 Summary of Changes to the Risk Management Plan over Time....92
Part VII Annexes....96
References....97

Table of Tables

Table 1 Incidence rate in thyroid cancer in several countries, age-adjusted and per 100,000 person-years 23

Table 2 Estimated patient exposure to levothyroxine (as reported in PSURs) 34

Table 3 Cumulative list of ICSRs retrieved with the applied query from the Company's safety database since its existence up to 05 Oct 2016 37

Table 4 Epidemiological Study Exposure 42

Table 5 Safety concerns from this module (to be carried through to Part II Module SVIII) 51

Table 6 Summary of safety concerns....70

Table 7 Summary of safety concerns and corresponding risk minimization measures 75

Table 8 Major changes to the Risk Management Plan over time 92

Table of Figures

Figure 1 Prevalence of hypothyroidism as demonstrated by several studies....19

Figure 2 Estimated incidence and mortality from thyroid cancer in both genders in 2012 (Ferlay, 2013).....24

Figure 3 Population-based Study results reporting on thyroid volumes obtained at ultrasound investigation vs. median urinary iodine concentration.....26

List of Abbreviations

ACTH	Adrenocorticotrophic hormone
ADR	Adverse Drug Reaction
AF	Atrial fibrillation
AP	Angina Pectoris
APC	Annual Percent Change
ATC	Anatomic Therapeutic Chemical
AV	Atrioventricular
BA	Bioavailability
BE	Bioequivalence
BW	Body Weight
CAS	Chemical Abstracts Service
CH	Congenital Hypothyroidism
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CSDS	Core Safety Data Sheet
DDD	Defined Daily Dose
df	Dosage form
DLP	Data Lock Point
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report

EU	European Union
FDA	Food and Drug Administration
FT3	Free Tri-iodothyronine
FT4	Free Thyroxine
FTI	Free Thyroxine Index
GDS	Global Drug Safety
GMP	Good Manufacturing Practice
GVP	Good Vigilance Practice
HR	Heart Rate
IBD	International Birth Date
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IST	Inappropriate Sinus Tachycardia
INN	International Non-proprietary Name
IQ	Intelligence quotient
KGaA	Kommanditgesellschaft auf Aktien (“partnership limited by shares”)
LD50	Lethal dose 50
LMS	Lead Member State
MAH	Marketing Authorization Holder
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NAG	N-acetyl-ß-d-glucosaminidase
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Health Lung and Blood Institute

OR	Odds ratio
PAES	Post Authorization Efficacy Study
PBRER	Periodic Benefit Risk Evaluation Report
PhV	Pharmacovigilance
PI	Product Information
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSVT	Paroxysmal Supraventricular Tachycardia
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PVC	Polyvinylchloride
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMS	Reference Member State
RSI	Reference Safety Information
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEARS	The Thyroid Epidemiology, Audit and Research Study
TBG	Thyroxine-Binding Globulin
TG Ab	Anti-thyroglobulin
TPO Ab	Thyroxin-Peroxidase Antibody

TSE	Transmissible Spongiform Encephalopathy
TSH	Thyroid Stimulating Hormone
T3	(Total) Tri-iodothyronine
T4	(Total) Thyroxine
UK	United Kingdom

Part I: Product(s) Overview

RMP version 5.0 was prepared as an outcome of the PRAC assessment report (PSUSA/00001860/201601; EMA/CHMP/527154/2016) received on 05 Oct 2016.

Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	October 2016	3.0
	SII Non-clinical part of the safety specification	October 2016	3.0
	SIII Clinical trial exposure	October 2016	3.0
	SIV Populations not studied in clinical trials	October 2016	3.0
	SV Post-authorization experience	October 2016	3.0
	SVI Additional EU requirements for the safety specification	October 2016	3.0
	SVII Identified and potential risks	October 2016	3.0
	SVIII Summary of the safety concerns	October 2016	3.0
Part III Pharmacovigilance Plan		October 2016	3.0
	III.3 Studies and Other Activities Completed Since last Update of Pharmacovigilance Plan	October 2016	3.0
Part IV Plan for post-authorization efficacy studies		October 2016	3.0
Part V Risk Minimization Measures		October 2016	3.0

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part VI Summary of RMP		October 2016	3.0
	VI.2.7 Summary of Changes to the Risk Management Plan Over Time	October 2016	3.0
Part VII	Annex 2 Current or proposed SmPC/PIL	October 2016	3.0
	Annex 3 Worldwide marketing status by country	October 2016	3.0
	Annex 4 Synopsis of clinical trial program	October 2016	3.0
	Annex 5 Synopsis of pharmacoepidemiological study program	October 2016	3.0
	Annex 6 Protocols for proposed and on-going studies in Part III	October 2016	3.0
	Annex 7 Specific adverse event follow-up forms	October 2016	3.0
	Annex 8 Protocols for studies in Part IV	October 2016	3.0
	Annex 9 Synopsis of newly available study reports in Parts III-IV	October 2016	3.0
	Annex 10 Details of proposed additional risk minimization activities	October 2016	3.0
	Annex 11 Mock up examples	October 2016	3.0
	Annex 12 Other supporting data	October 2016	3.0

Overview of Versions

This is the RMP version 5.0 for levothyroxine.

Recent RMP Versions under Evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	Not applicable	Not applicable

Invented name(s) in the European Economic Area (EEA)	Euthyrox®, Levothyrox®, Eutirox®, Supratirox®, Euthyrox N®
Further Invented name(s) outside the EEA, not mentioned above	YOU JIA LE® (China), Uthyrox® (India, planned), Eutiroks® (Russia), Novothyrox® (USA, not marketed), Levotiroxina sodica®, Levotiroxina G®
Authorization procedure	National Procedure Mutual Recognition Procedure (MRP)
Brief description of the product including: • chemical class • summary of mode of action • composition	• Thyroid hormone (ATC Code H03AA01) • Same pharmacological mode of action as the natural thyroid hormone • Sodium salt; synthetically produced thyroid hormone, chemically identical to the naturally secreted hormone by the follicular cells of the thyroid gland
Indications in the EEA Current	• 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 • *applies only to tablets of 25 – 100 µg:* Concomitant therapy during anti-thyroid medicinal treatment of hyperthyroidism • *applies only to tablets of 100 µg, 150 µg, 200 µg:* Diagnostic use for thyroid suppression testing
Proposed (if applicable)	Not applicable
Posology and route of administration in the EEA Current	**Route of administration:** Oral **Posology**: Treatment of euthyroid goitre 75 – 200 µg Prophylaxis of relapse after surgery for euthyroid goitre: 75 – 200 µg Substitution therapy in hypothyroidism Initial dose in adults: 25 - 50 µg Initial dose in children: 12.5 – 50 µg Maintenance dose in adults: 100 - 200 µg Maintenance dose in children: 100-150 µg/ m² body surface area Suppression therapy in thyroid cancer: 150- 300 µg Applies only to tablets of 25 - 100 µg: Concomitant therapy during antithyroid medicinal treatment of hyperthyroidism 50 -100 µg

	Applies only to tablets of 150 µg: Diagnostic use for thyroid suppression testing 75 µg (½ tablet), week 4 and 3 prior to test 150 µg (1 tablet), week 2 and 1 prior to test Applies only to tablets of 100 – 200 µg: Diagnostic use for thyroid suppression testing 200 µg, week 2 and 1 prior to test
Proposed (if applicable)	Not applicable
Pharmaceutical form and strengths Current formulation	Tablets Strengths available: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 or 200 µg of levothyroxine sodium **Excipients used:** Lactose Maize starch Gelatin Croscarmellose natrium Magnesium stearate **Packaging materials:** PVC (polyvinylchloride)/ aluminum blister
Proposed new formulation of levothyroxine sodium tablets	Tablets Strengths available: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 or 200 µg of levothyroxine sodium **Excipients used:** Mannitol Maize starch Gelatin Croscarmellose natrium Citric acid, anhydrous Magnesium stearate **Packaging material:** Aluminum/ aluminum blister

Country and date of first authorization worldwide	Germany	27 Oct 1972
Country and date of first launch worldwide	Germany	27 Oct 1972
Country and date of first authorization in the EEA	Germany	27 Oct 1972

Is the product subject to additional monitoring in the EU? Yes ☐ No X

Part II: Module SI - Epidemiology of the Indications and Target Population

SI.1.1 Epidemiology of the Disease Hypothyroidism

Thyroid disorders are among the most frequent medical conditions and can be linked to dietary, congenital, pregnancy-related, autoimmune or iatrogenic causes. Hypothyroidism can be classified by primary causes (Hashimoto´s disease, thyroidectomy, radioiodine therapy, neck irradiation) or secondary/tertiary causes (thyrotropin or thyrotropin-releasing hormone deficiencies).

Almost one-third of the world's population lives in areas of iodine deficiency (Zimmerman, 2008). In areas where the daily iodine intake is below 50 µg, goitre is usually endemic, and when the daily intake falls below 25 µg iodine, hypothyroidism can be the consequence. In iodine-replete areas, most patients with thyroid disorders have an autoimmune disease, ranging through primary atrophic hypothyroidism, Hashimoto's thyroiditis to thyrotoxicosis caused by Graves' disease. Congenital hypothyroidism affects about one newborn in 3,500 to 4,000 births and is a treatable cause of mental retardation (Vanderpump, 2005). There is an inverse relationship between age at diagnosis and intelligence quotient (IQ) in later life. In iodine-replete areas, 85 % of the cases are due to sporadic developmental defects of the thyroid gland (thyroid dysgenesis) such as the arrested migration of the embryonic thyroid (ectopic thyroid) or a complete absence of thyroid tissue (athyreosis). The remaining 15 % have thyroid dyshormonogenesis defects transmitted by an autosomal recessive mode of inheritance. Clinical diagnosis occurs in less than 5 % of newborns with hypothyroidism because symptoms and signs are often minimal. In adults, the presence of high serum concentrations of thyroid antibodies (anti-thyroid peroxidase antibodies [TPOAb] and anti-thyroglobulin [TGAb]) correlates with the presence of focal thyroiditis in thyroid tissue obtained by biopsy and at autopsy from patients with no evidence of hypothyroidism during life. Early post-mortem studies confirmed histological evidence of chronic autoimmune thyroiditis in 27 % of adult women, with a rise in frequency over 50 years, and 7 % of adult men, and diffuse changes in 5 % of women and 1 % of men (Vanderpump, 2005).

Incidence of hypothyroidism

The 20-year follow up of the Whickham cohort provided incidence data and allowed the determination of risk factors for spontaneous hypothyroidism in this 20-years period (Vanderpump, 1995). The mean annual incidence of spontaneous hypothyroidism in the surviving women during the 20 year follow up period was 3.5 per 1000 (95 % confidence interval [CI] 2.8 to 4.5), increasing to 4.1 per 1000 (95 % CI 3.3 to 5.0), if all cases including those who had received destructive treatment for thyrotoxicosis were included. The mean annual incidence during the 20-year follow-up period in men (all spontaneous except for one case of lithium-induced hypothyroidism) was 0.6 per 1000 (95 % CI 0.3 to 1.2). The other incidence data for hypothyroidism are from short (and often small) follow-up studies (McGrognan, 2008). In elderly subjects, the annual incidence rate of hypothyroidism varies widely between 0.2 and 7 % in the available studies. Data from the large population study in Tayside UK, have demonstrated that the standardized incidence of primary hypothyroidism varied between

3.90 and 4.89 per 1000 women per year between 1993 and 2001. The incidence of hypothyroidism in men significantly increased from 0.65 to 1.01 per 1000 per year (p = 0.0017). The mean age at diagnosis of primary hypothyroidism decreased in women from 1994 to 2001 (Flynn, 2004; Leese, 2008).

Prevalence of hypothyroidism

In iodine-replete communities, the prevalence of spontaneous hypothyroidism is between 1 % and 2 %, and it is more common in older women and ten times more common in women than in men (Vanderpump, 2005). In the Whickham survey, the prevalence of newly diagnosed overt hypothyroidism was 3 per 1000 women. The prevalence of previously diagnosed and treated hypothyroidism was 14 per 1000 women, increasing to 19 per 1000 women when possible but unproven cases were included. The overall prevalence in men was less than 1 case per 1000. One third had been previously treated by surgery or radioiodine for thyrotoxicosis. Excluding iatrogenic causes, the prevalence of hypothyroidism was 10 per 1000 women, increasing to 15 per 1000 when possible but unproven cases were included. The mean age at diagnosis was 57 years. Other studies in Northern Europe, Japan and the USA have found the prevalence to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 in men investigated. In the Colorado and NHANES III studies, the prevalence of newly diagnosed hypothyroidism was 4 per 1000 and 3 per 1000 respectively (Canaris, 2000; Hollowell, 2002). The prevalence is higher in surveys of the elderly in the community (Vanderpump, 2005). The overall prevalence of hypothyroidism, including those already taking levothyroxine (T4), in Birmingham, UK, of 1210 subjects aged 60 and over was 4 % of women and 0.8 % of men aged over 60 years. In subjects aged 60 years or more in Framingham, 4 % showed serum TSH concentration greater than 10 mU/L, of whom one-third had low serum T4 concentrations (McGrognan, 2008). Overt hypothyroidism was found in 7 % of 558 subjects aged between 85 and 89 years in Leiden, Netherlands (Gussekloo, 2004).

Figure 1 Prevalence of hypothyroidism as demonstrated by several studies

Study Name	N	Age (Years)	Test	Prevalence n/1000		Incidence n/1000/year		
				Men	Women	Follow-up	Men	Women
Whickham, UK	2779	18+	TSH, T4	0	3.3	20 years	0.6 (0.3–1.2)	3.5 (2.8–4.5)
Colorado, USA	25,862	18+	TSH	4.0				
NHANES III, USA	16,533	12+	TSH	2.0				
Pescopagano, Italy	992	15+	TSH, FT4	0	3.0			
Sapporo, Japan	4110	25+	TSH	2.4	8.5	–	–	–
Copenhagen, Denmark	2656	41–71	TSH, FT4	2.0	5.0			
Memphis/Pitttsburgh, USA	2797	70–79	TSH, FT4	5.4	13.0			
Leiden, Netherlands	558	85–89	TSH, FT4	70				
Tayside, UK (1993–1997)	390,000	0+	Treatment for hypo-thyroidism	–	–	4 years	0.88 (0.80–0.95)	4.98 (4.81–5.17)
Tayside, UK (1997–2001)	390,000	0+	As above			4 years	1.09 (0.95–1.25	4.75 (4.46–5.07)
Göteborg, Sweden	1283	44–66	TSH	–	6.4	4 years	–	1–2
Birmingham, UK	1210	60+	TSH	7.8	20.5	1 year	11.1	
Gothenburg, Sweden	1148	70+	TSH	–	–	10 years	–	2

Risk factors

Epidemiological studies have attempted to explore the risk factors for congenital hypothyroidism. A population-based case-control study was carried out by using the network created in Italy for the National Register of Infants with hypothyroidism (Medda, 2005). An increased risk was detected in twins by a multivariate analysis (odds ratio (OR) = 12.2, 95% confidence interval (CI): 2.4-62.3). A statistically significant association with additional birth defects, female gender and gestational age >40 weeks was also confirmed. Although not significant, an increased risk was observed among infants with a family history of thyroid diseases among parents (OR = 1.9, 95% CI: 0.7-5.2). Maternal diabetes was also found to be slightly associated (OR = 15.7, 95% CI: 0.9-523) in infants who were large for gestational age.

Recognized risk factors for acquired hypothyroidism include female gender, age over 60, a family history of thyroid disease or any autoimmune disease, Sjögren's syndrome, pernicious anemia, type 1 diabetes, rheumatoid arthritis, or lupus, a history of Turner's syndrome or other autoimmune disorders, anti-thyroid medications (treatment for hyperthyroidism) or treatment with radioactive iodine (treatment for thyroid cancer), thyroid surgery (as treatment for thyroid cancer or symptomatic goitre), exposure to radiation to the neck or upper chest area (Vanderpump, 2005).

Certain medical treatments and drugs have been linked to increase the risk of developing an underactive thyroid; these include Interferon Beta-1b, Interleukin-4, immunosuppressants, antiretrovirals, monoclonal antibody, bone marrow transplant and amiodarone.

Recently, lithium therapy for bipolar disorders has been correlated to the development of hypothyroidism. 143 participants in the Pittsburgh study of Maintenance Therapies in Bipolar Disorder who did not have a thyroid abnormality at entry were evaluated. Thirty-six percent of the 143 patients developed abnormal TSH and/or FTI (free thyroxine index) values. Thirty-eight percent of the 135 patients who received lithium developed abnormal TSH and/or FTI, spent significantly longer time in the acute treatment phase ($t = -3.6$, $df = 133$, $p = 0.0004$), and had significantly higher mean Hamilton Scale for Depression scores over the course of the maintenance phase ($t = -2.3$, $df = 71.6$, $p = 0.03$). Time on lithium and development of abnormal TSH and/or FTI were positively correlated ($r = 0.25$, $p = 0.004$). The authors concluded that thyroid dysfunction can be frequent in patients exposed to lithium treatment for bipolar I disorder; lithium-induced thyroid disorder also appears to be correlated with a slower response to acute treatment, and may be related to more relapses of bipolar disorders in the long-term (Fagiolini, 2006).

Mortality

There is considerable heterogeneity in the studies evaluating mortality attributable to hypothyroidism and major confounding by treatment.

All-cause mortality among patients with subclinical hypothyroidism has been evaluated in four meta-analyses. Although these meta-analyses had considerable differences in exclusion and inclusion criteria, the overall results from all four meta-analyses show a trend towards increased all-cause mortality in individuals with subclinical hypothyroidism compared with the corresponding euthyroid control groups: the pooling of data from the 12 studies in subclinical

and 10 studies in overt hypothyroidism led to global mortality estimates of 1.17 (1.00–1.37) and 1.24 (0.94–1.62), respectively. However, these results were highly confounded by treatment (Thvilum, 2012).

In a more recent observational cohort study from January 1, 1978 until December 31, 2008 using record-linkage data from nationwide Danish health registers, 3587 singletons and 682 twins diagnosed with hypothyroidism were identified. Hypothyroidism was associated with an excess mortality of around 50%, which to some degree was explained by co-morbidity. In addition, the finding of an association between hypothyroidism and mortality within disease discordant dizygotic but not monozygotic twin pairs indicates that the association between hypothyroidism and mortality is also influenced by genetic confounding (Thvilum, 2013).

Main treatment options

Whatever the cause of acquired hypothyroidism is, therapy consists of lifelong thyroid hormone administration (Hehrmann, 1994; Lazarus, 1996; Singer et al., 1995). Levothyroxine is the treatment of choice for the routine management of hypothyroidism (Singer et al., 1995), therapy consists of thyroid hormone replacement unless the hypothyroidism is transient (as after painless thyroiditis or subacute thyroiditis) or reversible (due to a drug that can be discontinued).

The goal of therapy is restoration of the euthyroid state, which can be readily accomplished in almost all patients by oral administration of synthetic thyroxine (T4). Appropriate treatment reverses all the clinical manifestations of hypothyroidism. Synthetic thyroxine (T4) is given as treatment for correction of hypothyroidism. Approximately 80 percent of a dose of T4 is absorbed and, because the plasma half-life of T4 is long (seven days), once-daily treatment results in nearly constant serum T4 and triiodothyronine (T3) concentrations when a steady state is reached (Fish, 1987).

T4 is a prohormone with very little intrinsic activity. It is deiodinated in peripheral tissues to form T3, the active thyroid hormone. This deiodination process accounts for about 80 percent of the total daily production of T3 in normal subjects; as a result, serum T3 concentrations are within the normal range in hypothyroid patients receiving adequate T4 therapy. This was illustrated in a prospective study of recently athyreotic patients receiving T4 therapy to normalize serum TSH concentrations; serum T3 levels on treatment were, in most cases, comparable to the patients' pre-operative T3 values (Jonklaas, 2008). The prohormone nature of T4 is an advantage over other thyroid hormone preparations, because the patient's own physiologic mechanisms control the production of active hormone.

SI.1.2 Epidemiology of Thyroid Cancer

Globally, thyroid cancer accounts for 2.1% of all cancers (excluding non-melanoma skin cancer) (Ferlay, 2012). By gender, thyroid cancer accounts for 0.9% of all cancers in men and for 3.5% of all cancers in women, excluding non-melanoma skin cancer. Based on recent data, thyroid cancer ranks 16 amongst all cancers, and in men it ranks 18 globally (Ferlay, 2012). However, thyroid cancer is the eighth most common cancer in women (Ferlay, 2012); in Italy, it is the second most frequent cancer in women below 45 years of age (Dal Maso, 2011).

Thyroid cancer is the most common endocrine cancer, approximately 1.0%–1.5% of all new cancers diagnosed each year in the USA (Curado, 2007). In USA, the American Cancer Society estimated 62,980 new cases of thyroid cancer in 2014, with approximately 1,890 deaths occurring amongst the estimated 566,708 people living with thyroid cancer in the United States. The US age-adjusted new cases of thyroid cancer were of 14.3 per 100,000 men and women per year (Davies, 2014). By gender, the incidence rate was of 21.4 in women and of 6.9 in men per 100,000 US subjects (Davies, 2014). The number of deaths of thyroid cancer was of 0.5 per 100,000 men and women per year (The American Cancer Society, 2014).

Table 1 summarizes the international thyroid cancer incidence rates from recent publications. Figure 2 presents estimated incidence and mortality from thyroid cancer in both genders in 2012. In Europe (2012), the highest world age-standardized incidence rates for thyroid cancer were observed in Italy for men and in Lithuania for women; the lowest rates were observed in Montenegro for men and in Albania for women (Ferlay, 2013). Although there is considerable variation in cancer incidence worldwide (Ferlay, 2012), the incidence of thyroid cancer has continuously increased in the last three decades all over the world (Pellegriti, 2013). This trend is present on every continent (Pellegriti, 2013) except Africa (Kilfoy, 2009), where detection is possibly insufficient. Reports of escalating incidence over the past decades have been published in Italy, Iceland, Canada, China, Denmark, Finland, France, Israel, Japan, Spain, Switzerland, United Kingdom, USA, and the South Pacific (Pellegriti, 2013; Wartofsky, 2010). The increasing incidence is indicated by the annual percent change (APC) that in the USA was 2.4% from 1980 to 1997 and 6.6% from 1997 to 2009 (both genders) (The American Cancer Society, 2010). Only in few countries (Norway, Sweden) thyroid cancer incidence decreased (Kilfoy, 2009).

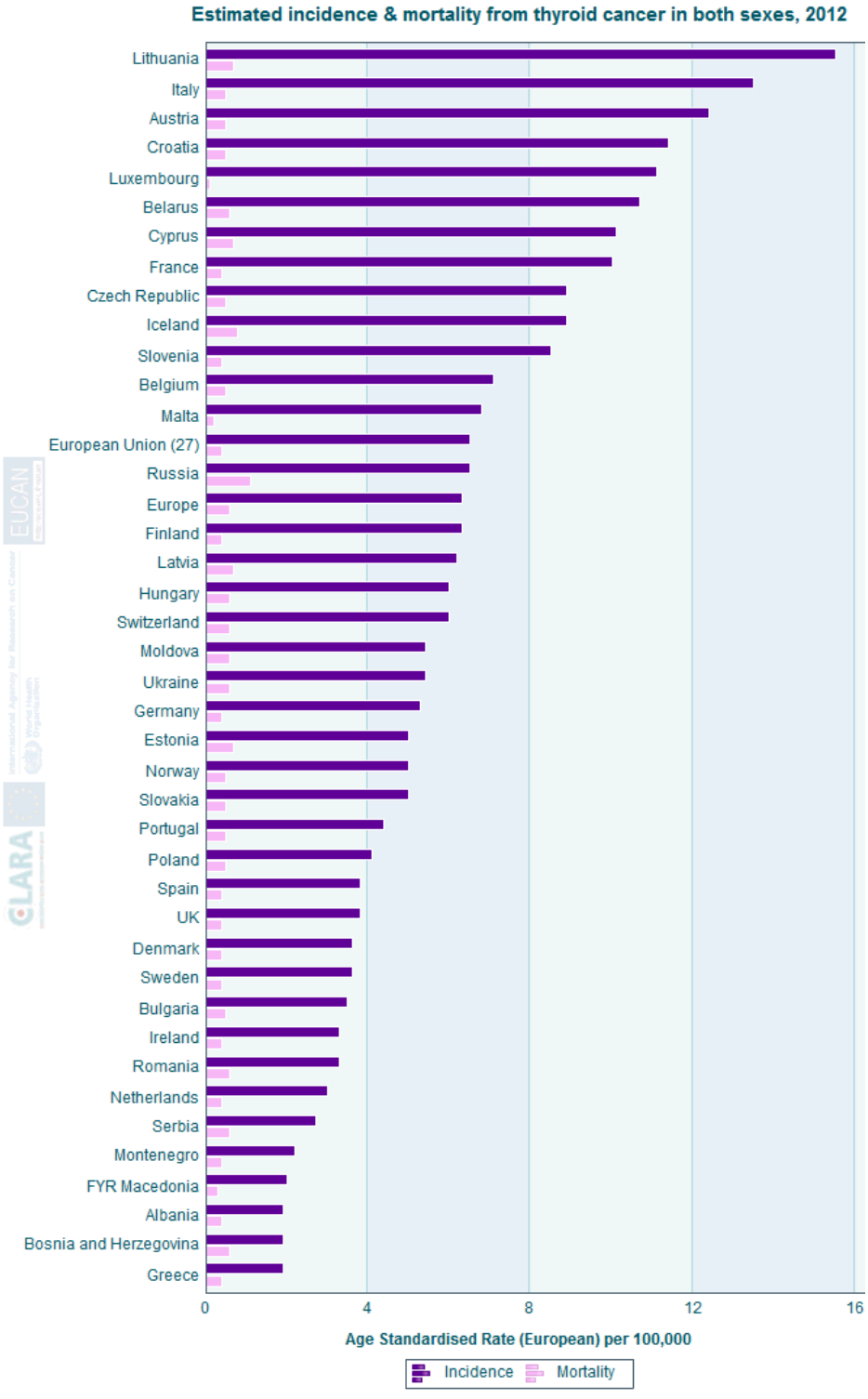
Genetic factors, environmental influences, screening and diagnostic methods, and access to medical care can easily explain the high variability (up to nearly tenfold) in the thyroid cancer incidence by geographic area and ethnicity. Recent reports indicated similar age-specific trends by racial/ethnic groups. Although the lowest rates of thyroid cancer are observed in blacks, the greatest rate of papillary thyroid cancer acceleration occurs in black females (Aschebrook-Kilfoy, 2013). Male and female annual percent change was 6.3% and 7.1% for white patients, 4.3% and 8.4% for black, 4.2% and 6.7% for Hispanic and 3.4% and 6.4% for Asian/Pacific Islander patients respectively (Kilfoy, 2009). In any case, the continuously increasing rate of thyroid cancer is independent of the underlying incidence rates (Kilfoy, 2009).

Data reported by SEER for the period 1988-2009 (The American Cancer Society, 2014), indicates a significant increase of thyroid cancer mortality (+0.8% annual percent change, APC), primarily in males. This increase in mortality rate occurred in spite of early diagnosis and better treatment of high risk thyroid cancers, and has also been observed in Europe (Pellegriti, 2013).

Table 1 **Incidence rate in thyroid cancer in several countries, age-adjusted and per 100,000 person-years**

Country	Source	Year data correspond to	Overall	Male	Female
UK	(McNally, 2012)	2005	Not specified	15-29 y: 3.3 30-49 y: 12.7	15-29 y: 12.4 30-49 y: 42.3
Scotland	(Reynolds, 2005)	2002	Not specified	1.25	3.54
Denmark	(Blomberg, 2012)	2008	Not specified	1.57	4.11
Italy	(Dal Maso, 2011)	2005	Not specified	3	8
Canada	(Pathak, 2013)	2010	9.37	4.94	13.75
USA	(Davies, 2014)	2009	14.3	6.9	21.4
Australia	(Haggar, 2012)	2007	Not specified	10	4

Figure 2 **Estimated incidence and mortality from thyroid cancer in both genders in 2012 (Ferlay, 2013)**



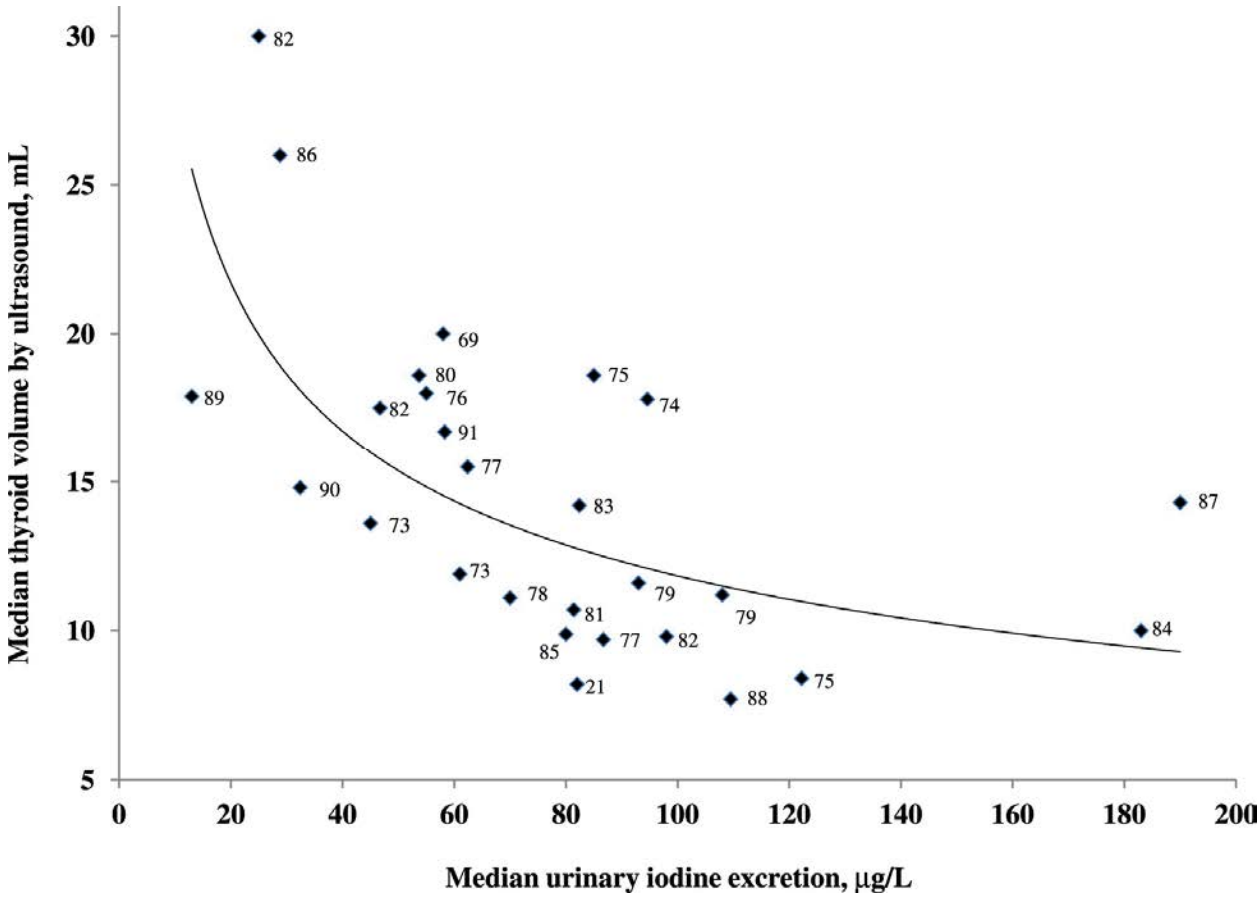
SI.1.3 Epidemiology of Euthyroid Goitre/Relapse of Euthyroid Goitre

More than one tenth of the world population is to some degree affected by goitre and most of these goitres show nodules (Carlé, 2014). Simple (diffuse) physiological goitre is the most common thyroid disease in the community (Vanderpump, 2011). Autopsy and ultrasound studies provide robust estimations of thyroid volumes, and to a somewhat lesser degree also on thyroid nodule prevalence (Vanderpump, 2005).

The prevalence of goitre may depend on several factors (Hegedus, 1990). Genes have some impact (Carlé, 2014), but undoubtedly iodine deficiency is the major cause of goitre worldwide. Therefore, goitre is a condition predominantly seen in iodine deficient areas of the world, and currently almost one-third of the world's population lives in areas of iodine deficiency (Zimmerman, 2009). The prevalence of goitre in areas of severe iodine deficiency can be as high as 80%. In areas where the daily iodine intake is <50 µg, goitre is usually endemic, and when the daily intake falls <25 µg, congenital hypothyroidism is seen.

Thyroid volume provides a more accurate measure to established comparison between studies; given that in prevalence studies the definition of thyroid goitre used varies largely. In iodine-replete areas, a normal thyroid gland is <18 mL in women, and <25 mL in men. Figure 3 presents the results of 21 studies, with more than 100,000 thyroid ultra-scans performed. Clearly, iodine intake is a major determinant for thyroid volumes also in these studies. The median thyroid volume spanned from 20 mL in areas with moderate iodine insufficiency to 15 mL in mildly iodine insufficient areas, whereas values around 10 mL were obtained in countries with optimal iodine intake (Carlé, 2014).

Figure 3 **Population-based Study results reporting on thyroid volumes obtained at ultrasound investigation vs. median urinary iodine concentration**



Most ultrasound studies revealed an inverse U-shaped association between thyroid volume and age with the highest values among 40–60 year old subjects (Carlé, 2014). The greatest prevalence of simple diffuse goitre is in pre-menopausal women, and the ratio of women to men is at least 4:1 (Tunbridge, 1977). When iodine intake is low, thyroid volume tends to increase with age (at least up to 40–60 years of age). This increase in volume is mostly driven by an increase in the prevalence of multinodular goitre (Carlé, 2014).

With regards to European data, in mildly and moderately iodine-deficient regions in Denmark, goitre (as determined by ultrasonography) was present in 15 and 22.6 percent of the population, respectively (Knudsen, 2000) before the legislation on mandatory iodization of salt for households and for bread production in 2000. In Germany, an area of relative iodine deficiency, thyroid nodules or goitre were found in 33% of 96 278 working adults aged 18–65 years screened by an ultrasound scan (Reiners, 2004). Thyroid nodules >1 cm were found in 12% of this population and increased with age.

In the United States, where significant iodine deficiency does not exist, multinodular goitre, chronic autoimmune (Hashimoto's) thyroiditis, and Graves' disease are more common causes of goitre. In the elderly, multinodular goitre is most common.

SI.2 Concomitant Medication(s) in the Target Population

Hypothyroidism patients usually show higher levels of total cholesterol, low-density lipoproteins, triglycerides, and other lipid molecules associated with heart disease. Hypothyroidism is especially related to depression (Haggerty, 1995), and frequently observed in bipolar patients (Bauer, 2008). Myxedema is associated with severe mental disorders including psychoses. Both subclinical hypothyroidism and subclinical hyperthyroidism increase the risk for Alzheimer's disease, especially in women (Tan, 2008). Co-medications associated with hypothyroidism will cover these co-morbidities according to their standard treatments as specified in clinical guidelines.

Regarding thyroid cancer, hypertension is the most frequent co-morbidity (18%), followed by 'other cancers' (7%), cardiovascular diseases (6%) and diabetes mellitus (6%) (Kuijpens, 2006). Therefore, most frequent co-medications in patients with thyroid cancer will be related with this co-morbidity profile and follow guidelines as regularly updated in each country.

Euthyroid goitre, diffuse or nodular, in which thyroid gland is normo-functional in terms of thyroxine or T3 levels produced, is not associated with co-morbidities and therefore does not require special co-medications.

SI.3 Important Co-morbidities Found in the Target Population

Co-morbidities in Hypothyroidism

In infants, hypothyroidism is the primary cause for intellectual development defects (Zimmermann, 2008). Cretinism arises from a diet deficient in iodine. It has affected many patients worldwide and continues to be a major public health problem in many countries. Iodine deficiency is the most common preventable cause of intellectual impairment worldwide. Iodine deficiency results in the impairments in varying degrees of physical and mental development (Counts, 2009).

In adults, thyroid hormones show a profound effect on the heart and peripheral vasculature. Hypothyroidism is associated with an increase in the number of coronary heart disease (CHD) risk factors including dyslipidemia, hypertension, and elevated levels of homocysteine. Several CHD risk factors including age, male gender, systolic blood pressure, triglycerides, and fibrinogen are more common in hypothyroid patients. Prevalence of CHD was more common in hypothyroid patients, and resulting all-cause mortality was higher in hypothyroid patients. Higher mortality in these groups was observed in both genders, patients under 65 years of age, and patients not on thyroid replacement therapy, but was not observed in patients over 65 years of age (McQuade, 2011).

Morbidity data were examined from 1993 to 2001 for the TEARS dataset i.e. patients treated and stabilized from either hyper- or hypothyroidism. This included 15,889 patients with primary hypothyroidism and 3,888 with initial hyperthyroidism. Cardiovascular morbidity was increased in treated hypothyroidism (SIR 1.25; 1.16–1.35), due to ischemic heart disease (1.23; 1.1–1.36) and dysrhythmias (1.32; 1.11–1.57). Overall cardiovascular disease and strokes were not

increased in treated stabilized hyperthyroidism, despite an increase in dysrhythmias (2.71; 1.63-4.24) (Thvilum, 2012).

Co-morbidities in Thyroid cancer

A population-based study in the Netherlands examined the co-morbidities in 417 newly diagnosed thyroid cancer patients (Kuijpens, 2006). According to the results of 378 patients (91%) for whom information on co-morbidity was available, co-morbidity was present in a third (32%) of the patients; 23% had one and 12% had two or more concomitant diseases. As expected, the prevalence of co-morbidity increased with age. Hypertension was the most frequently observed co-morbidity in this population (18%), followed by 'other cancers' (7%), cardiovascular diseases (6%) and diabetes mellitus (6%).

Comorbidities in Euthyroid goitre

Euthyroid goitre, diffuse or nodular, in which thyroid gland is normofunctional in terms of thyroxine or T3 levels produced, was not found to be associated with co-morbidities.

Part II: Module SII - Non-clinical Part of the Safety Specification

Levothyroxine (T4) or O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-l-tyrosine is one of the hormones secreted by the thyroid gland. Levothyroxine sodium is its sodium salt with CAS (Chemical Abstracts Service) registry number 55-03-8, molecular formula C15H10I4NNaO4, and molecular weight 798.9. Levothyroxine sodium containing tablets are manufactured in different strengths from 25 µg to 200 µg and marketed under the trade names Euthyrox®, Levothyrox®, Eutirox®, Supratirox®, Levotiroxina sodica®, L-Thyroxine Merck®, Euthyrox N®, Levotiroxina G® and Novothyrox®. For this RMP, bibliographical data on T4 supplemented by original data of the marketing authorization holder (MAH) Merck KGaA are available.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicology	
• **Single and repeat-dose toxicity:** The acute oral toxicity in male and female Wistar rats with a post-dose observation period of 28 days was determined with an LD50 (Lethal dosis 50) of >16,000 mg/kg showing that levothyroxine sodium is essentially nontoxic (Kieser, 1982). In a 4-week repeat-dose oral toxicity study in male Wistar rats, high doses of levothyroxine sodium (1 mg/kg) produced alterations consistent with known effects of thyroxine on the mammalian organism (Roesener, 1995), including increase of reticulocyte counts, changes in serum substrates (e.g. increased glucose, decreased cholesterol), decreases of total protein and albumin, increases of alkaline phosphatase (AP), decreased concentrations of urinary sodium and chloride, increased concentration of urinary NAG (N-acetyl-ß-d-glucosaminidase), increased heart, kidney, spleen, and adrenal weights, and decreased thyroid weights. Histologically, changes were observed in liver (e.g. decreased glycogen deposition), thyroids (colloid storage) and kidneys (tubules with cytoplasmic basophilia) •	• The human "toxicity" of T4 can be estimated from its endogenous production in patients with thyrotoxicosis. In severe cases, the endogenous production rate may increase from the normal range (about 100 µg T4 and 50 µg T3/day) to more than 600 µg/day for both hormones (Larsen, 2003). One tablet containing 100 µg or 125 µg levothyroxine corresponds to about 1/10 of the combined daily T4+T3 (1,200 nmol) output in thyrotoxicosis. Serious toxicity is rare even after massive thyroxine overdose (Singh, 1991). • Levothyroxine may reduce the effect of antidiabetic agents. Thus, blood glucose levels should be checked frequently at the start of thyroid hormone therapy and the dosage of the antidiabetic agent has to be adapted, if necessary. This finding is mentioned in the Reference Safety Information of levothyroxine (MRP SPC Levothyroxine, dated May 2015, section 4.5 Interaction with other medicinal products and other forms of interaction)
• **Reproductive and developmental toxicity** Formal reproductive toxicity studies in animals have not been performed. Early animal teratogenicity studies with T4 gave inconsistent results (Schardein, 2000). No developmental defects were observed in guinea pigs and rabbits, although thyroid atrophy occurred, as expected.	• It was shown that there is no evidence of drug-induced teratogenicity and/or fetal toxicity in humans at the recommended therapeutic dose level. The current Reference Safety Information states: There is no evidence of drug-induced teratogenicity and/or feto-toxicity in humans at the recommended therapeutic dose level. Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on fetal and postnatal development (MRP SPC Levothyroxine, dated May 2015, section 4.6 Pregnancy and lactation). • No signal of concern for human use.
• **Nephrotoxicity**	• No signal of concern for human use.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicology	
• **Hepatotoxicity**	No signal of concern for human use.
• **Genotoxicity** • Data on the mutagenic potential of thyroid hormones are not available (Monograph, 2005; Snyder, 2001). However, as levothyroxine is identical to the physiological T4 produced by the human thyroid gland, it is not expected to be genotoxic.	No signal of concern for human use.
Carcinogenicity Although animal studies to determine the carcinogenic potential of thyroid hormones have not been performed, it should be noted that levothyroxine in Euthyrox® is identical to endogenous T4 and that levothyroxine is not known to have carcinogenic effects (Dollery, 1999).	• No signal of concern for human use.
General safety pharmacology:	•
• **Cardiovascular:** The exogenous administration of T4 to rats is associated with induction of a hypermetabolic state characterized by an increased basal metabolic rate, body weight loss or weight gain suppression, induction of hepatic enzymes involved in carbo-hydrate metabolism, and induction of a cardiac hyperdynamic state. The cardiac hyperdynamic state is characterized by increased heart rate, increased blood pressure, increased volume load, and increased contractility. Cardiac hypertrophy involving both ventricles is consistently seen in association with hyperthyroidism. Thyroid hormones increase rat cardiac β-receptor density, with receptor numbers rapidly returning to control levels after cessation of treatment (Sipes, 1997). •	• Where the individual tolerance limit for levothyroxine sodium is exceeded or after overdose the following clinical symptoms (amongst others) that are typical of hyperthyroidism can occur, especially if the dose is increased too quickly at the start of treatment: cardiac arrhythmias (e.g. atrial fibrillation and extrasystoles), tachycardia, palpitations, anginal conditions (MRP SPC Levothyroxine, dated May 2015, section 4.8 Undesirable effects and section 4.9 Overdose)
• **Neurological** • No neurological effects are described (Nonclinical Overview 2012 Levothyroxine)	No signal of concern for human use.
• **Mechanisms for drug interactions** • No formal non-clinical interaction studies with T4 have been performed.	Interactions with other medicinal products or other forms of interactions have been described in context of human use (MRP SPC Levothyroxine, dated May 2015, section 4.5 Interaction with other medicinal products and other forms of interaction)), especially enzyme inducing medicinal products such as barbiturates or carbamazepine can increase hepatic clearance of levothyroxine.
High protein binding capacity	Due to its high protein binding levothyroxine undergoes neither hemodialysis nor hemoperfusion and can displace anti-coagulative drugs from plasma proteins
Other toxicity-related information or data As an endogenous compound, T4 is not considered allergenic or immunotoxic. No local toxicity is exerted by levothyroxine in oral formulations.	No signal of concern for human use.

No non-clinical safety data with T4 are available from juvenile animals. However, experience in human pediatric populations is available resulting in the following dose recommendations: for neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 µg per kg body weight 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 (MRP SPC Levothyroxine, dated May 2005, section 4.2 Posology and method of administration).

No non-clinical safety data are available concerning the transfer of T4 into breast milk. However, from human use it has been established that levothyroxine is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant (MRP SPC Levothyroxine, dated May 2015, section 4.6 Pregnancy and lactation).

SII Conclusions on Non-clinical Data

Safety concerns	
Important identified risks (confirmed by clinical data)	Cardiovascular adverse effects at high multiples of the human therapeutic dose level
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	No reproductive, developmental, genotoxicity or carcinogenicity studies are described, because levothyroxine is identical to the T4 produced by the human thyroid gland and its extensive use in humans for >10 years which has not identified concerns, no concerns in humans are expected

Non-clinical safety findings were seen only at high multiples of the human therapeutic dose level. The effects on the cardiovascular system observed in rats (Sipes, 1997), such as an induced hyperdynamic state characterized by increased heart rate, increased blood pressure, increased volume load and contractility are contributable to an exaggerated pharmacodynamic effect of levothyroxine and are covered in the current Reference Safety Information in the overdose section (MRP SPC Levothyroxine, dated May 2015, section 4.9 Overdose). Levothyroxine revealed no developmental defects in early animal studies and no carcinogenic effects are expected (Dollery, 1999). Although no formal data from reproductive and developmental toxicity studies in animals is available, studies in pregnant women treated with oral levothyroxine have not shown a risk of fetal abnormalities.

In conclusion, based on the available non-clinical safety information and considering the extensive clinical safety/ pharmacovigilance data available from decades of human therapeutic use, no need for further collection of non-clinical safety data is identified.

Part II: Module SIII - Clinical Trial Exposure

This section is omitted based on GVP V.C.3.1.f (Risk management plan for medicinal products on the market in the EU for 10 years).

Part II: Module SIV - Populations not Studied in Clinical Trials

This section is omitted based on GVP V.C.3.1.f (Risk management plan for medicinal products on the market in the EU for 10 years).

Part II: Module SV - Post-authorization Experience

SV.1 Action Taken by Regulatory Authorities and/or Marketing Authorization Holders for Safety Reasons

Until the Data Lock Point of this RMP (05 Oct 2016), no marketing authorization withdrawal or suspension or revocation, no failure to obtain a marketing authorization renewal, no restrictions on distribution, no clinical trial suspension or modification, no dosage modification, no changes in target population or indication, no formulation changes, nor urgent safety restrictions were performed for safety reasons.

The RSI for levothyroxine is the Core Safety Data Sheet (CSDS) version 5.0, dated 23 May 2014. The RSI was implemented in the EU SmPC, dated May 2015.

Changes to the Company Reference Safety Information from the Core Safety Data Sheet (CSDS v.4) to the current version CSDS v.5 included the following sections: in section 6 (Warnings and precautions), interactions of levothyroxine and orlistat were included. Further, recommendations for levothyroxine therapy in patients at risk of psychotic disorders were added. In section 7 (Interactions), the drug-drug interaction with orlistat was included. In section 10 (Overdose) acute psychosis due to levothyroxine overdose was incorporated. The national texts attached to this document (Annex 2) are the latest approved ones of each country in Europe where levothyroxine is authorized, hence, are based on the version CSDS. The implementation of the CCDS v 5.0 into the national product information has been approved in EU SmPC (MRP SPC Levothyroxine, dated May 2015). Since 2015 there have been no changes to the RSI.

SV.2 Non-study Post-authorization Exposure

The following Table 2 shows the estimated patient exposure to levothyroxine during the period of each corresponding PSUR:

Table 2 Estimated patient exposure to levothyroxine (as reported in PSURs)

PSUR No Review period	Total exposure (patient-years)
PSUR Levothyroxine No. 01 – 01 Jun 1991 to 31 May 1996	1,816,167
PSUR Levothyroxine No. 02 – 01 Jun 1996 to 31 May 1997	1,024,143
PSUR Levothyroxine No. 03 - 01 Jun 1997 to 31 May 1998	1,278,333
PSUR Levothyroxine No. 04 - 01 Jun 1998 to 31 Aug 2001	4,531,675
PSUR Levothyroxine No. 05 - 01 Sep 2001 to 28 Feb 2002	5,089,868
PSUR Levothyroxine No. 06 - 01 Mar 2002 to 28 Feb 2003	4,379,892
PSUR Levothyroxine No. 07 - 01 Mar 2003 to 29 Feb 2004	5,709,210
PSUR Levothyroxine No. 08 - 01 Mar 2004 to 31 Aug 2004	5,620,093
PSUR Levothyroxine No. 09 - 01 Sep 2004 to 31 Oct 2006	12,935,000
PSUR Levothyroxine No. 10 - 01 Nov 2006 to 31 Aug 2007	7,044,000

PSUR No Review period	Total exposure (patient-years)
PSUR Levothyroxine No. 11 - 01 Sep 2007 to 18 May 2009	10,500,330
PSUR Levothyroxine No. 12 - 19 May 2009 to 31 Dec 2010	15,527,487
PBRER Levothyroxine No. 1 - 01 Jan 2011 to 31 Dec 2016	76,603,455
Since the previous PSUR until the date of preparing this RMP (01 Feb 2016 to 05 Oct 2016)*	10,376,769
Total	**162,436,422**

* For this period, the calculation method changed according to the WHO Defined Daily Dose.

The total post-marketing patient exposure to levothyroxine, as presented in all previous PSURs until the cut-off date of this RMP, is estimated to be **162,436,422 patient-years** approximately (**from 01 Jun 1991 to 05 Oct 20166)**. Exposure data before Jun 1991 are not available to the Company.

SV.2.1 Method Used to Calculate Exposure

The patient exposure has been calculated using the defined daily dose (DDD). Until the PSUR DLP of 31 Dec 2013, DDD was defined by the Company as one tablet per day. It was assumed that 100% of the sales were dispensed and administered to patients and that each patient took one tablet per day. The number of patient years was calculated using the formula: Number of tablets/365. A stratification by age group or gender was not possible. Sales figures were obtained from IMS®.

Redefinition of DDD:

For the most recent periodic report period (01 Feb 2016 to 05 Oct 2016), sales data were obtained from internal Company controlling and DDD was re-defined as 150 µg levothyroxine according to the WHO recommendations.

Thus, the patient exposure is calculated as:

$$\text{Patient exposure} = \frac{\text{items issued x amount of drug per item}}{\text{DDD}}$$

The patient exposure is then divided by 365 in order to obtain the patient years.

SV.3 Post-authorization Use in Populations not studied in Clinical Trials

Not applicable, see section Part II, Module SIV.

SV.4 Post-authorization Off-label Use

Fifty three (53) cases of off-label-use were reported to the Company cumulatively in the post-marketing experience until the DLP of this RMP (05 Oct 2016). Based on the patient exposure provided above (SV 2), this constitutes a reporting incidence of **0.033 per 100,000 patient years.**

Off-label use for weight reduction

Of those reported cases of off-label use, seven (7) cases referred to off-label use for weight reduction. Based on the patient exposure provided above (SV 2), this constitutes a reporting incidence of **0.0043 per 100,000 patient years.**

The topic of "off label use of levothyroxine for weight reduction" was cumulatively reviewed in the Merck global safety database with a data-lock point of 05 Oct 2016 using the following search criteria:

A standard validated function of all ICSRs, serious and non-serious, from all sources (including non-health care professionals and serious clinical trial reports), regardless of event ranking and causality assessment by the reporter or by the Company that contain the standard search function for off-label use" (PTs 10053762 Off label use and 10076481 Off label use of device) and levothyroxine as suspect drug was performed. In addition, cases flagged in the global safety database for off-label use were taken into consideration. The results were then checked for signs of off-label use for weight reduction.

Table 3 Cumulative list of ICSRs retrieved with the applied query from the Company's safety database since its existence up to 05 Oct 2016

Mfr Ctrl Nr	Age (years)	Gender	Event preferred term	Medically confirmed	Action taken	Event outcome	Relevant medical history	Relevant co-medications	Company assessment / comments
7011692(0)	55	female	Ischaemic cerebral infarction Atrial fibrillation Hyperthyroidism	Yes	Levothyroxine discontinued	Recovered without sequelae from hyperthyroidism Recovered with sequel from ischemic cerebral infarction	Anorexia nervosa for 7 years Worsening of weight loss for about 7 months	Calcium carbonate and colecalciferol Unspecified vitamins	mildly extensive superficial and deep left sylvian infarction after complete arrhythmia by auricular fibrillation probably related to drug-induced hyperthyroidism was diagnosed in a patient with eating disorders and multiple deficiencies TSH was reported as < 0.01 µU/mL
7097960(0)	34	Female	Thyroid disorder Off-label use	Yes	Levothyroxine discontinued	unknown	Renal failure, dialysis, waiting for kidney transplant, Previous hospitalization for lactic acidosis	metformin	Indication for levothyroxine was reported as "weight loss" TSH was 0.46 mU/L

Mfr Ctrl Nr	Age (years)	Gender	Event preferred term	Medically confirmed	Action taken	Event outcome	Relevant medical history	Relevant co-medications	Company assessment / comments
7163559(1)	32	Female	Thyrotoxic periodic paralysis Drug abuse Off-label use	Yes	Not reported	Not reported	None reported	None reported	Indication for levothyroxine was reported as “weight loss” Thyroid investigation revealed thyrotoxic state Sinus tachycardia Patient informed about dietary changes and intake of 100µg levothyroxine in the mornings for the last 3 months, as recommended by a local gym instructor. In addition, patient experienced hypokalemia [laxative abuse speculated??]
8002968(0)	unk	male	Off-label use	No	Levothyroxine discontinued	Not reported	None reported	None reported	**Levothyroxine was used for weight gain**. Minimal information provided.
8021109(0)	48	Female	Confusional state Purging Hyperthyroidism Off-label use	Yes	Not reported	resolved	Previous episode of Confusional state which required hospitalization.		Patient was diagnosed with a purging disorders.

Mfr Ctrl Nr	Age (years)	Gender	Event preferred term	Medically confirmed	Action taken	Event outcome	Relevant medical history	Relevant co-medications	Company assessment / comments
8030778(0)	40	Female	Colitis microscopic Pernicious anemia Acute prerenal failure Drug intolerance Drug abuse Off-label use	Yes	Levothyroxine discontinued	Not reported	Obesity Previous colonoscopy revealed normal biopsy result	Metformin Diazepam Chlordiazepoxide Butylamine-chlorophenyl-propanone Asian Caralluma Fimbriata Centella Bilberry extract Equisetum Fucus vesiculosus Cascara Sagrada extract vitamin A (retinol	Lymphocytic colitis assumed to be associated with the autoimmune disease
8074883(0)	Unk	Unk	Insomnia Off-label Use	No (patient)		resolved	Not reported	Not reported	Dosage of levothyroxine was deliberately increased for weight loss

Mfr Ctrl Nr	Age (years)	Gender	Event preferred term	Medically confirmed	Action taken	Event outcome	Relevant medical history	Relevant co-medications	Company assessment / comments
8078173(0)	62	female	Weight decreased Off-label use	No (patient)					The patient reported that after her relative died, she experienced anxiety, discomfort feeling, headache and weight increased. She went for consultation and the physician prescribed Eutirox and Glucophage XR to reduce weight which were off label indications for both the drugs. Currently she had lost 40 kg. She did not want to be contacted again

The applied search for off-label use cases for weight reduction retrieved a total of 7 ICSRs, as one of the cases (#8002968) pertained to weight gain on a male patient. Six cases (6) were reported in female patients, one in a patient of unknown gender.

In the PRAC assessment report (PSUSA/00001860/201601; EMA/CHMP/527154/2016) *off-label use for weight reduction* was considered to be an important potential risk for levothyroxine. The comment of the Lead Member State/PRAC Assessment was that *"The misuse of levothyroxine in order to reduce weight is currently known. The major risk with this practice is the induced hyperthyroidism which could be lead to thyrotoxicosis up to fatal outcome, with frequent misuse and abuse as a slimming drug, by the general population and sportsmen. These practices are absolutely disapproved. LMS approves the MAH conclusion and strongly recommended the other MAHs to add the safety concern "off label use for weight reduction" as an important potential risk."*

Off-label use per definition refers to a "Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information" (GVP Module VI, 2013).

In the comment of the PRAC Assessment report, also misuse of levothyroxine is addressed. The Company is of the opinion that off-label use does not cover the risk fully and thus considers to comprise misuse and abuse cases together with the important potential risk of *off-label use for weight reduction.*

The RMP will thus be updated with the important potential risk of **off-label-use/abuse and misuse of levothyroxine for weight reduction** accordingly (also see section SVI.3 Potential for Misuse for Illegal Purposes).

SV.5 Epidemiological Study Exposure

The following epidemiological studies are or have been conducted to elucidate safety or efficacy issues, study drug utilization or measure effectiveness of risk minimization measures. No specific safety issues were addressed.

Table 4 Epidemiological Study Exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)
EMR200007_504 DEuTSH Non-randomized, non-comparative, multi-center Observational	Descriptive study on individually titrated levothyroxine in the management of South African hypothyroid patients	South Africa	24 months	290
EMR200007_502 ORCHIDEE Open-label, non-randomized, non-comparative Observational	Observation of medical care of initial hypothyroidism in France	France	5 months	1285
EMR200007_606 BRAZIL Open-label, non-randomized, non-comparative, multi-center Observational	Evaluation of the treatment of primary hypothyroidism in different regions in Brazil	Brazil	26.5 months	2500

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Harm from Overdose

Cumulatively, the Company has received 391 case reports of overdose in the post-marketing experience. Based on the patient exposure provided above (SV2), this constitutes a reporting incidence of **0.24 per 100,000 patient years.**

Dose tolerance limit of the thyroid hormone levothyroxine varies from patient to patient and often overdose is reported, as soon as the individual dose tolerance is exceeded.

Accidental overdose can also occur after intake of the wrongly prescribed or wrongly dispensed strength or after voluntary or accidental intake of too many tablets.

Typical symptoms of overdose are clinical signs of hyperthyroidism, such as cardiac arrhythmias, tachycardia, palpitations, angina pectoris, muscular weakness, tremor, restlessness, insomnia, diarrhea, and weight loss. As a first measure, levothyroxine should be withdrawn for several days and the daily dose has to be reduced. Beta-sympathomimetic effects such as tachycardia, agitation or hyperkinesia can be relieved by beta-blockers. In extreme cases of overdose, plasmapheresis may be indicated.

At this point in time, no other measures than described in the Company's Reference Safety Information (MRP SPC Levothyroxine, dated May 2015, section 4.9 Overdose) are deemed required.

SVI.2 Potential for Transmission of Infectious Agents

All the materials used in the manufacturing of levothyroxine formulations are controlled in accordance with international industrial standards. The possibility of transmission of infectious agents from this substance is very unlikely.

The finished product (tablet) is manufactured in accordance with good manufacturing practice (GMP) requirements, with ingredients which meet the specifications of the European Pharmacopeia and United States Pharmacopeia.

Regarding the risk of transmitting TSE (Transmissible Spongiform Encephalopathy), Merck KGaA as the responsible manufacturer of levothyroxine tablets declares that no material related to the risk of transmitting TSE is present in this product:

The current formulation of levothyroxine tablets contains lactose monohydrate (the new levothyroxine formulation does no longer contain lactose):

Lactose monohydrate

According to the Note for Guidance (EMEA/410/01 Rev. 2), milk is unlikely to present any risk of TSE contamination. Milk derivates shall be considered compliant with the Note for Guidance,

if the milk is sourced from healthy animals and in the same conditions as milk from human consumption, and if no other ruminant materials with the exception of calf rennet are used in the preparation of such derivates.

The lactose monohydrate used for the manufacturing of levothyroxine sodium tablets is sourced from healthy animals and no ruminant materials except calf rennet are used in the preparation of it. The lactose does therefore fulfill the requirements of the Note for Guidance.

Ingredients present in both new and current formulation:

Gelatin

The gelatin used for the manufacture of the drug product is sourced from non-ruminant material (pork or fish), and is therefore excluded from the scope of the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Magnesium stearate

The magnesium stearate used by Merck KGaA for tablet manufacturing is of vegetable origin.

Further ingredients in the new formulation of levothyroxine, (not present in the current formulation):

Mannitol

The mannitol used by Merck KGaA for tablet manufacturing is of organic, non-animal origin.

Citric acid, anhydrous

The citric acid, anhydrous, used by Merck KGaA for tablet manufacturing is of organic, non-animal origin.

Levothyroxine new formulation tablets do no longer contain lactose.

SVI.3 Potential for Misuse for Illegal Purposes

The drug levothyroxine may be abused/misused in order to increase the metabolism and to burn fat- particularly known among athletes (Chandler, 2013; Lenehan, 1996; Peters, 1997; Skårberg, 2009 and Strauss, 1985). In general, levothyroxine may potentially be misused for weight loss purposes (Sagoe, 2015).

Cumulatively until 05 Oct 2016, the Company has received 413 case reports of drug abuse/misuse in the post-marketing experience. Based on the patient exposure provided above (SV2), this constitutes a reporting incidence of **0.25 per 100,000 patient years** for abuse/misuse cases in general.
Of the reported abuse/misuse cases, nine (9) cases were found to be abuse/misuse cases explicitly for weight loss purposes: #2000319, #6021370(1), #6022828(3), #6057280, #7163559(1), #7255668, #8018029, #8030778, #8105193(2).

It seems that self-administration of excessive thyroid hormone is a weight control strategy used by some eating disorder patients (Crow et al, 1997; Kornhuber, 1996). The manner of misuse is given in example case #2000319: A 30-year-old patient had self-administered levothyroxine for weight loss. The patient lost around 14 kilograms and developed a coarse tremor of her upper extremities, insomnia, and tachycardia. Patient recovered after ending the misuse/outcome is not given.

In the PRAC assessment report (PSUSA/00001860/201601; EMA/CHMP/527154/2016) *off-label use for weight reduction* was considered to be an important potential risk for levothyroxine. The comment of the Lead Member State/PRAC Assessment was *that "The misuse of levothyroxine in order to reduce weight is currently known. The major risk with this practice is the induced hyperthyroidism which could be lead to thyrotoxicosis up to fatal outcome, with frequent misuse and abuse as a slimming drug, by the general population and sportsmen. These practices are absolutely disapproved. LMS approves the MAH conclusion and strongly recommended the other MAHs to add the safety concern "off label use for weight reduction" as an important potential risk."*

Off-label use per definition refers to a "Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information" (GVP Module VI, 2013).

In the comment of the PRAC Assessment report, misuse of levothyroxine is also addressed. The Company is of the opinion that off-label use does not cover the risk fully and thus considers to include misuse and abuse cases together with the important potential risk of *off-label use for weight reduction.*

The reported nine (9) cases of misuse/abuse of levothyroxine indicate that levothyroxine is misused/abused for weight loss purposes. The RMP will thus be updated with the important potential risk of **off-label-use/abuse and misuse of levothyroxine for weight reduction** accordingly.

Further actions are not considered necessary for the time being, since the MRP SPC Levothyroxine states a warning of not using levothyroxine for weight loss purposes: "Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9 of the EU SmPC)." (V.1 Risk Minimization Measures by Safety Concern).

SVI.4 Potential for Medication Errors

The likelihood of a potential medication error is assessed to be low.

The product is only available as white tablets in different strengths; the strength of the tablet is prescribed by the physician and dispensed by the pharmacist. Accidental overdose due to intake of the wrongly prescribed or wrongly dispensed strength or too many tablets is addressed in section SVI.1. The potential for medication errors emanating from a prescription error is not elevated for levothyroxine in comparison to other medicinal products. The potential for a

medication error emanating from a dispensing error by a pharmacist may be assumed slightly lower, since the packages of the strengths have differently colored outer package boxes. In addition, the medication error could be recognized by patients, also due to the differently colored outer boxes and also the differently colored blisters of the different tablets' strengths.

To minimize any potential for medication errors in post-marketing, detailed instructions for use regarding dose recommendations and administration have been developed and are addressed in the relevant sections of the Company's Reference Safety Information, to be reflected in the respective Product Information texts.

SVI.4.1 Description of Medication Errors during the Clinical Trial Program

Not applicable.

SVI.4.2 Preventive Measures for the Final Product Being Marketed

Not applicable.

SVI.4.3 Effect of Device Failure

Not applicable.

SVI.4.4 Reports of Medication Errors with the Marketed Product

995 ICSRs reporting medication errors have been received cumulatively with levothyroxine by the Company (until cut-off date 05 Oct 2016 of this RMP, version 4.0), providing an incidence of **0.61 per 100,000 patient years.**

The most commonly reported PTs within the SMQ of medication errors were the following:

- Accidental exposure to product by child
- Incorrect dose administered
- Medication error
- Drug prescribing or dispensing error
- Inappropriate schedule of drug administration
- Drug dose omission
- Drug administration error
- Wrong drug administered
- Accidental exposure to product

In the previous RMP (version 3.0. cut-off date Feb 2015), the incidence was 0.23 per 100,000 patient years with 346 case reports. This increase of about 650 medication error cases in less than 1.5 years is mainly considered to be driven by the refined search strategy due the updated

broader MedDRA SMQ on medication errors in the frame of MedDRA update from version 18.1 to version 19.1. In previous MedDRA version 18.1. the search for medication errors contained about 80 PT terms, in the updated it is 131 PT terms (see Annex 12: the excel file "Comparison_Medication error terms_MedDRA update"). This increase in included terms in MedDRA version 19.1 leads to an increased inclusion and increased capturing of cases into the cumulative medication error listings and means that in general and for all medicinal products, more medication error cases are retrieved. This can be considered the main explanation for the observed increase for medication error cases with levothyroxine.

In addition, following the update of the EMA Medication Error Practice Guides the increase of reported medication error cases can be explained by an increased awareness of reporting of medication errors following the new EMA guides (Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors (PRAC, EMA/762563/2014); Good Practice Guide on Risk Minimization and Prevention of Medication Errors (PRAC, EMA/606103/2014)).

No safety issue is observed with medication error cases reported and no action is considered necessary by the MAH at this point in time, even though the numbers are increased owing to the refined search strategy and increased awareness.

SVI.5 Potential for Off-label Use

From the number of case reports received, the potential for off-label use of levothyroxine seems to be low..53cases (incidence of 0.032 per 100,000 patient years) have been reported to the Company cumulatively (until cut-off date 05 Oct 2016) in the post-marketing experience.

Clusters of off-label use cases are shortly summarized in the following:

In seven (7) of the reported 50 off-label use cases, the patient took levothyroxine for weight loss (#7163559(1), #7097960, #7011692, #8021109, #8030778, #8074883, #8078173).
In four (4) cases, the off-label use referred to the other reported suspect drugs:

- #7249600 - choriogonadotropin alfa used for virilization induction
- #7133244(2) - metformin to assist weight loss
- #7271425(1)) - metformin used for impaired glucose tolerance and insulin resistance
- #8108120(1) - metformin was used off-label for PCOS

As further detailed in section SV.4 and section SVI.3, the RMP will be updated with the important potential risk of **off-label-use/abuse and misuse of levothyroxine for weight reduction** accordingly.

SVI.6 Specific Pediatric Issues

SVI.6.1 Issues Identified in Pediatric Investigation Plans

The company did not conduct a Pediatric Investigation Plan.

In 2009, levothyroxine was subject of the Work-sharing Procedure according to EC Regulation 1901/2006 ('Pediatric Regulation'). Sweden was the Rapporteur (SE/W/004/pdWS/001).

Pediatric Work-sharing Procedure

Congenital hypothyroidism

Congenital hypothyroidism (CH) was first described in the late 19th century and different preparations of thyroid hormones have long been used to treat hypothyroidism. Levothyroxine has been in use for more than 50 years in the treatment of hypothyroidism in both pediatric and adult patients. There are a number of different levothyroxine products, most being nationally approved. Thus, the knowledge on how to use levothyroxine is mainly based on vast clinical experience and to some extent on retrospective studies or non-controlled trials.

Congenital hypothyroidism affects approximately one in 3000 to 4000 infants. It has long been known that mental development in children with congenital hypothyroidism is related to adequacy of treatment. Beginning treatment before three months of age improves the prognosis for mental development in these children (Rogers, 1994). Therefore, newborn screening programs have been initiated such as the program described by Grant in 1995 (Grant, 1995).

Guidelines for neonatal screening programs for congenital hypothyroidism have been published in 1993 by the European Society for Pediatric Endocrinology (Grueters, 1993). Regarding the initial treatment, these guidelines state that levothyroxine is the medication of choice and should be immediately instituted in all cases with markedly elevated Thyroid Stimulating Hormone (TSH), with a dose of 10-15 µg/kg. A monitoring of treatment should be done using hormonal measurements. These treatment recommendations were not changed in an update review published in 2007 (Grueters, 2007).

The dose recommendations for the treatment of CH are supported by clinical trials (Germak, 1990). The same dose recommendations for treatment of CH are given by the European Society for Pediatric Endocrinology (Grueters, 2007) and the American Academy of Pediatrics (Rose, 2006). The importance of fast normalization of thyroid status in CH to ensure normal neurodevelopment is well known, although there is still insufficient knowledge on the optimal dose regimen especially with regards to the long-term effects on growth and development.

Acquired hypothyroidism

Acquired hypothyroidism in children includes autoimmune thyroiditis, drug-induced hypothyroidism, and endemic goitre due to nutritional iodide deficiency, irradiation of the thyroid and surgical excision of the thyroid. Once the diagnosis of hypothyroidism is confirmed, levothyroxine therapy should be started with an initial dosage of 0.05 mg per day (Rogers, 1994).

One author (Lafranchi, 1992) proposed levothyroxine dosages in children with hypothyroidism resulting from thyroiditis, which decreases on a weight basis with age.

In case of the treatment of acquired hypothyroidism in the pediatric population, rapid normalization of thyroid hormone status is not as important as in CH, therefore, treatment can be started with somewhat lower doses that then are titrated until full substitution is achieved.

Several studies were published regarding identification of the optimal dosage:

Selva (2002) carried out a randomized, 12-week study with infants of birth weight 3 to 4 kg with CH (n = 47) detected by newborn screening were randomly assigned into three levothyroxine treatment dose arms: 37.5 µg/day (group 1), 62.5 µg/day for 3 days, then 37.5 µg/day (group 2), 50 µg/day (group 3).

The objective was to determine the optimal initial treatment dose of levothyroxine in congenital hypothyroidism by evaluating the time course of rise of thyroxine (T4) and free T4 concentrations into an established "target range" and normalization of thyroid-stimulating hormone (TSH) and to reevaluate the "target range" for T4 and free T4 concentrations during the first 2 weeks of CH treatment. Serum T4, free T4, triiodothyronine (T3), free T3, and TSH were measured before treatment and at 3 days and 1, 2, 4, 8, and 12 weeks after treatment.

The results showed that T4 and free T4 concentrations increased into the target range (10 to 16 µg/dL) by 3 days of therapy in infants in groups 2 and 3 and by 1 week in group 1. 50 µg/day (average 14.5 µg/kg/day) provided the most rapid normalization of TSH by 2 weeks.

With the use of linear regression analysis of T4 versus TSH or free T4 versus TSH plots, the intercept at the lower range of normal for TSH (1.7 mU/L) showed T4 = 19.5 µg/dL and free T4 = 5.23 ng/dL.

Conclusion: The authors concluded that initial dosing of 50 µg/day (12-17 µg/kg per day) raised serum T4 and free T4 concentrations to target range by 3 days and normalized TSH by 2 weeks of therapy. They recommended consideration of a somewhat higher "target range" of 10 to 18 µg/dL for T4 and 2 to 5.0 ng/dL for free T4 during the first 2 weeks of levothyroxine treatment. After 2 weeks of treatment, the target range drops to 10 to 16 µg/dL for T4 and 1.6 to 2.2 for free T4.

Ng et al (2009) investigated “High versus low dose of initial thyroid hormone replacement for congenital hypothyroidism”: One of the main issues in the management of CH relates to the initial dose of levothyroxine to be used in order to achieve optimal results in terms of intellectual development. Currently, it remains unclear whether high dose thyroid hormone replacement is more effective than low dose in the treatment of CH. The objectives of this review were to determine the effects of high versus low dose of initial thyroid hormone replacement for congenital hypothyroidism.

Randomized controlled trials investigating the effects of high versus low dose of initial thyroid hormone replacement for congenital hypothyroidism were identified by searching The Cochrane Library, MEDLINE and EMBASE and reference lists of published papers.

The initial search identified 1014 records which identified 13 publications for further examination. After screening the full text of the 13 selected papers, only one study evaluating 47 babies finally met the inclusion criteria. This study was described in Selva K, et al (Selva, 2002; Selva, 2005). Growth and adverse effects were not reported in the included trial.

According to authors' conclusions, there is currently only one randomized controlled trial evaluating the effects of high versus low dose of initial thyroid hormone replacement for CH. There is inadequate evidence to suggest that a high dose is more beneficial compared to a low dose initial thyroid hormone replacement in the treatment of CH.

An insufficient levothyroxine supply to the fetus should already be avoided during pregnancy by adequately treating the mother (Glinoer, 1994; Porterfield, 1993; Roberts, 2004; Vijlder, 1996; Wassersturm, 1995).

Compared to the doses in adults, these levothyroxine doses are relatively high (Roberts, 2004). 25µg levothyroxine per day is recommended in the initial postpartum phase, 50µg levothyroxine per day from the 3rd to 12th month of life and 50µg/day plus 5µg levothyroxine per kg weight gain from the first year onwards. In severe congenital hypothyroidism, even a higher initial dose in neonates is recommended in order to improve the early development outcome of the infants (Dubuis, 1996).

Conclusions of the Work-sharing procedure:

Dose recommendations

The choice of initial dose in the treatment of CH is still a matter of some discussion; however, in current guidelines an initial dose of 10-15 µg/kg is recommended. This corresponds rather well to the higher dose intervals used in all studies described above. Both studies show similar results with normalization of TSH within 2 weeks. The long-term data are, however, too scarce to allow any conclusions on possible beneficial effects on neurodevelopmental outcome when using a higher dose. This is further supported by the thorough literature search done by the authors of the Cochrane review. This review only included the data published by Selva (Selva 2002; Selva 2005).

Safety

The safety review revealed no new concerns about using levothyroxine in the pediatric population.

Label changes following the Pediatric Work-sharing Procedure (in 2010):

In conclusion, the reviewed data during the WS Procedure support the current posology in the treatment of congenital hypothyroidism and do not require the addition of any new information in the SPC.

The wording of the posology section, however, differed between MAHs and for the same MAH in different countries. It was therefore proposed that the wording of the pediatric posology was changed in section 4.2:

Section 4.2:

Pediatric patients

The maintenance dose is generally 100 to 150 micrograms per m² body surface area. For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 to 15 micrograms per kg BW (body weight) 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. 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. Infants should be given the total daily dose at least half an hour before the first meal of the day.

When applicable:

Tablets are to be disintegrated in some water (10 to 15 mL) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 to 10 mL).

SVI.6.2 Potential for Pediatric Off-label Use

Levothyroxine is authorized in all pediatric age groups, from neonate to teenage age, and no limited treatment options in the pediatric population exist. Therefore the potential for a special case of pediatric off-label use is limited. Therapy of congenital hypothyroidism with levothyroxine is important for normal development of the child, as described above in section SVI.6.1.

SVI.7 Conclusions

Table 5 Safety concerns from this module (to be carried through to Part II Module SVIII)

Safety concern	Comment
Off-label use/abuse and misuse for weight reduction as important potential risk	In the PRAC assessment report (PSUSA/00001860/201601; EMA/CHMP/527154/2016) off-label use for weight reduction was considered to be a potential risk for levothyroxine. The Company is of the opinion that off-label use does not cover the risk fully and thus considers to comprise misuse and abuse cases together with the important potential risk of off-label use for weight reduction.

As specified in section SVI-Additional EU Requirements for the Safety Specification, regarding the potential harm from overdose, the potential for transmission of infectious agents, the potential for medication errors, no further actions are currently deemed required other than specified in the Company's Reference Safety Information (MRP SPC Levothyroxine, dated May 2015).

Overall, the benefit/risk balance of levothyroxine in the approved indications and in all populations remains positive.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Newly Identified Safety Concerns (Since this Module was last Submitted)

Important Potential Risk: off label use/abuse and misuse for weight reduction	
Frequency	In post marketing experience, cumulatively, 7 ICSRs falling under the search criteria for off-label use in addition to 9 ICSRs pertaining to abuse/misuse in connection with weight loss were received by the Company. Cumulative reporting rate for the 16 ICSRs received until cut-off date of this report (05 Oct 2016) is calculated as **0.0098 in 100,000 patient years**, based on MedDRA query as described below.
Seriousness/outcomes	The risks associated with an off-label use for weight loss can be non-serious, but also develop into a serious condition, representing a risk to the patient's health.
Background incidence/prevalence	No data that quantified the magnitude of off label use for weight reduction is available. However, it is known that thyroid hormones have been inappropriately used in attempts to induce weight loss in obese euthyroid patients, alone or in combination with methylphenidate (Apovian, 2015), Based on a descriptive meta-synthesis study for the Polypharmacy of anabolic-androgenic steroid users, thyroxine has been reported frequently as one of the main substances that have been misused previously by this group (Sagoe, et al., 2015). The main reasons were burning fat, and increasing metabolism.
Risk groups or risk factors	Obese euthyroid patients Athletes' use of polypharmacy and anabolic-androgenic steroid drugs for performance increase (Sagoe et al., 2015).
Potential mechanisms	Levothyroxine has an accelerating effect on metabolism and energy provision. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids.
Impact on individual patient	Depending on the seriousness, patients may be slightly or severely impacted.
Potential public health impact of safety concern	The impact on public health is deemed minimal.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases from the literature.

Important Potential Risk: off label use/abuse and misuse for weight reduction	
MedDRA terms	Standard search function for off-label use comprises the following PTs: PT 10053762 Off label use, MedDRA version 19.1 PT 10076481 Off label use of device, MedDRA version 19.1 Standard search function for misuse/abuse is the following: SMQ Drug abuse, dependence and withdrawal, broad scope, MedDRA version 19.1 For the previous version of the RMP 3.0, DLP Feb 2015, MedDRA version 18.1 was applied.

SVII.2 Recent Study Reports with Implications for Safety Concerns

Not applicable.

SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)

Important Identified Risk: clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	
Frequency	In post marketing experience, cumulatively, 1,459 ICSRs within the SMQ Hyperthyroidism including thyrotoxicosis have been received by the Company. This constitutes a cumulative reporting incidence until cut-off date of this report (05 Oct 2016) of **0.89 per 100,000 patient years**, based on MedDRA query as described below. Clinical symptoms of hyperthyroidism are the main adverse events patients exposed to levothyroxine may experience. Thus, an increase in overall adverse event reporting due to increasing awareness of the requirement to report ADRs in general due to updated legislations and also increased consumer reporting of adverse events may explain the rise in ICSRs received from the recent RMP version 3.0 to the current RMP version.
Seriousness/outcomes	Clinical signs of hyperthyroidism can range from non-serious to serious conditions that have an impact on the patient's health. Thyrotoxicosis or thyrotoxic crisis is a rare but severe and potentially life-threatening complication; it is a medical emergency situation and requires prompt medical treatment.
Background incidence/ prevalence	Hyperthyroidism is more common in women than men (5:1 ratio). The overall prevalence of hyperthyroidism, which is approximately 1.3 percent, increases to 4 to 5 percent in older women (Hollowell, 2002). Hyperthyroidism is also more common in smokers (Asvold, 2007).

Important Identified Risk: clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	
	Several different disorders can cause hyperthyroidism. The most common cause of hyperthyroidism with a normal or high radioiodine uptake is Graves' disease. Other causes include Hashitoxicosis, toxic adenoma, and toxic multinodular goitre. High doses of iodide or drugs that contain iodide may cause hyperthyroidism. Drug-induced clinical signs of hyperthyroidism are mainly caused by medicines containing the active thyroid hormone liothyronine (T3) or the pro-drug, levothyroxine (T4) as contained in levothyroxine sodium tablets. Hyperthyroidism induced by drugs might occur in patients on chronic amiodarone treatment and in those using radio contrast agents. Patients who receive radiographic contrast agents, which contain as much as 50 percent iodine by weight, may develop hyperthyroidism within several weeks after exposure (Martin, 1993). The effect of iodide administration or drugs that contain iodide in patients with abnormal thyroid glands differs from that in normal subjects and depends upon the underlying disease process. Iodine-induced hyperthyroidism can rarely occur in patients without underlying thyroid disease (e.g., iodine-induced thyroiditis) (Skare, 1980). In one study, as an example, only 2 of 788 unselected patients from an iodine deficient area developed hyperthyroidism within 12 weeks after coronary angiography (Hintze, 1999). In North America and other iodine replete populations, iodine-induced hyperthyroidism may occasionally occur in patients with autonomous thyroid nodules after treatment with high doses of iodine, usually in the form of drug therapy or exposure to iodinated contrast agents during diagnostic radiography (e.g., computed tomography or angiography) (Buergi, 2010; Roti, 2001; Fradkin, 1983; Rhee, 2012). As an example, in a prospective study of 73 patients (mean age 65.7 years), only two developed hyperthyroidism after exposure to radiographic contrast (Conn, 1996). In another study, the risk was higher in patients who had subnormal serum TSH concentrations and increased technetium thyroid uptake prior to radiographic contrast exposure (Fricke, 2004). Interferon-alfa and interleukin-2 have been associated with the same two types of hyperthyroidism (Graves' disease and painless thyroiditis) in a few patients, presumably by initiating or exacerbating thyroid autoimmune disease. Hyperthyroidism after ipilimumab and alemtuzumab has also been reported (Hamnvik, 2011; Aranha, 2013; Daniels, 2014). Thyrotoxic crisis is a rare, life-threatening condition characterized by severe clinical manifestations of thyrotoxicosis (Sarlis, 2003). Its incidence is about 1-2% among patients with known hyperthyroidism (Karger, 2008). The incidence in Germany is between 0.8 and

Important Identified Risk: clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	
	1.4 cases per 100,000 inhabitants (Dietrich JW, 2012). In a national survey from Japan, the incidence of thyroid storm in hospitalized patients was 0.20 per 100,000 per year (Akamizu, 2012). A thyrotoxic crisis occurs predominantly in the elderly and is three to five times more common in women than in men (Swee, 2015). Main risk factors are noncompliance with treatment in patients with a prior diagnosis of hyperthyroidism, followed by infection. Mortality rate of thyrotoxic crisis is substantial, ranging from 10 to 30% (Akamizu, 2012; Swee, 2014; Angell, 2015).
Potential mechanism	Levothyroxine intake is titrated according to the individual patient's thyroid hormone requirements and regularly controlled through blood sample tests. Since the individual hormonal requirement can vary and can often not be exactly predicted, a patient might take a dosage exceeding the individual dose tolerance limit, which can lead to clinical signs of hyperthyroidism. In addition, residual activity of the thyroid can vary, leading to a change in the hormonal requirement.
Preventability	Clinical signs of drug-induced hyperthyroidism can be avoided or limited through slow initiation of levothyroxine therapy and regular check-ups of thyroid laboratory values. This is pointed out in the RSI of levothyroxine (MRP SPC Levothyroxine, dated May 2015)): *The individual daily dose should be determined on the basis of laboratory tests and clinical examinations.* Thyrotoxicosis can be prevented by identification and prevention or early treatment of precipitating factors, such as infection or other acute illness, withdrawal of or non-compliance with antithyroid medication, recent trauma, including surgical stress, myocardial infarction or stroke, drugs: radio-iodine, amiodarone, radiographic contrast media, overdose of thyroid hormone tablets, vigorous palpation of the thyroid gland in hyperthyroid patients, recent thyroid surgery (Migneco, 2005).
Risk group	In principal, all patients taking levothyroxine medication may develop drug-induced hyperthyroidism at some point during treatment with levothyroxine. The risk is usually less pronounced in patients on long-term, well-established therapy and patients undergoing regular check-up of therapy. The risk of a drug-induced thyrotoxicosis is rather low, provided that the patient considers the physician's prescribed daily dose intake. Hyperthyroidism can result from numerous etiologies, including autoimmune, drug-induced, infectious, idiopathic, iatrogenic, and malignancy. Thyroid storm is a rare and potentially fatal complication of hyperthyroidism. It typically occurs in patients with untreated or partially treated thyrotoxicosis who experience a precipitating event such as surgery, infection, or trauma. Thyroid storm must be recognized and treated on clinical grounds alone, as laboratory confirmation often cannot be obtained in a timely manner. Patients typically appear markedly hypermetabolic with high fevers, tachycardia, nausea and vomiting, tremulousness, agitation, and psychosis. Late in the progression of disease, patients may become stuporous or comatose with hypotension.

Important Identified Risk: clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	
Impact on individual patient	Hyperthyroidism can be asymptomatic, non-serious, serious or even life-threatening. Thyrotoxicosis is a serious condition that can be life-threatening.
Potential public health impact of safety concern	Drug-induced hyperthyroidism secondary to the use of levothyroxine resolves upon discontinuation of the product. Thyrotoxic crisis is a medical emergency requiring prompt treatment (Migneco, 2005).
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
MedDRA terms	SMQ Hyperthyroidism (20000161), broad scope, MedDRA version 19.1

Important Identified Risk: adrenal insufficiency up to adrenal crisis in predisposed patients	
Frequency	In post marketing experience, cumulatively, 13 ICSRs with the PTs comprising adrenal crisis as described below have been received. Cumulative reporting incidence until cut-off date of this report (05 Oct 2016) is calculated as **0.008 in 100,000 patient years**, based on the query with the specified PTs as described below.
Seriousness/outcomes	Adrenal crisis is a rare but severe and potentially life-threatening complication; it is a medical emergency situation and requires prompt medical treatment.
Background incidence/prevalence	There are three types of adrenal insufficiency classified according to the underlying mechanisms: primary, secondary, and tertiary (Charmandari, 2014). Chronic primary adrenal insufficiency has a prevalence of 93–140 per million and an incidence of 4·7–6·2 per million in white populations (Kong, 1994; Willis 1997; Laureti 1999; Lovas 2002; Erichsen, 2009). These recent numbers are higher than those reported during the 1960s and 1970s (Mason, 1968; Nerup 1974). This has occurred despite a continuous decline in tuberculous adrenalitis in high income countries, which was the most common cause of primary adrenal insufficiency during the first half of the 20th century. This suggests an increasing incidence of autoimmune adrenalitis (Laureti 1999; Lovas 2002), which has become the most common form of primary adrenal insufficiency (Cooper, 2003). In a series of 615 patients with Addison's disease, studied between 1969 and 2009, the autoimmune form was diagnosed in 82% of cases, the tuberculosis related form in 9%, and other causes in about 8% of cases (Betterle, 2011). The age at diagnosis peaks in the fourth decade of life, with women more frequently affected than men (Kong, 1994; Lovas, 2002). Secondary adrenal insufficiency is more common than primary adrenal insufficiency (Arlt, 2003). Secondary adrenal insufficiency has an estimated prevalence of 150–280 per million (Laureti, 1999; Bates, 1996; Nilsson, 2000; Regal, 2001; Tomlinson, 2001). It also affects women more frequently than men and age at diagnosis peaks in the sixth decade of life (Nilsson,

Important Identified Risk: adrenal insufficiency up to adrenal crisis in predisposed patients	
	2000; Regal, 2001). A systematic review and meta-analysis of reported prevalences of hypopituitarism in adult patients who had received cranial irradiation for non-pituitary tumours showed that the point prevalence of any degree of hypopituitarism was 0.66 (95% CI 0.55–0.76) and the prevalence of corticotropin deficiency was 0·22 (0.15–0.30) (Appelman-Dijkstra, 2011). The most common cause of tertiary adrenal insufficiency is thought to be therapeutic glucocorticoid administration (Gomez, 1993). Adrenal crisis is a life-threatening emergency contributing to the excess mortality of patients with adrenal insufficiency (Allolio, 2015). Studies in patients on chronic replacement therapy for adrenal insufficiency have revealed an incidence of 5 - 10 adrenal crises per 100 patient years (Hahner, 2010; Reisch, 2012; Ritzel, 2013; White, 2010) and suggest a mortality from adrenal crisis of 0.5 per 100 patient years (Hahner, 2015). Infections are the major precipitating cause of adrenal crisis (Allolio, 2015).
Risk groups or risk factors	The risk of developing adrenal crisis exists primarily in patients with a concomitant disease of the adrenal glands or an underlying adrenal insufficiency, also if this disease is treated. Patients at greatest risk are those with present hypoadrenalism, for example as in autoimmune polyglandular syndrome, that is undiagnosed and treatment of a presenting hypothyroid state is started. This may precipitate Addisonian crisis through two mechanisms. First, hypothyroidism reduces cortisol clearance. The addition of thyroid hormone replacement increases cortisol clearance, thus decreasing circulating cortisol availability. Second, hypothyroidism reduces the metabolic rate thereby reducing the need for cortisol. The increased metabolic rate accompanying thyroxine replacement increases the cortisol requirements that cannot be provided by the failing adrenals (Graves, 2003).
Potential mechanisms	Adrenal crisis is caused due to deficiency of cortisol, which may be due to Addison's disease, congenital adrenal hyperplasia, corticosteroid biosynthetic enzyme defects or pituitary disorders (such as Sheehan's syndrome, pituitary adenoma, inactive or underactive pituitary) causing failure to activate the adrenal glands. Levothyroxine leads to increased metabolic clearance of glucocorticoids (Gordon, 1977). Levothyroxine influences the overall metabolism and therefore increases the physical requirements of cortisol in the body, which may result in a deficiency of cortisol. In patients with unknown adrenal insufficiency, levothyroxine intake may precipitate an adrenal crisis.
Preventability	In patients with a medical history of adrenal insufficiency, adrenal crisis is triggered by physiological stress (such as trauma) (Graves, 2003). Administering the correct dosage of levothyroxine and regular monitoring thyroid function could prevent development of adrenal crisis. In addition, an underlying adrenal insufficiency should be excluded or adequately treated.

Important Identified Risk: adrenal insufficiency up to adrenal crisis in predisposed patients	
	Before starting therapy with levothyroxine, adrenal insufficiency must be excluded or adequately treated. (MRP SPC Levothyroxine, dated May 2015).
Impact on individual patient	Adrenal crisis is serious and may develop into a life-threatening condition.
Potential public health impact of safety concern	Adrenal crisis resolves with adequate medical treatment. Adrenal crisis is a medical emergency requiring prompt treatment with injectable hydrocortisone and fluid replacement
Evidence source	Clinical trials and post marketing experience, cumulative review of cases.
MedDRA terms	Specified PTs used in the search for term 'adrenal crisis': 10001324 Adrenal atrophy 10001389 Adrenocortical insufficiency acute 10020537 Hydroxycorticosteroids urine decreased 10064591 Tetrahydrocortisone urine decreased 10001367 Adrenal insufficiency 10005447 Blood corticosterone decreased 10005457 Blood cortisol decreased 10001382 Adrenal suppression 10061466 Glucocorticoids decreased 10064589 Tetrahydrocortisol urine decreased 10065675 ACTH stimulation test abnormal 10001130 Addison's disease 10005295 Blood aldosterone decreased 10011201 Cortisol free urine decreased

Important Identified Risk: cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris)	
Frequency	In post marketing experience, cumulatively, 1,111 ICSRs corresponding to the SMQ cardiovascular disorders as described below have been received. Cumulative reporting incidence until cut-off date of this report (05 Oct 2016) is calculated as **0.68 in 100,000 patient years**, based on this query as described below.
Seriousness/outcomes	Cardiovascular disorders such as cardiac arrhythmias, tachycardia and angina pectoris can be non-serious, serious or life-threatening.
Background incidence/ prevalence	Atrial fibrillation (AF) is the most common arrhythmia. AF is considered a global healthcare problem with evidence suggesting an increasing prevalence and incidence worldwide (Lip, 2012; Ball, 2013; Chugh, 2014). A systematic review of worldwide population-based studies (n = 184) estimated that the number of individuals with AF in 2010 was 33.5 million and that there are about 5 million new cases each year. In 1990, the estimated age-adjusted prevalence rates (per 100,000 population) were 570 in men and 360 in women; the estimated age-adjusted incidence rates (per 100,000 person-years) were 61 in men and 44 in women

Important Identified Risk: cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris)	
	(Chugh, 2014). In 2010, the prevalence rates increased to 596 and 373 and the incidence rates increased to 78 and 60 in men and women, respectively. The age-adjusted prevalence rate (per 100,000 population) was highest in North America (700 to 775) and lowest in Japan and South Korea (250 to 325). The rate in China was also relatively low (325 to 400). The prevalence of AF is greater in older subjects and with underlying heart disease (Chugh, 2001; Majeed, 2001; Feinberg, 1995; Heeringa, 2006; Go, 2001). The incidence of AF also increases with advancing age and with the presence of cardiovascular disease (Kannel, 1982; Psaty, 1997; Krahn, 1995; Lloyd-Jones, 2004). The lifetime risk for the development of AF was analysed in a report from the Framingham Heart Study (Lloyd-Jones, 2004). A total of 8725 patients were followed from 1968 to 1999 (176,166 person-years of follow-up); 936 developed AF. The risk of developing AF from age 40 to age 95 was 26 percent for men and 23 percent for women. Lifetime risk did not change substantially with increasing index age because AF incidence rose with age; the risk of developing AF from age 80 to age 95 was 23 percent for men and 22 percent for women. Tachycardias form a large, heterogenous group of disorders in adults. Sinus tachycardia is the most common cause of tachycardia, as it is usually a normal physiological response to emotional or physical stimulation. Inappropriate sinus tachycardia (IST) is a nonparoxysmal tachyarrhythmia characterized by an increased resting heart rate and/or an exaggerated HR response to minimal exertion or a change in body posture (Kalman, 1997). The prevalence of inappropriate sinus tachycardia is not well known. In a sample of 604 middle-aged subjects it was estimated at 1.16% (Still, 2005). The underlying mechanisms are likely to be multifactorial, but patients are often young (age 15 to 50 years) and female, and are often healthcare professionals (Olshansky, 2013). The prevalence of the Wolff–Parkinson–White syndrome has been reported at 0.15–0.31% (Guize, 1985), and of ectopic atrial tachycardia at 0.46% (Poutiainen, 1999). Paroxysmal supraventricular tachycardia (PSVT), defined as intermittent supraventricular tachycardia (AV node re-entry tachycardia, AV reciprocating tachycardia, or atrial tachycardia) has an incidence of 36 cases per 100,000 person-years and a prevalence of 2.29 cases per 1000 people (Orejarena, 1998). Females are twice as likely to develop PSVT, and the incidence is 5 times greater in people older than 65 years compared with younger people (Orejarena, 1998). Most cases of supraventricular tachycardia are due to AV nodal re-entrant tachycardia (60% of cases) (Lowenstein, 1996); The prevalence of ventricular tachyarrhythmia is highly dependent on its type and duration (Roberts-Thomson, 2011).

Important Identified Risk: cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris)	
	The 2014 Heart Disease and Stroke Statistics update of the American Heart Association reported 7.8 million men and 7.6 million women with angina pectoris (Lloyd-Jones, 2010), resulting in a prevalence of 3.2% in men and 2.9 in women (Go, 2014).The reported prevalence increases with age for both women and men (Go, 2014). The annual rates per 1000 population of new episodes of AP for nonblack men are 28.3 for those 65 to 74 years of age, 36.3 for those 75 to 84 years of age, and 33.0 for those ≥85 years of age. For nonblack women in the same age groups, the rates are 14.1, 20.0, and 22.9, respectively. On the basis of 1987 to 2001 data from the ARIC study of the NHLBI, the annual rates per 1000 population of new episodes of AP for nonblack men are 8.5 for those 45 to 54 years of age, 11.9 for those 55 to 64 years of age, and 13.7 for those 65 to 74 years of age (National Heart, Lung and Blood Institute, 2006). Globally, age-standardized angina prevalence has decreased since 1990 (Moran, 2014).
Risk groups or risk factors	Patients susceptible to cardiac arrhythmias either due to medical history or a predisposition are the main risk group. Factors associated with increased risk of angina pectoris involve genetic disposition, obesity, cigarette smoking, physical inactivity, dyslipidemia, hypertension, diabetes mellitus and age (≥ 55 years for men, ≥ 65 for women) (Go, 2014).
Potential mechanisms	Inadequate dosing of levothyroxine and administering a dosage too high for the individual patient increases the systemic hemodynamic and T3-mediated effects on cardiac myocyte-specific gene expression (Kahali, 2005). The authors found a prevalence of 13.3% for atrial fibrillation (AF) in patients with low TSH concentration (< 0.4 mU/l) compared with 2.3 % in patients with normal serum TSH values and concluded that a low serum TSH is associated with a more than 5-fold higher likelihood for the presence of AF with no significant difference between subclinical and overt hyperthyroidism. On the other hand, they found ventricular arrhythmias to be rare in hyperthyroid patients without cardiac disease. Levothyroxine influences the metabolic rate and therefore the oxygen demand of the heart muscle. In patients with coexisting heart disease this may lead to angina pectoris (Fauci, 2008).
Preventability	Administering the correct dosage of levothyroxine and regular monitoring thyroid function could prevent cardiovascular disorders such as cardiac arrhythmias, tachycardia and angina pectoris. In patients with cardiac arrhythmias, coronary insufficiency or underlying heart disease, even slight drug-induced hyperthyroidism should be avoided (MRP SPC Levothyroxine, dated May 2015, section 4.2 and section 4.4).
Impact on individual patient	Depending on the seriousness, patients may be slightly or severely impacted.

Important Identified Risk: cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris)	
Potential public health impact of safety concern	Cardiovascular disorders such as cardiac arrhythmias, tachycardia and angina pectoris are listed in the RSI of levothyroxine as adverse reactions. The impact on public health is deemed minimal.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases.
MedDRA terms	SMQ Cardiac Arrhythmias (20000050 & 2000051), broad scope SMQ Other ischemic heart disease (20000043), broad scope

Important Identified Risk: hypersensitivity	
Frequency	In post marketing experience, cumulatively, 1,261 ICSRs falling under the SMQ hypersensitivity have been received by the Company. In post marketing experience, cumulative reporting incidence until cut-off date of this report (05 Oct 2016 2016) is **0.77 in 100,000 patient years**, based on MedDRA query as described below.
Seriousness/outcomes	Hypersensitivity can be non-serious, serious or life-threatening.
Background incidence/ prevalence	Hypersensitivity reactions to drugs or type B reactions make up 10 to 15 percent of adverse drug reactions (Lazarou, 1998). A meta-analysis of prospective studies aimed to estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients. Of the all severities adverse events recorded, 23.8% (95% CI: 18.6%-29.0%) were type B reactions (Lazarou, 1998). Regarding anaphylaxis, according to a study of primary healthcare data from the United Kingdom the annual incidence of anaphylaxis is 8.4 cases per 100 000 individuals in the general population, and the most frequent causes are insect venoms (32%), drugs (30%), and foods (22%) (Peng, 2004). A recent meta-analysis of 18 international epidemiological studies on drug-induced anaphylaxis in adults and children published from 1994 to 2009 reported that a predominance of cases were seen in males aged under 15 years and the highest rate was seen in adults aged 55 to 84 years (3.8/100 000 individuals) (Thong, 2011). Drugs are considered the main trigger of adult-age anaphylaxis, particularly in individuals aged over 65 years (Simons, 2012; Cianferoni, 2001).
Risk groups or risk factors	Hypersensitivity can occur in every patient taking levothyroxine. Patients with a history of hypersensitivity to any of the ingredients of levothyroxine are likely to experience a hypersensitivity reaction after intake of levothyroxine.

Important Identified Risk: hypersensitivity	
Potential mechanisms	Hypersensitivity (also called hypersensitivity reaction or intolerance) refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. They are classified in four groups (Gell & Coombs, 1963).
Preventability	Hypersensitivity cannot be prevented completely.
Impact on individual patient	Depending on the seriousness, patients may be slightly or severely impacted.
Potential public health impact of safety concern	Hypersensitivity is listed in the RSI of levothyroxine as an adverse reaction. The impact on public health is deemed minimal.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
MedDRA terms	SMQ Hypersensitivity (20000124), broad scope

Important Potential Risk: osteoporosis	
Frequency	In post marketing experience, cumulatively, 35 ICSRs falling under the SMQ Osteoporosis were received by the Company. Cumulative reporting rate until cut-off date of this report (05 Oct 2016) is calculated as **0.02 in 100,000 patient years**, based on MedDRA query as described below.
Seriousness/outcomes	Osteoporosis can be non-serious, but also develop into a serious condition, impacting a patient's quality of life.
Background incidence/prevalence	Large international variations in osteoporotic fracture rates had been reported (Leslie, 2014), with temporal trends that differ between populations (Cooper, 2011). Although most American women under the age of 50 have normal bone mineral density, 27% are osteopenic and 70% are osteoporotic at the hip, lumbar spine, or forearm by the age of 80 years (Denninson, 2005). Epidemiologic studies from North America have estimated the remaining lifetime risk of common fragility fractures to be 17.5% for hip fracture, 15.6% for clinically diagnosed vertebral fracture, and 16% for distal forearm fracture among white women aged 50 years (Schuit, 2004). The corresponding risks among men are 6%, 5%, and 2.5%, respectively. A British study using the General Practice Research Database estimated the lifetime risk of any fracture to be 53.2% at age 50 years among women and 20.7% at the same age among men (Van Staa, 2004).
Risk groups or risk factors	Postmenopausal women are the patient group at greatest risk. The Company's RSI warns about supraphysiological levels of levothyroxine in this risk group and advices on close monitoring of thyroid function.
Potential mechanisms	Levothyroxine over replacement may contribute to osteoporosis, as prolonged hyperthyroid state can cause loss of bone mass, as the overall metabolism is increased (Simonelli, 2006).
Impact on individual patient	Depending on the progression and extent of osteoporosis, patients may be slightly or severely impacted.
Potential public health impact of safety concern	Osteoporosis is responsible for millions of fractures annually, mostly involving the lumbar vertebrae, hip, and wrist.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases.
MedDRA terms	SMQ Osteoporosis/ Osteopenia (20000178)

Important Potential Risk: seizures in patients with known history of epilepsy	
Frequency	In post marketing experience, cumulatively, 39 ICSRs falling under the SMQ convulsions were received by the Company. Cumulative reporting rate until cut-off date of this report (05 Oct 2016) is calculated as **0.024 in 100,000 patient years**, based on MedDRA query as described below.
Seriousness/outcomes	The seriousness as well as signs and symptoms of seizures vary depending on the type. Seizures are serious and may also be life-threatening and in the worst case have a fatal outcome. Seizures have an impact on the patient's quality of life.
Background incidence/prevalence	There are three types of nonepileptic seizures: febrile convulsions, provoked seizures, and single seizures (Bortz, 1997). The non-epileptic origin of these seizures was illustrated in a population-based cohort study of 1195 patients with newly diagnosed or suspected epileptic seizures (Sanders, 1990). Of those, 631 had a seizure with a non-epileptic cause (52.8%) (Sanders, 1990). 1. Febrile convulsions are observed in the 3-5% of the children younger than 5 years (Verity, 1998; Offringa, 1991). 2. Provoked seizures can be caused by alcohol withdrawal, metabolic factors, toxins, drugs, sleep deprivation and acute infection, tumours, vascular disease, or trauma may trigger seizures (Fields, 2013). The incidence of seizures after the following conditions are: 4.8% after heart transplantation (Navarro, 2010); 6.3% after stroke (Beghi, 2010), 3.1% during the acute phase of stroke (within the first 24 hours of stroke onset) (Szaflarski, 2008), 4.5% in patients receiving clozapine treatment (Steinert, 2011), and 0.2% after thyrotoxicosis (Song, 2010). 3. In the case of isolated (single) seizures, two-thirds of people with a 'single seizure' have, on detailed questioning, other milder seizures (for example, myoclonus or simple partial seizures such as déjà vu or rising epigastric aura) (Angus-Leppan, 2008). This makes the questioning of patients for other subtle seizures essential, and the difference between a single seizure and epilepsy often depends on seizure types milder than the presenting one (Angus-Leppan, 2008).

Important Potential Risk: seizures in patients with known history of epilepsy	
Risk groups or risk factors	Patients with an underlying history of epilepsy or seizures have a higher risk when under levothyroxine therapy (Fields, 2013). General risk factors for developing seizures are: • Abnormal blood vessels in the brain • Brain hemorrhage, • Serious brain injury or lack of oxygen to the brain • Brain tumors • Infections of the brain: abscess, meningitis, or encephalitis • Stroke resulting from blockage of arteries • Cerebral palsy • Family history of epilepsy or fever-related seizures • Alzheimer's disease (late in the illness) • Autism spectrum disorder • Fever-related (febrile) seizures that are unusually long • Long episodes of seizures or repeated seizures called status epilepticus • Use of illegal drugs such as cocaine
Potential mechanisms	Seizures (generalized and partially) may be associated with exogenous levothyroxine intoxication, but may also occur in patients with endogenous hyperthyroidism and without reported medical history of seizures or other concomitant neurological diseases (Kahaly G, 1989). Recurrent hyperthyroidism can lead to a recurrence of seizures (Li Voon, 2000) and patients with juvenile myoclonic epilepsy can experience an increase of frequency and severity of seizures (Obeid T, 1996).
Impact on individual patient	Depending on the rate of occurrence and severity of seizure attacks, patients may be slightly or severely impacted. Patients may develop injuries following seizure attacks
Potential public health impact of safety concern	Seizures in predisposed patients are listed in the overdose section of the RSI. The overall impact on public health is deemed minimal.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases.
MedDRA terms	SMQ Convulsions (20000079), broad scope

SVII.4 Identified and Potential Interactions

SVII.4.1 Overview of Potential for Interactions

The primary pathway of thyroid hormone metabolism is through sequential deiodination. The liver is the main site where both T3 and T4 are metabolized, with T4 deiodination occurring at several other sites, including the kidney (Novothyrox Monograph USPI). In addition to deiodination, thyroid hormones are also metabolized through conjugation and glucuronidation and excreted directly into the bile and the gut where they undergo enterohepatic recirculation.

More than 99% of circulating thyroid hormones are bound to plasma proteins including thyroxine-binding globulin, thyroxine-binding prealbumin, and albumin. Only the free hormone is metabolically active.

Half-life elimination is estimated to 6-7 days for euthyroid patients; 9-10 days for hypothyroid patients; 3-4 days for hyperthyroid patients. Thyroid hormones are primarily eliminated by the kidneys (approximately 80%), with urinary excretion decreasing with age. The remaining 20% of T4 is eliminated in the stool.
Due to the high percentage of levothyroxine bound to plasma proteins (>99%), drug-drug interactions in terms of displacement and competition of binding sites are likely to occur.

Interacting substance	Coumarin derivatives
Effect of interaction	Levothyroxine may intensify the effect of anticoagulants by displacing them from plasma protein bounds which may increase the risk of hemorrhage.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Regular check-up of coagulation parameters at start of and during concomitant therapy is recommended. If necessary, the anticoagulant dose has to be adjusted (MRP SPC Levothyroxine, dated May 2015).
Potential health risk	The risk is adequately addressed in the RSI of levothyroxine.

Interacting substance	(Oral) anti-diabetic medicinal products
Effect of interaction	Levothyroxine may reduce the effect of anti-diabetics.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Regular blood glucose checks at the start of thyroid hormone therapy. If necessary, the anti-diabetic dose has to be adjusted (MRP SPC Levothyroxine, dated May 2015).
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal.

Interacting substance	Amiodarone
Effect of interaction	Amiodarone inhibits the peripheral conversion of T4 to T3. In addition, amiodarone can trigger hyperthyroidism as well as hypothyroidism.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Caution is advised in the case of nodular goitre with possibly unrecognized autonomy.
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal.

Interacting substance	Phenytoin
Effect of interaction	Phenytoin may influence the effect of levothyroxine by displacing it from plasma proteins resulting in an elevated fT4 and fT3 fraction. On the other hand, phenytoin increases the hepatic metabolization of levothyroxine.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Close monitoring of thyroid parameters is recommended. If necessary, the levothyroxine dose has to be adjusted (MRP SPC Levothyroxine, dated May 2015).
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal.

Interacting substance	Protease inhibitors
Effect of interaction	Protease inhibitors may influence the effect of levothyroxine.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Close monitoring of thyroid parameters is recommended. If necessary, the levothyroxine dose has to be adjusted (MRP SPC Levothyroxine, dated May 2015).
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal.

Interacting substance	Oestrogens
Effect of interaction	The need for levothyroxine may be increased in women using oestrogen-containing contraceptives or in postmenopausal women under hormone-replacement therapy.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Dosage adjustments may be necessary, on the basis of laboratory tests and clinical examination.
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal.

Interacting substance	Aluminium & iron-containing products, calcium carbonate
Effect of interaction	Products containing aluminium, iron or calcium have been reported to potentially decrease the effect of levothyroxine.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	It is recommended to take levothyroxine at least 2 hours prior to the administration of products containing aluminium, iron or calcium.
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal

Interacting substance	Soy products
Effect of interaction	Soy containing products can decrease the intestinal absorption of levothyroxine.
Evidence source	Clinical trials and post marketing experience, cumulative review of cases
Recommended action	Dose adjustment of levothyroxine may be necessary, in particular at the beginning or after termination of nutrition with soy supplements (MRP SPC Levothyroxine, dated May 2015).
Potential health risk	The risk is adequately covered and the impact on public health is deemed minimal

SVII.4.2 Important Identified and Potential InteractionsSVII.5 Pharmacological Class Effects

SVII.5.1 Pharmacological Class Risks Already Included as Important Identified or Potential Risks

Levothyroxine belongs to the pharmacological class of thyroid hormones, to which also belong the thyroid hormone triiodothyronine (also called liothyronine) and combination products of both hormones.

H03AA Thyroid hormones
H03AA01 Levothyroxine sodium
H03AA02 Liothyronine sodium
H03AA03 Combinations of levothyroxine and liothyronine
H03AA04 Tiratricol
H03AA05 Thyroid gland preparations

No frequency of adverse events are available from clinical trials and no frequency is specified in the current RSI of levothyroxine.

In addition, no frequency data are seen in comparator SPCs of levothyroxine, liothyronine or combination products of both levothyroxine and liothyronine.

Risks	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (source of data/journal reference)
Drug-induced clinical signs of hyperthyroidism/ thyrotoxicosis (important identified risk)	Not available	Not available
Adrenal insufficiency up to adrenal crisis in predisposed patients	Not available	Not available
Cardiovascular disorders (e.g. cardiac arrhythmias. tachycardia and angina pectoris) (important identified risk)	Not available	Not available
Hypersensitivity (important identified risk)	Not available	Not available
Off label use/abuse and misuse for weight reduction (important potential risk)	Not available	Not available
Osteoporosis (important potential risk)	Not available	Not available
Seizures in patients with known history of epilepsy	Not available	Not available

SVII.5.2 Important Pharmacological Class Effects not Discussed Above

There are no additional important identified class effects of thyroid hormones not discussed in sections SVII.3 and SVII.4 above.

Part II: Module SVIII - Summary of the Safety Concerns

Table 6 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis • Adrenal insufficiency up to adrenal crisis in predisposed patients • Cardiovascular disorders (e.g. cardiac arrhythmias. Tachycardia and angina pectoris) • Hypersensitivity
Important potential risks	• Off label use/abuse and misuse for weight reduction • Osteoporosis • Seizures in patients with known history of epilepsy
Missing information	None

Part III: Pharmacovigilance Plan

III.1 Safety Concerns and Overview of Planned Pharmacovigilance Actions

Safety concern: Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis (important identified risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
none	routine pharmacovigilance activities	

Safety concern: Adrenal insufficiency up to adrenal crisis in predisposed patients (important identified risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
none	routine pharmacovigilance activities	

Safety concern: Cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris) (important identified risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
none	routine pharmacovigilance activities	

Safety concern: Hypersensitivity (important identified risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
none	routine pharmacovigilance activities	

Safety concern: off label use/abuse and misuse for weight reduction (important potential risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Assessment of occurrence and nature of off-label use, abuse and misuse cases for weight reduction in post-marketing use	Routine pharmacovigilance activities, including close monitoring. Cumulative re-analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.	To monitor the frequency and severity of reports of off label use, abuse and misuse for weight reduction following the use of levothyroxine

Safety concern: osteoporosis (important potential risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Assessment of occurrence of osteoporosis in post-marketing use, and evaluation of possible causal relationship	Routine pharmacovigilance activities, including close monitoring. Cumulative re-analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.	To monitor the frequency and severity of reports of osteoporosis following the use of levothyroxine and the circumstances in which osteoporosis occurs in patients, to elucidate whether the event is related to levothyroxine treatment or attributable to other factors/ underlying disease.

Safety concern: Seizures in patients with known history of epilepsy (important potential risk)		
Area requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None, as this potential risk is described in section overdose of the RSI	Routine pharmacovigilance activities Cumulative re-analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.	To monitor the frequency and severity of reports of occurrence of seizures following the use of levothyroxine and the circumstances in which seizures occur in patients, to elucidate whether the event is related to levothyroxine treatment or attributable to other factors/ underlying disease.

III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimization Measures

Not applicable.

III.3 Studies and Other Activities Completed Since last Update of Pharmacovigilance Plan

No studies were completed since the last RMP version (version 4.0, DLP April 2015).

III.4 Details of Outstanding Additional Pharmacovigilance Activities

Not applicable.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Not applicable.

III.5.2 Table of Completed Studies/Activities from the Pharmacovigilance Plan

Not applicable.

Part IV: Plans for Post-authorization Efficacy Studies

IV.1 Applicability of Efficacy to all Patients in the Target Population

Due to the long-term experience with levothyroxine there is no specific need for further post-authorization efficacy studies in the listed indications. There is no gap in knowledge in the target group. Therefore, the MAH is currently not planning or conducting any PAES studies.

IV.2 Tables of Post-authorization Efficacy Studies

At the time of this report, no PAES studies are planned or ongoing.

IV.3 Summary of Post authorization Efficacy Development Plan

Not applicable.

IV.4 Summary of Completed Post Authorization Efficacy Studies

Not applicable.

Part V: Risk Minimization Measures

V.1 Risk Minimization Measures by Safety Concern

The following Table 7 shows a summary of the safety concerns and the corresponding risk minimization measures.

Table 7 Summary of safety concerns and corresponding risk minimization measures

Safety concern: Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product.
Routine risk minimization measures	Listed in the SmPCs in sections Contraindications: untreated thyrotoxicosis Warnings and precautions: Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism. Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases. Adverse reactions: clinical signs of hyperthyroidism
	Other routine risk minimization measures: Prescription only medicine

Effectiveness of risk minimization measures	Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis (Identified Risk)
How effectiveness of risk minimization measures for the safety concern will be measured	Routine post marketing surveillance
Criteria for judging the success of the proposed risk minimization measures	No increase in incidence of events
Planned dates for assessment	Continuously (at least once monthly), in the context of signal management. A cumulative analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.
Results of effectiveness measurement	Not applicable
Impact of risk minimization	No impact on prescribers or patients
Comment	None

Safety concern: Adrenal insufficiency up to adrenal crisis in predisposed patients	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product.
Routine risk minimization measures	Listed in the SmPCs in sections: Contraindication: untreated adrenal insufficiency Warnings and precautions: Before starting therapy with thyroid hormones or before performing a thyroid suppression test, adrenal insufficiency must be excluded or treated.
	Other routine risk minimization measures: Prescription only medicine

Effectiveness of risk minimization measures	Adrenal insufficiency up to adrenal crisis in predisposed patients (Identified Risk)
How effectiveness of risk minimization measures for the safety concern will be measured	Routine post marketing surveillance
Criteria for judging the success of the proposed risk minimization measures	No increase in incidence of events
Planned dates for assessment	Continuously (at least once monthly), in the context of signal management. A cumulative analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.
Results of effectiveness measurement	Not applicable
Impact of risk minimization	No impact on prescribers or patients
Comment	None

Safety concern: Cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris)	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product.
Routine risk minimization measures	Listed in the SmPCs in sections Warnings and precautions: Even slight drug-induced hyperthyroidism must be avoided in patients with coronary insufficiency, heart failure or tachycardia arrhythmias. Frequent checks of thyroid parameters must be performed in these cases. Before starting therapy with thyroid hormones, angina pectoris must be excluded or treated. Adverse reactions: cardiac arrhythmias given as example of typical symptoms of clinical signs of hyperthyroidism.
	Other routine risk minimization measures: Prescription only medicine

Effectiveness of risk minimization measures	Cardiovascular disorders (e.g. cardiac arrhythmias, tachycardia and angina pectoris) (identified risk)
How effectiveness of risk minimization measures for the safety concern will be measured	Routine post marketing surveillance
Criteria for judging the success of the proposed risk minimization measures	No increase in incidence of events
Planned dates for assessment	Continuously (at least once monthly), in the context of signal management. A cumulative analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.
Results of effectiveness measurement	Not applicable
Impact of risk minimization	No impact on prescribers or patients
Comment	None

Safety concern: Hypersensitivity	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product.
Routine risk minimization measures	Listed in the SmPCs in section Adverse reactions: In case of hypersensitivity to any ingredients of Euthyrox allergic reactions particularly of the skin and the respiratory tract may occur; cases of angioedema have been reported
	Other routine risk minimization measures: Prescription only medicine

Effectiveness of risk minimization measures	Hypersensitivity (identified risk)
How effectiveness of risk minimization measures for the safety concern will be measured	Routine post marketing surveillance
Criteria for judging the success of the proposed risk minimization measures	No increase in incidence of events
Planned dates for assessment	Continuously (at least once monthly), in the context of signal management. A cumulative analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available.
Results of effectiveness measurement	Not applicable
Impact of risk minimization	No impact on prescribers or patients
Comment	None

Safety concern: Off label use/abuse and misuse for weight reduction (potential risk)	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product.
Routine risk minimization measures	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9). The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets Thyroid hormones are not suitable for weight reduction. Intake of thyroid hormones will not reduce your weight, if your thyroid hormone level is in a normal range. Serious or even life threatening side effects may occur if you increase the dose without special advice from your doctor.
Additional risk minimization measure(s)	None

Safety concern: Osteoporosis (potential risk)	
Objective of the risk minimization measures	To provide appropriate information to healthcare professionals and patients on this risk, thereby ensuring optimal and safe use of the product. None proposed (potential risk)
Routine risk minimization measures	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely. The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets Speak to your doctor, if you are in the menopause or post-menopausal; your doctor may need to check your thyroid function regularly because of the risk of osteoporosis.
Additional risk minimization measure(s)	None

Safety concern: Seizures in patients with known history of epilepsy (potential risk)	
Objective of the risk minimization measures	None proposed (potential risk)
Routine risk minimization measures	The EU SmPC contains the following wording in section 4.9 overdose: • In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded. The EU PIL contains following wording in section 3 • If you take more levothyroxine sodium tablets than you should: If you have taken a higher dose than prescribed, you may experience symptoms such as […] agitation or unintended movements. In patients with a disorder affecting the neurological system such as epilepsy, seizures may occur in isolated cases. If any of this happens, contact your doctor.
Additional risk minimization measure(s)	None

V.2 Risk Minimization Measure Failure (if applicable)

Not applicable.

V.2.1 Analysis of Risk Minimization Measure(s) Failure

Not applicable.

V.2.2 Revised Proposal for Risk Minimization

Not applicable

V.3 Summary Table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	Listed in the SmPCs in sections Contraindications: untreated thyrotoxicosis Warnings and precautions: Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism. Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases. Adverse reactions: clinical signs of hyperthyroidism Other routine risk minimization measures: Prescription only medicine	Not applicable
Adrenal insufficiency up to adrenal crisis in predisposed patients	Listed in the SmPCs in sections: Contraindication: untreated adrenal insufficiency Warnings and precautions: Before starting therapy with thyroid hormones or before performing a thyroid suppression test, adrenal insufficiency must be excluded or treated. Other routine risk minimization measures: Prescription only medicine	Not applicable
Cardiovascular disorders (e.g. cardiac arrhythmias , tachycardia and angina pectoris)	Listed in the SmPCs in sections Warnings and precautions: Even slight drug-induced hyperthyroidism must be avoided in patients with coronary insufficiency, heart failure or tachycardic arrhythmias. Frequent checks of thyroid parameters must be performed in these cases. Before starting therapy with thyroid hormones, angina pectoris must be excluded or treated. Adverse reactions: cardiac arrhythmias given as example of typical symptoms of clinical signs of hyperthyroidism. Other routine risk minimization measures: Prescription only medicine	Not applicable
Hypersensitivity	Listed in the SmPCs in section Adverse reactions: in case of hypersensitivity to any of the ingredients, allergic reactions may occur; cases of angioedema have been reported Other routine risk minimization measures: Prescription only medicine	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Off label use/abuse and misuse for weight reduction	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9). The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets: Thyroid hormones are not suitable for weight reduction. Intake of thyroid hormones will not reduce your weight, if your thyroid hormone level is in a normal range. Serious or even life threatening side effects may occur if you increase the dose without special advice from your doctor.)	Not applicable
Osteoporosis	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use: In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely. The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets: Speak to your doctor,-if you are in the menopause or post-menopausal; your doctor may need to check your thyroid function regularly because of the risk of osteoporosis.	Not applicable
Seizures in patients with known history of epilepsy	The EU SmPC contains the following wording in section 4.9 overdose: • In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded. The EU PIL contains following wording in section 3 • If you take more levothyroxine sodium tablets than you should: If you have taken a higher dose than prescribed, you may experience symptoms such as […] agitation or unintended movements. In patients with a disorder affecting the neurological system such as epilepsy, seizures may occur in isolated cases. If any of this happens, contact your doctor.	Not applicable

Part VI: Summary of Activities in the Risk Management Plan by Product

VI.1 Elements for Summary Tables in the EPAR

VI.1.1 Summary Table of Safety Concerns

Summary of safety concerns	
Important identified risks	Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis Adrenal insufficiency up to adrenal crisis in predisposed patients Cardiovascular disorders (e.g. cardiac arrhythmias , tachycardia and angina pectoris) Hypersensitivity
Important potential risks	Off label use/abuse and misuse for weight reduction Osteoporosis Seizures in patients with known history of epilepsy
Missing information	None

VI.1.2 Table of On-going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3 Summary of Post Authorization Efficacy Development Plan

Not applicable.

VI.1.4 Summary Table of Risk Minimization Measures

Safety concern	Routine risk minimization measures
Clinical signs of hyperthyroidism/ drug-induced hyperthyroidism/ thyrotoxicosis	Listed in the SmPCs in sections Contraindications: untreated thyrotoxicosis Warnings and precautions: Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism. Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases. Adverse reactions: clinical signs of hyperthyroidism Other routine risk minimization measures: Prescription only medicine
Adrenal insufficiency up to adrenal crisis in predisposed patients	Listed in the SmPCs in sections: Contraindication: untreated adrenal insufficiency Warnings and precautions: Before starting therapy with thyroid hormones or before performing a thyroid suppression test, adrenal insufficiency must be excluded or treated. Other routine risk minimization measures: Prescription only medicine
Cardiovascular disorders (e.g. cardiac arrhythmias , tachycardia and angina pectoris)	Listed in the SmPCs in sections Warnings and precautions: Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism. Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases. Before starting therapy with thyroid hormones, angina pectoris must be excluded or treated. Adverse reactions: cardiac arrhythmias given as example of typical symptoms of clinical signs of hyperthyroidism. Other routine risk minimization measures: Prescription only medicine
Hypersensitivity	Listed in the SmPCs in section Adverse reactions: in case of hypersensitivity to any of the ingredients, allergic reactions may occur; cases of angioedema have been reported Other routine risk minimization measures: Prescription only medicine

Safety concern	Routine risk minimization measures
Off label use/abuse and misuse for weight reduction	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use: Thyroid hormones are not suitable for weight reduction. Physiological doses do not result in any weight loss in euthyroid patients. Supraphysiological doses may cause severe or even life-threatening undesirable effects (see section 4.9). The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets: Thyroid hormones are not suitable for weight reduction. Intake of thyroid hormones will not reduce your weight, if your thyroid hormone level is in a normal range. Serious or even life threatening side effects may occur if you increase the dose without special advice from your doctor.)
Osteoporosis	The EU SmPC contains following recommendation: • Section 4.4 Special warnings and precautions for use: In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely. The EU PIL contains following recommendation: • Section 2 What you need to know before you take levothyroxine sodium tablets: Speak to your doctor,if you are in the menopause or post-menopausal; your doctor may need to check your thyroid function regularly because of the risk of osteoporosis.
Seizures in patients with known history of epilepsy	The EU SmPC contains the following wording in section 4.9 overdose: • In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded. The EU PIL contains following wording in section 3 • If you take more levothyroxine sodium tablets than you should: If you have taken a higher dose than prescribed, you may experience symptoms such as […] agitation or unintended movements. In patients with a disorder affecting the neurological system such as epilepsy, seizures may occur in isolated cases. If any of this happens, contact your doctor.

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

An overview of the disease epidemiology of the four indications of levothyroxine is provided in this section.

Levothyroxine is indicated to treat benign goitre- a swelling of the neck or larynx resulting from a benign or non-cancerous enlargement of the thyroid gland- in patients with normal thyroid function, to prevent recurrence of goitre after surgery, to replace natural thyroid hormones, when the thyroid gland does not produce enough hormones and to suppress tumor growth in patients with thyroid cancer. Levothyroxine -as contained in levothyroxine sodium tablets- is chemically identical to the hormone naturally produced and secreted by the thyroid gland.

Benign goitre (non-cancerous enlargement of the thyroid gland)

Worldwide, over 90% cases of goitre are caused by iodine deficiency (a dietary intake of iodine below the required need) (Hoermann, 2005).

Goitre is more common among women. If the thyroid gland is producing too much thyroid hormone, radioactive iodine is given to the patient to shrink the gland. If goitre is caused by iodine deficiency, small doses of iodide are given. If the goitre is associated with an underactive thyroid, thyroid hormone, such as levothyroxine is given as treatment. If goitre is interfering with breathing or swallowing, and it has not responded to other forms of treatment, the patient may need surgery to remove part or all of the thyroid gland. This procedure is known as a thyroidectomy (removal of thyroid gland), and is followed by life-long intake of levothyroxine.

Prevention of recurrence of goitre after surgery

After removal of the thyroid, the intake of levothyroxine can help to avoid the recurrence of goitre. Recurrence of goitre under replacement therapy is reported to happen in about 2-39 % of cases. Recurrence of goitre without replacement therapy with levothyroxine is reported in around 70% (Capellani, 2008).

Hypothyroidism (underactive thyroid): to replace natural thyroid hormones, when the thyroid gland does not produce enough hormones.

Hypothyroidism, also called underactive thyroid gland, is a disorder in which the thyroid gland does not produce enough thyroid hormone as it should. It can cause a number of symptoms, such as tiredness, poor ability to tolerate cold temperatures, and weight gain. In children, hypothyroidism leads to delays in growth and intellectual development, which, in severe cases was previously known as cretinism. The diagnosis of hypothyroidism, when suspected, can be confirmed with blood tests. Worldwide, too little iodine in the diet is the most common cause of hypothyroidism. In countries with enough dietary iodine, it occurs in 1-2% of the population and it is more common in older women and ten times more common in women than in men (Vanderpump, 2008). In Western countries, hypothyroidism occurs in 0.3–0.4% of people while

subclinical hypothyroidism (relating to a stage in the development of the disease before symptoms become apparent) occurs in 4.3–8.5% of people.

Suppression of tumor growth in patients with thyroid cancer

Globally, thyroid cancer accounts for 2.1% of all cancers (Ferlay, 2012). Thyroid cancer accounts for 0.9% of all cancers in men and for 3.5% of all cancers in women.

Thyroid cancer is treated by surgically removing all or part of the thyroid gland. This is followed by radioactive iodine ablation of thyroid cells that may remain after this operation. Even after radioactive iodine therapy and surgery, it is possible that thyroid cancer may recur, sometimes years - or even decades - after the initial treatment for the disease. Thyroid hormone therapy uses hormones to help halt the growth of cancer cells by lowering the level of thyroid stimulating hormone, a hormone that directly promotes thyroid gland activity and is associated with thyroid cancer growth. In other thyroid cancers, thyroid hormone may be used to help maintain normal levels of thyroid hormone in the body.

VI.2.2 Summary of Treatment Benefits

Hypothyroidism, often called underactive thyroid or low thyroid, is a disorder in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as tiredness, poor ability to tolerate cold temperatures, and weight gain. In children, hypothyroidism leads to delays in growth and intellectual development.

Levothyroxine is a synthetic thyroid hormone that is chemically identical to the thyroid hormone which is naturally produced by the cells of the thyroid gland.

Levothyroxine sodium tablets are indicated as replacement or supplement of thyroid hormone to prevent the symptoms of hypothyroidism. It is also indicated to treat goitre via its ability to lower the hormone that stimulates goitre growth. Levothyroxine is further indicated as therapy in patients with thyroid cancer to help halt the growth of cancer cells by lowering the level of thyroid stimulating hormone (TSH), a hormone that addresses the thyroid directly and is associated with thyroid cancer growth. Levothyroxine can also be used in the testing of thyroid function.

Due to the long-term experience with levothyroxine, the efficacy, safety and tolerability profile of levothyroxine is well established for the therapy of goitre in patients with normal thyroid function, prevention of recurrence of goitre after surgery therapy of hypothyroidism, replacement of natural thyroid hormones when the thyroid gland is under-active, suppression of tumour growth in patients with thyroid cancer as well as the testing of thyroid function."

VI.2.3 Unknowns Relating to Treatment Benefits

Due to long-term experience with levothyroxine there are no specific unknowns relating to treatment benefits of levothyroxine in therapy of goitre with normal thyroid function, prevention of recurrence of goitre after surgery, replacement of natural thyroid hormones of under-active thyroid gland and suppression of tumor growth and testing of thyroid function.

Based on the long-term experience with levothyroxine, there is no indication that levothyroxine is less efficient or has an unfavorable benefit/ risk balance in any specific group of the patient population for whom it is authorized to be used.

VI.2.4 Summary of Safety Concerns

Important identified risks

Risk	What is known	Preventability
Too much thyroid activity, causing symptoms such as headache, muscle weakness or cramps, warmth and redness of the face (flushing), fever, vomiting, problems with menstrual period (disorders of menstruation), increased pressure in the head with eye swelling (Pseudotumor cerebri), trembling, restlessness, sleep disturbances, sweating, weight loss and diarrhea. (Medication-induced hyperthyroidism; drug-induced hyperthyroidism).	The term hyperthyroidism refers to any condition in which there is too much thyroid hormone in the body. This could either occur due to an overactive thyroid gland producing a too high amount of thyroid hormone or it could be caused due to intake of too much medication containing thyroid hormone such as levothyroxine sodium tablets.	Levothyroxine should be taken strictly as prescribed and not more than the prescribed dosage should be taken. If any of these symptoms of too much thyroid activity are observed, it is advised that the patient contacts his/ her doctor. The treating doctor may decide to interrupt the therapy for several days or reduce the daily dose. The symptoms of medication-induced hyperthyroidism are described in the patient information leaflet (PIL) of levothyroxine (PIL Levothyroxine, 2015).

Risk	What is known	Preventability
Excessive overproduction of thyroid hormones/ excessive levels of thyroid hormones in the blood leading to medical emergency with failure of one or more organ systems (thyrotoxic crisis).	Thyrotoxic crisis is an acute, life-threatening condition. Individuals with existing high thyroid levels in the blood may develop thyrotoxic crisis after experiencing trauma, surgery, severe emotional distress, stroke, heart problems, or blood clots in the lungs. Thyrotoxic crisis may also occur in association with enlargement of the thyroid gland, containing areas that have increased in size and formed nodules. One or more of these nodules produce too much thyroid hormone. Another cause of thyrotoxic crisis may be a complication of a disease of the thyroid gland secreting an overabundance of thyroid hormones. Symptoms of thyrotoxic crisis may include: •racing heart rate (tachycardia) that exceeds 140 beats per minute and atrial fibrillation •high fever •persistent sweating •shaking •agitation •restlessness •confusion •diarrhea •unconsciousness	The following precautions are described in the patient information leaflet (PIL) of levothyroxine (PIL Levothyroxine, 2015): Patients with excessive levels of thyroid hormone in the blood (thyrotoxicosis) should not take levothyroxine (described under contraindications in the patient information leaflet of levothyroxine (PIL Levothyroxine, 2015). The doctor will investigate if the patient has a dysfunction of the thyroid gland with uncontrolled overproduction of thyroid hormones (thyroid autonomy), because this condition must be medically controlled before a patient can start taking levothyroxine or before a thyroid suppression test is performed.

Risk	What is known	Preventability
Dysfunction of the adrenal gland up to crisis in patients with a medical history of adrenal gland disease (Adrenal crisis in predisposed patients).	The adrenal gland is a gland found over each kidney that helps regulate blood pressure and stress. When there is a dysfunctioning of this gland, the body does not produce enough of the hormones cortisol and aldosterone. Cortisol helps responding effectively to stress. It also plays a role in bone health, immune response, and the metabolism of food. People who have a disease of the adrenal glands called Addison's disease do not produce enough cortisol or aldosterone. Low levels of cortisol may cause weakness, fatigue and low blood pressure. Aldosterone regulates sodium and potassium levels. When levels of cortisol fall rapidly, people develop Addisonian crisis. Addisonian crisis, also called acute adrenal insufficiency, is a serious emergency condition and could also be deadly. Those people most at risk for Addisonian crisis are: •individuals suffering from Addison's disease •people who have damage to the pituitary gland (this is the gland that sits under the brain and makes and secretes many hormones, including some that control other glands), where adrenal insufficiency may be a result •patients being treated for any kind of adrenal disease and who do not take their medication •people who are experiencing some kinds of physical trauma and stress •surgical patients •individuals who are experiencing dehydration	Levothyroxine should not be taken in patients with untreated dysfunction of the adrenal gland. Before treatment with levothyroxine, the doctor will investigate if the patient has a dysfunction of the adrenal gland, because this condition must be medically controlled before a patient can start taking levothyroxine tablets or before a thyroid suppression test is performed. The precautions stated above are described in the patient information leaflet (PIL Levothyroxine, 2015).

Risk	What is known	Preventability
Heart problems such as changes from the normal heart beat, irregular heart beat (cardiac arrhythmias) or **rapid heartbeat** (tachycardia) or c**hest pain due to decreased oxygen being supplied to the heart, insufficient blood flow in the blood vessels of the heart** (angina pectoris), cardiovascular disorders, e.g. cardiac arrhythmias, tachycardia and angina pectoris)	Excess of thyroid hormone increases the heart rate and may also cause irregular heartbeat. The work of the heart is greatly increased with excess thyroid hormone. Excess thyroid hormone increases the force of contraction of the heart muscle, and increases the amount of oxygen demanded by the heart.	Levothyroxine should be taken strictly as prescribed and not more than the prescribed dosage should be taken. If any of these heart symptoms are observed, it is advised that the patient contacts his/ her doctor. The treating doctor may decide to interrupt the therapy for several days or reduce the daily dose, to help reduce heart problems The adverse reactions are described in the patient information leaflet of levothyroxine (PIL Levothyroxine, 2015).
Over sensitivity, causing allergic reactions (hypersensitivity)	The active hormone contained in levothyroxine sodium tablets is chemically identical to the natural hormone, but allergic reactions may occur to any of the ingredients of levothyroxine tablets (see PIL section 6. 'What levothyroxine sodium tablets contain').	All medicines can cause allergic reactions although serious allergic reactions are rare. Allergic reactions may include swelling of the face or throat (angioedema). Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching especially affecting the whole body should be reported to a doctor immediately. If a patient had been allergic to any of the ingredients contained in levothyroxine tablets in the past, it is possible that the allergic reaction occurs with levothyroxine sodium tablets intake and this should be discussed with a doctor before intake. The adverse reactions are described in the patient information leaflet of levothyroxine (PIL Levothyroxine, 2015).

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use of the drug levothyroxine in order to lose weight (off label use/abuse and misuse for weight reduction)	Levothyroxine should not be used for weight loss, as this may lead to dangerous side effects which may harm the patient's health.
Loss of calcium from bone tissue resulting in bones that break easily; prevalent in postmenopausal women (osteoporosis)	Women in and after the menopause who take levothyroxine may be at an increased risk of developing bones that break easily. Since levothyroxine has been on the market, a few patients have been reported to have experienced osteoporosis while they were taking levothyroxine. However, it is not possible to say whether this is definitely caused by the levothyroxine. The Patient Leaflet advises patients to *speak to their doctor, if they are in the menopause or post-menopausal; regular check of thyroid function may be required because of the risk of osteoporosis* (MRP PIL Levothyroxine, dated May 2015). The Company is continuously and carefully monitoring all reports on this issue due to its potential seriousness.
Sudden, uncontrolled muscle spasms and loss of consciousness resulting from abnormal brain function in patients with a known history of such disease (Seizures in patients with known history of epilepsy)	If more than the prescribed dosage of levothyroxine is taken, sudden, uncontrolled muscle spasms and loss of consciousness resulting from abnormal brain function may be a consequence, especially in patients with a known history of such disease (Kahaly, 1989). The Patient Leaflet advises patients to *speak to their doctor, if they experience a seizure* (MRP PIL Levothyroxine, dated May 2015). The adverse reactions seizures in isolated cases are described in the section overdose of the patient information leaflet of levothyroxine (PIL Levothyroxine, 2015).

Missing information

Levothyroxine has been used since its first launch in 1972. There is no significant missing information relating to its use.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the patient information leaflet (PIL).

There are no additional risk minimization measures for levothyroxine.

VI.2.6 Planned Post Authorization Development Plan

The company is currently not planning to conduct further studies which are a condition of the marketing authorization or required for post-authorization development.

VI.2.7 Summary of Changes to the Risk Management Plan over Time

Table 8 Major changes to the Risk Management Plan over time

Version	Date	Changes performed
2.0	Jan 2015	**Signature page** Signature of Head of GDS not required any longer as per Company internal SOPs **Part I: Product Overview** Proposed new formulation added to the Pharmaceutical Form and Strengths for current Further invented trade names outside the EEA added **Part II SVI.2 Potential for Transmission of Infectious Agents** Information on excipients of new formulation added **Part II: SV.2Non-study Post-authorization Exposure** Exposure data updated **Part III.3 Studies and other activities completed since last update if Pharmacovigilance Plan** Study results of the bioequivalence phase I trials with the new formulation of levothyroxine added. **Part II: Module SVI - Additional EU Requirements for the Safety Specification** Frequencies of cumulative data updated until DLP 31 Dec 2014 **SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)** Frequency of risks updated cumulatively until DLP 31 Dec 2014 **Whole RMP document** Where applicable- data updated to DLP 31 Dec 2014

Version	Date	Changes performed
3.0	Feb 2015	**Part II: SV.2 Non-study Post-authorization Exposure** Exposure data updated until 15 Feb 2015 **Part SVII.3 Important Identified and Potential Risks** Important identified risks modified as follows: Important identified risks: • clinical signs of hyperthyroidism/ thyrotoxic crisis • adrenal insufficiency up to adrenal crisis in predisposed patients • cardiovascular disorders (e.g. Cardiac arrhythmias, Tachycardia and Angina pectoris) • hypersensitivity Important potential risks: • osteoporosis • seizures in patients with known history of epilepsy **Part SVII.4.2 Important Identified and Potential Interactions** Table on interactions moved to part SVII.4.1 **Part III.3 Studies and other activities completed since last update of Pharmacovigilance Plan** First sentence on the PV system deleted **Part II: Module SVI - Additional EU Requirements for the Safety Specification** Frequencies of cumulative data updated until DLP 15 Feb 2015 **SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)** Frequency of risks updated cumulatively until DLP 15 Feb 2015 **VI.2.4 Summary of Safety Concerns** The following important identified and potential risks were added in lay language: • Cardiovascular disorders (e.g. Cardiac arrhythmias, Tachycardia and Angina pectoris • Adrenal insufficiency up to adrenal crisis in predisposed patients • Seizures in patients with known history of epilepsy **Whole RMP document** Where applicable- data updated to DLP 15 Feb 2015

Version	Date	Changes performed
4.0	Aug 2016	**Part II: Module SVI - Additional EU Requirements for the Safety Specification** Frequencies of cumulative data updated until DLP 05 Oct 2016 **SVI.3 Potential for Misuse for Illegal Purposes** Section updated regarding the new risk **SVI.5 Potential for Off-label Use** Section updated **Part SVII.3 Important Identified and Potential Risks** Addition of the important potential risk "off label use/abuse and misuse for weight reduction" **SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)** • Addition of the new potential risk off-label use/abuse and misuse for weight reduction • Frequency of risks updated cumulatively until DLP 05 Oct 2016 **VI.2.4 Summary of Safety Concerns** The following important potential risk was added in lay language: • Off label use/abuse and misuse for weight reduction **Whole RMP document** Where applicable- data was updated to DLP 05 Oct 2016 Where applicable- reference to RSI was changed to the MRP SmPC and MRP PIL, dated May 2015), in previous RMP version 3.0, it was usually referenced to the CSDS.

Version	Date	Changes performed
4.1	Aug 2017	**Title page of the RMP** Deletion of the invented names outside the EEA on the title page of the RMP (request of HA in PVAR DE/H/xxxx/WS/382) **Part I: Product(s) Overview** Recent RMP Versions under Evaluation: All information in the table of the RMP was deleted/replaced by 'not applicable' (request of HA in PVAR DE/H/xxxx/WS/382) **SVII.3 Details of Important Identified and Potential Risks from Clinical Development and Post-authorization Experience (including newly identified)** Important Identified Risk: adrenal insufficiency up to adrenal crisis in predisposed patients: - Background incidence/prevalence-: Reconstitution of the accidently deleted information concerning the background incidence and prevalence (request of HA in PVAR DE/H/xxxx/WS/382) **Part V: Risk Minimization Measures** **V.1 Risk Minimization Measures by Safety Concern** The following statement has been included (request of HA in PVAR DE/H/xxxx/WS/382): Continuously (at least once monthly), in the context of signal management. A cumulative analysis will be performed at the time of each PSUR (PBRER), or whenever significant new information becomes available. **Data lock point** DLP in agreement with HA remains 05 Oct 2016 as there were no changes regarding scientific/medical content.
5.0	Oct 2017	Version number of the RMP updated to 5.0 during closing sequence in agreement with HA in FVAR DE/H/xxxx/WS/382. **Data lock point** DLP in agreement with HA remains 05 Oct 2016 as there were no changes regarding scientific/medical content.

Part VII Annexes

Annex 1 EudraVigilance Interface (available in electronic format only)

Annex 2 SmPC and Patient Information Leaflet

Annex 3 Worldwide marketing authorization by country (including EEA)

Annex 3.1 Licensing status in the EEA

Annex 3.2 Licensing status in the rest of the world

Annex 4 Synopsis of on-going and completed clinical trial program

Annex 5 Synopsis of on-going and completed pharmacoepidemiological study program

Annex 6 Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part III
(not applicable)

Annex 7 Specific adverse event follow-up forms
(not applicable)

Annex 8 Protocols for proposed and on-going studies in RMP Part IV
(not applicable)

Annex 9 Newly available study reports for RMP Parts III & IV
(not applicable)

Annex 10 Details of proposed additional risk minimization measures
(not applicable)

Annex 11 Mock-up of proposed additional risk minimization measures
(not applicable)

Annex 12 Other supporting data (Excel spreadsheet comparing Medication error terms in MedDRA 18.1 and MedDRA 19.1)

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RMP (GVP) Levothyroxine (Euthyrox), Oct 2017, Version 5.0 - Report

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
GREGAN Bernd	Business Approval	09-Oct-2017 16:52 GMT+02
TAYROUZ Yorki	Business Approval	09-Oct-2017 16:55 GMT+02
ANDERSEN Berit Nautrup	Business Approval	09-Oct-2017 16:59 GMT+02

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Euthyrox 25 microgram tablets
Euthyrox 50 microgram tablets
Euthyrox 75 microgram tablets
Euthyrox 88 microgram tablets
Euthyrox 100 microgram tablets
Euthyrox 112 microgram tablets
Euthyrox 125 microgram tablets
Euthyrox 137 microgram tablets
Euthyrox 150 microgram tablets
Euthyrox 175 microgram tablets
Euthyrox 200 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet Euthyrox 25 microgram contains 25 microgram levothyroxine sodium.
1 tablet Euthyrox 50 microgram contains 50 microgram levothyroxine sodium.
1 tablet Euthyrox 75 microgram contains 75 microgram levothyroxine sodium.
1 tablet Euthyrox 88 microgram contains 88 microgram levothyroxine sodium.
1 tablet Euthyrox 100 microgram contains 100 microgram levothyroxine sodium.
1 tablet Euthyrox 112 microgram contains 112 microgram levothyroxine sodium.
1 tablet Euthyrox 125 microgram contains 125 microgram levothyroxine sodium.
1 tablet Euthyrox 137 microgram contains 137 microgram levothyroxine sodium.
1 tablet Euthyrox 150 microgram contains 150 microgram levothyroxine sodium.
1 tablet Euthyrox 175 microgram contains 175 microgram levothyroxine sodium.
1 tablet Euthyrox 200 microgram contains 200 microgram levothyroxine sodium.

Excipients: Contains lactose, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Off white, round, flat on both sides, with a bevelled edge, a dividing score and an inscription on top:

Euthyrox 25 microgram	EM 25
Euthyrox 50 microgram	EM 50
Euthyrox 75 microgram	EM 75
Euthyrox 88 microgram	EM 88
Euthyrox 100 microgram	EM 100
Euthyrox 112 microgram	EM 112
Euthyrox 125 microgram	EM 125
Euthyrox 137 microgram	EM 137
Euthyrox 150 microgram	EM 150
Euthyrox 175 microgram	EM 175
Euthyrox 200 microgram	EM 200

The tablet can be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Euthyrox 25 - 200 microgram:
- 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

Euthyrox 25 – 100 microgram:
- Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism

Euthyrox 100/150/200 microgram:
- Diagnostic use for thyroid suppression testing

4.2 Posology and method of administration

Posology
In order to treat each patient according to his/her individual needs, tablets are available with a levothyroxine sodium content ranging from 25 to 200 microgram. Patients therefore usually need to take only one tablet per day.

The dosage recommendations given are only for guidance.

The individual daily dose should be determined on the basis of laboratory tests and clinical examinations. As a number of patients show elevated concentrations of T_4 and fT_4, basal serum concentration of thyroid-stimulating hormone provides a more reliable basis for following treatment course.
Thyroid hormone therapy should be started at low dose and increased gradually every 2 to 4 weeks until the full replacement dose is reached.

Paediatric population
For neonates and infants with congenital hypothyroidism, where rapid replacement is 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. In older patients, in patients with coronary heart disease, and in patients with severe or long-existing hypothyroidism, special caution is required when initiating therapy with thyroid hormones, that is, a low initial dose (for example 12.5 microgram/day) should be given which should then be increased slowly and at lengthy intervals (e.g. a gradual increment of 12.5 microgram/day fortnightly) with frequent monitoring of thyroid hormones. A dosage, lower than optimal dosage giving complete replacement therapy, consequentially not resulting in a complete correction of TSH level, might therefore need to be considered.

Experience has shown that a lower dose is sufficient in low-weight patients and in patients with a large nodular goitre.

Indication	**Recommended dose** (microgram levothyroxine sodium/day)				
Treatment of benign euthyroid goitre	75 - 200				
Prophylaxis of relapse after surgery for euthyroid goitre	75 - 200				
Substitution therapy in hypothyroidism in adults					
- initial dose	25 - 50				
- maintenance dose	100 - 200				
Substitution therapy in hypothyroidism in children					
- initial dose	12.5 - 50				
- maintenance dose	100 - 150 microgram/m² body surface				
Concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism	50 - 100				
Suppression therapy in thyroid cancer	150 - 300				
Diagnostic use for thyroid suppression testing		Week 4 prior to test	Week 3 prior to test	Week 2 prior to test	Week 1 prior to test
	Euthyrox 200 microgram	------	-------	1 Tabl/day	1 Tabl/day
	Euthyrox 100 microgram			2 Tabl/day	2 Tabl/day
	Euthyrox 150 microgram	1/2 Tabl/day	1/2 Tabl/day	1 Tabl/day	1 Tabl/day

Method of administration
The daily doses can be given in a single administration.
Ingestion: as a single daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with a little liquid, (for example, half a glass of water).

Infants receive the entire dose at once at least 30 minutes before the first meal of the day. Tablets are to be disintegrated in some water and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid.

Duration of treatment is usually for life in the case of substitution in hypothyroidism and after strumectomy or thyroidectomy and for relapse prophylaxis after euthyroid goitre removal. Concomitant therapy of hyperthyroidism after achieving euthyroid status is indicated for the period in which the anti-thyroid drug is given.

For benign euthyroid goitre, a treatment duration of 6 months up to 2 years is necessary. If the medical treatment was not sufficient within this time, surgery or radioiodine therapy of the goitre should be considered.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Euthyrox must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.
- Combination therapy of levothyroxine and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Before starting therapy with thyroid hormones or before performing a thyroid suppression test, the following diseases or medical conditions should be excluded or treated: coronary failure, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency. Thyroid autonomy should also be excluded or treated before starting therapy with thyroid hormones.

When initiating levothyroxine therapy in patients at risk of psychotic disorders, it is recommended to start at a low levothyroxine dose and to slowly increase the dosage at the beginning of the therapy. Monitoring of the patient is advised. If signs of psychotic disorders occur, adjustment of the dose of levothyroxine should be considered.

Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases.

In the case of secondary hypothyroidism the cause must be determined before replacement therapy is given and if necessary replacement treatment of a compensated adrenal insufficiency must be commenced.

Where thyroid autonomy is suspected a TRH test should be carried out or a suppression scintigram obtained before treatment.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine should be avoided, and, therefore, thyroid function should be checked closely.

Levothyroxine should not be given in hyperthyreotic states other than as concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

Thyroid hormones should not be given for weight reduction. In euthyroid patients, treatment with levothyroxine does not cause weight reduction. Substantial doses may cause serious or even life-threatening undesirable effects. Levothyroxine in high doses should not be combined with certain substances for weight reduction, i.e. sympathomimetics (see section 4.9).

Once a levothyroxine treatment has been established, it is recommended to adjust the dosage following the patient's clinical response and laboratory test, in case of switching the brand.

Hypothyroidism and / or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered (see section 4.5). Patients taking levothyroxine should be advised to consult a doctor before starting or stopping or changing treatment with orlistat, as orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted. Further, it is recommended to monitor the patient by checking the hormone levels in the serum.

This medicinal product contains lactose, and therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For diabetic patients and patients under anticoagulant therapy, see section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-diabetic agents:

Levothyroxine may reduce the effect of antidiabetic agents. For this reason, blood glucose levels should be checked frequently at the start of thyroid hormone therapy and the dosage of the antidiabetic agent has to be adapted, if necessary.

Coumarin derivates:

The effect of anti-coagulant therapy can be intensified as levothyroxine displaces anti-coagulative drugs from plasma proteins, which may increase the risk of haemorrhage, e.g. CNS or gastrointestinal bleeding, especially in elderly patients. Therefore it is necessary for coagulation parameters to be checked regularly at the start of and during concomitant therapy. If necessary, the dosage of the anti-coagulative drug has to be adapted.

Protease inhibitors:

Protease inhibitors (e.g. ritonavir, indinavir, lopinavir) may influence the effect of levothyroxine. Close monitoring of thyroid hormone parameters is recommended. If necessary, the levothyroxine dose has to be adjusted.

Phenytoin:

Phenytoin may influence the effect of levothyroxine by displacing levothyroxine from plasma proteins resulting in an elevated fT4 and fT3 fraction. On the other hand phenytoin increases the hepatic metabolisation of levothyroxine. Close monitoring of thyroid hormone parameters is recommended.

Colestyramine, Colestipol:

Ingestion of ion exchange resins such as cholestyramine and colestipol inhibits the absorption of levothyroxine sodium. Levothyroxine sodium should therefore be taken 4-5 hours before administration of such products.

Aluminium, iron, and calcium salts:

Aluminium-containing drugs (antacids, sucralfate) have been reported in the pertinent literature as potentially decreasing the effect of levothyroxine. Drugs containing levothyroxine should therefore be administered at least 2 hours prior to the administration of aluminium-containing drugs.
The same applies to medicinal products containing iron and calcium salts.

Salicylates, dicumarol, furosemide, clofibrate:

Salicylates, dicumarol, furosemide in high doses (250 mg), clofibrate and other substances can displace levothyroxine sodium from plasma proteins, resulting in an elevated fT4 fraction.

Orlistat:

Hypothyroidism and / or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of iodine salts and / or levothyroxine.

Sevelamer:

Sevelamer may decrease levothyroxine absorption. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine dose has to be adjusted.

Tyrosine kinase inhibitors:

Tyrosine kinase inhibitors (e.g. imatinib, sunitinib) may decrease the efficacy of levothyroxine. Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine dose has to be adjusted.

Propylthiouracil, glucocorticoids, beta-sympatholytics, amiodarone and iodine containing contrast media:

These substances inhibit the peripheral conversion of T4 to T3.
Due to its high iodine content amiodarone can trigger hyperthyroidism as well as hypothyroidism. Particular caution is advised in the case of nodular goitre with possibly unrecognized autonomy.

Sertraline, chloroquine/proguanil:

These substances decrease the efficacy of levothyroxine and increase the serum TSH level.

Enzyme inducing medicinal products:

Enzyme inducing medicinal products such as barbiturates or carbamazepine can increase hepatic clearance of levothyroxine.

Estrogens:

Women using oestrogen-containing contraceptives or postmenopausal women under hormone-replacement therapy may have an increased need for levothyroxine.

Soy-containing compounds:

Soy-containing compounds can decrease the intestinal absorption of levothyroxine. Therefore, a dosage adjustment of Euthyrox may be necessary, in particular at the beginning or after termination of nutrition with soy supplements.

4.6 Pregnancy and lactation

Treatment with levothyroxine should be given consistently during pregnancy and breast-feeding in particular. Dosage requirements may even increase during pregnancy. Since elevations in serum TSH may occur as early as 4 weeks of gestation, pregnant women taking levothyroxine should have their TSH measured during each trimester, in order to confirm that the maternal serum TSH values lie within the trimester-specific pregnancy reference range. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine. Since postpartum TSH levels are similar to preconception values, the levothyroxine dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6–8 weeks postpartum.

<u>Pregnancy</u>
Experience has shown that there is no evidence of drug-induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose level. Excessively high dose levels of levothyroxine during pregnancy may have a negative effect on foetal and postnatal development.

Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy. Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

Thyroid suppression diagnostic tests should not be carried out during pregnancy, as the application of radioactive substances in pregnant women is contraindicated.

Breast-feeding
Levothyroxine is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, since levothyroxine is identical to the naturally occurring thyroid hormone, it is not expected that Euthyrox has any influence on the ability to drive and use machines.

4.8 Undesirable effects

Where the individual tolerance limit for levothyroxine sodium is exceeded or after overdose it is possible for the following clinical symptoms typical of hyperthyroidism to occur, expecially if the dose is increased too quickly at the start of treatment: cardiac arrhythmias (e.g. atrial fibrillation and extrasystoles), tachycardia, palpitations, anginal conditions, cephalalgia, muscular weakness and cramps, flushing, fever, vomiting, disorders of menstruation, pseudotumor cerebri, tremor, restlessness, insomnia, hyperhidrosis, weight loss, diarrhoea.
In such cases the daily dose should be reduced or the medication withdrawn for several days. Therapy may be carefully resumed once the adverse reactions have disappeared.

In case of hypersensitivity to any ingredients of Euthyrox allergic reactions particularly of the skin and the respiratory tract may occur. Cases of angioedema have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

An elevated T3 level is a reliable indicator of overdose, more than elevated T4 or fT4 levels.
After overdose the symptoms of a sharp increase in the metabolic rate occur (see section 4.8).
Depending on the extent of the overdose it is recommended that treatment with the tablets is interrupted and that tests are carried out.

Symptoms consisting of intense beta-sympathomimetic effects such as tachycardia, anxiety, agitation and hyperkinesia can be relieved by betablockers. After extreme doses plasmapheresis may be of help.

In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded.

Overdose of levothyroxine may result in symptoms of hyperthyroidism and could lead to acute psychosis, especially in patients at risk of psychotic disorders.

Several cases of sudden cardiac death have been reported in patients with long years of levothyroxine abuse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thyroid hormones

ATC-Code: H03A A01

The synthetic levothyroxine contained in Euthyrox is identical in effect with the naturally occurring major hormone secreted by the thyroid. It is converted to T3 in peripheral organs and, like the endogenous hormone, develops its specific effects at the T3 receptors. The body is not able to differentiate between endogenous and exogenous levothyroxine.

5.2 Pharmacokinetic properties

Orally given levothyroxine is absorbed almost exclusively in the upper small intestine. Depending on the galenical formulation absorption amounts up to 80 %. t_{max} is approximately 5 to 6 hours.

Following oral administration the onset of action is seen after 3-5 days. Levothyroxine exhibits an extremely high binding to specific transport proteins of about 99.97 %. This protein hormone binding is not covalent and so the bound hormone in plasma is in continuous and very rapid exchange with the fraction of the free hormone.

Due to its high protein binding levothyroxine undergoes neither haemodialysis nor haemoperfusion.

The half-life of levothyroxine is on average 7 days. In hyperthyroidism it is shorter (3-4 days) and in hypothyroidism it is longer (approx. 9-10 days). The volume of distribution amounts to about 10-12 l. The liver contains 1/3 of the entire extra-thyroidal levothyroxine, which is rapidly exchangeable with the levothyroxine in serum. Thyroid hormones are metabolized mainly in the liver, kidneys, brain and muscles. The metabolites are excreted with urine and faeces. The overall metabolic clearance for levothyroxine is about 1.2 l plasma/day.

5.3 Preclinical safety data

Acute toxicity:
Levothyroxine has a very slight acute toxicity.

Chronic toxicity:
The chronic toxicity of levothyroxine was studied in various animal species (rat, dog). At high doses, signs of hepatopathy, increased occurrence of spontaneous nephroses as well as changes in organ weights were observed in rats.

Reproduction toxicity:
Reproductive toxicity studies in animals have not been performed.

Mutagenicity:
No information is available on this subject. So far no indications of any kind have become known suggesting damage to the progeny due to changes in the genome caused by thyroid hormones.

Carcinogenicity:
No long-term animal studies have been carried out with levothyroxine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Croscarmellose sodium
Gelatine
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Shelf-life after first opening of the bottle: 3 months.

6.4 Special precautions for storage

Do not store above 25° C. Keep container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Blister pack:
Polypropylene base film and aluminium cover foil, or alternatively PVC base film with aluminium cover foil.

Pack sizes:
- cartons of 20, 25, 30, 50, 60, 90, and 100 tablets,
- calendar packs of 28 and 84 tablets,
- hospital packs: 500 (10 x 50) tablets.

Additionally for Euthyrox 25 / 50 / 100 microgram tablets
Bottles:
HDPE bottle with a polypropylene screw cap.

Pack sizes:
- hospital packs: 100 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

XX/2017

[To be completed nationally]

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACKS

1. NAME OF THE MEDICINAL PRODUCT

Euthyrox 25 microgram tablets
Euthyrox 50 microgram tablets
Euthyrox 75 microgram tablets
Euthyrox 88 microgram tablets
Euthyrox 100 microgram tablets
Euthyrox 112 microgram tablets
Euthyrox 125 microgram tablets
Euthyrox 137 microgram tablets
Euthyrox 150 microgram tablets
Euthyrox 175 microgram tablets
Euthyrox 200 microgram tablets
Levothyroxine sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 microgram levothyroxine sodium.
Each tablet contains 50 microgram levothyroxine sodium.
Each tablet contains 75 microgram levothyroxine sodium.
Each tablet contains 88 microgram levothyroxine sodium.
Each tablet contains 100 microgram levothyroxine sodium.
Each tablet contains 112 microgram levothyroxine sodium.
Each tablet contains 125 microgram levothyroxine sodium.
Each tablet contains 137 microgram levothyroxine sodium.
Each tablet contains 150 microgram levothyroxine sodium.
Each tablet contains 175 microgram levothyroxine sodium.
Each tablet contains 200 microgram levothyroxine sodium.

3. LIST OF EXCIPIENTS

Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets
28 tablets
25 tablets
30 tablets
50 tablets
60 tablets
84 tablets
90 tablets
100 tablets
500 (10 x 50) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Keep blisters in the outer carton, in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Euthyrox 25 microgram tablets
Euthyrox 50 microgram tablets
Euthyrox 75 microgram tablets
Euthyrox 88 microgram tablets
Euthyrox 100 microgram tablets
Euthyrox 112 microgram tablets
Euthyrox 125 microgram tablets
Euthyrox 137 microgram tablets
Euthyrox 150 microgram tablets
Euthyrox 175 microgram tablets
Euthyrox 200 microgram tablets
Levothyroxine sodium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE INNER AND OUTER PACKAGING

CARTON FOR BOTTLES AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Euthyrox 25 microgram tablets
Euthyrox 50 microgram tablets
Euthyrox 100 microgram tablets

Levothyroxine sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 microgram levothyroxine sodium.
Each tablet contains 50 microgram levothyroxine sodium.
Each tablet contains 100 microgram levothyroxine sodium.

3. LIST OF EXCIPIENTS

Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after first opening of the bottle: 3 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Keep container in the outer carton, in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the user

Euthyrox 25 microgram tablets
Euthyrox 50 microgram tablets
Euthyrox 75 microgram tablets
Euthyrox 88 microgram tablets
Euthyrox 100 microgram tablets
Euthyrox 112 microgram tablets
Euthyrox 125 microgram tablets
Euthyrox 137 microgram tablets
Euthyrox 150 microgram tablets
Euthyrox 175 microgram tablets
Euthyrox 200 microgram tablets
Levothyroxine sodium

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Euthyrox is and what it is used for
2. What you need to know before you take Euthyrox
3. How to take Euthyrox
4. Possible side effects
5. How to store Euthyrox
6. Contents of the pack and other information

1. What Euthyrox is and what it is used for

Levothyroxine, the active substance in Euthyrox, is a synthetic thyroid hormone for the treatment of diseases and dysfunctions of the thyroid gland. It has the same effect as the naturally occurring thyroid hormones.

Euthyrox is used
- to treat benign goitre in patients with normal thyroid function,
- to prevent recurrence of goitre after surgery,
- to replace natural thyroid hormones, when your thyroid gland does not produce enough,
- to suppress tumour growth in patients with thyroid cancer.

Euthyrox 25 microgram, 50 microgram, 75 microgram, 88 microgram and 100 microgram are also used to balance thyroid hormone levels, when overproduction of hormones is treated with antithyroid medicines.

Euthyrox 100 microgram, 150 microgram, and 200 microgram may also be used in the testing of your thyroid function. **
*** the respective information will only be included in the package leaflets of Euthyrox 100 microgram, 150 microgram or 200 microgram.*

2. What you need to know before you take Euthyrox

Do not take Euthyrox
if you have any of the following:
- allergy (hypersensitivity) to the active substance or to any of the other ingredients of Euthyrox (listed in section 6),
- untreated dysfunction of the adrenal gland, pituitary gland or excessive overproduction of thyroid hormones (thyreotoxicosis),
- acute heart disease (myocardial infarction or heart inflammation).

Do not take Euthyrox together with antithyroid medicines if you are pregnant (see section Pregnancy and breast-feeding below).

Warnings and precautions
Talk to your doctor or pharmacist before taking Euthyrox if you have any of the following heart diseases:
- insufficient blood flow in the blood vessels of the heart (angina pectoris),
- heart failure,
- rapid and irregular heart beat,
- high blood pressure,
- fatty deposits in your arteries (arteriosclerosis).

They must be under medical control **before** you start taking Euthyrox or before a thyroid suppression test is performed. You **must** have frequent checks of your thyroid hormone levels while you are on Euthyrox. If you are not sure whether any of these conditions applies to you, or if you do not receive treatment, contact your doctor.

Your doctor will investigate if you have a dysfunction of the adrenal or pituitary gland or a dysfunction of the thyroid gland with uncontrolled overproduction of thyroid hormones (thyroid autonomy), because this must be medically controlled before you start taking Euthyrox or before a thyroid suppression test is performed.

Speak to your doctor,
- if you are in the menopause or post-menopausal; your doctor may need to check your thyroid function regularly because of the risk of osteoporosis.
- if you switch from one levothyroxine-containing medicine to another one. The effect may be slightly different and you may need closer monitoring and dose adjustment.
- before you start or stop taking orlistat, or change the treatment with orlistat (medication to treat obesity; you may need closer monitoring and dose adjustment)

if you experience signs of psychotic disorders (you may need closer monitoring and dose adjustment)

Other medicines and Euthyrox
Tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines, because Euthyrox may influence their effect:
- Anti-diabetic medicines (blood-sugar-lowering medicines):
  Euthyrox may **reduce** the effect of your anti-diabetic medicine, so you may need additional checks of your blood sugar levels, especially at the start of Euthyrox treatment. While you are taking Euthyrox, adjustment of the dose of your anti-diabetic medicine may be necessary.
- Coumarin derivatives (medicines used to prevent blood clotting):
  Euthyrox may **intensify** the effect of these medicines, which may increase the risk of bleeding events, especially in elderly people. You may need regular checks of your blood clotting values, at the start of and during Euthyrox treatment. While you are taking Euthyrox, adjustment of the dose of your coumarin medicine may be necessary.

Make sure that you stick to the recommended time intervals, if you need to take any of the following medicines:
- Medicine used to bind bile acids and to lower high cholesterol (such as cholestyramine or cholestipol):

Make sure that you take Euthyrox 4 - 5 hours **before** these medicines, because they may block the uptake of Euthyrox from the intestine.
- Antacids (for the relief of acid indigestion), sucralfate (for ulcers of the stomach or intestine), other aluminium-containing medicines, iron-containing medicines, calcium-containing medicines:
  Make sure that you take Euthyrox at least 2 hours before these medicines, because otherwise they may reduce the effect of Euthyrox.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines, because they may **reduce** the effect of Euthyrox:
- propylthiouracil (antithyroid medicine),
- glucocorticoids (anti-allergic and anti-inflammatory medicines),
- beta-blockers (blood-pressure-lowering medicines also used to treat heart diseases),
- sertraline (antidepressive medicine),
- chloroquine, or proguanil (medicine to prevent or treat malaria),
- medicines activating certain liver enzymes such as barbiturates (sedatives, sleeping pill) or carbamazepine (anti-epileptic medicine, also used to modify some types of pain and to control mood disorders),
- oestrogen-containing medicines used for hormone replacement during and after the menopause or for prevention of pregnancy,
- sevelamer (phosphate binding drug, used to treat patients with chronic renal failure),
- tyrosine kinase inhibitors (anti-cancer and anti-inflammatory medicines).
- orlistat (medication to treat obesity)

Tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines, because they may **intensify** the effect of Euthyrox:
- salicylates (medicine used to relief pain and to reduce fever),
- dicumarol (medicine to prevent blood clotting),
- furosemide in high doses of 250 mg (diuretic medicine),
- clofibrate (blood-lipid-lowering medicine).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines, because they may influence the effect of Euthyrox:
- ritonavir, indinavir, lopinavir (protease inhibitors, medicines to treat HIV infection),
- phenytoin (anti-epileptic medicine).

You may need regular checks of your thyroid hormone parameters. An adjustment of your dose of Euthyrox may be necessary.

Tell your doctor, if you are taking amiodarone (medicine used to treat irregular heart beat), because this medicine may influence the function and activity of your thyroid gland.

If you need to have a diagnostic test or scan with iodine–containing contrast media, tell your doctor that you take Euthyrox, because you may receive an injection that may influence your thyroid function.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Thyroid hormones should not be used for weight reduction. Intake of thyroid hormones will not reduce your weight, if your thyroid hormone level is in a normal range. Serious or even life-threatening side effects may occur if you increase the dose without special advice from your doctor. High doses of thyroid hormones should not be taken together with certain medicines for weight reduction, such as amfepramone, cathine and phenylpropanolamine, as the risk of serious or even life-threatening side effects may increase.

Euthyrox with food and drink
Tell your doctor, if you eat soy products, especially if you change the amount you eat. Soy-products may lower the uptake of Euthyrox from the intestine and therefore, an adjustment of your Euthyrox dose may be necessary.

Pregnancy and breast-feeding
If you are pregnant continue taking Euthyrox. Speak to your doctor, because the dose may need to be changed.

If you have taken Euthyrox together with an antithyroid medicine to treat an overproduction of thyroid hormones, your doctor will advise you to stop Euthyrox treatment when you become pregnant.

If you are breast-feeding, continue taking Euthyrox as advised by your doctor. The amount of drug that is excreted into the breast milk is so small that it will not affect the child.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.
It is not expected that Euthyrox has any influence on the ability to drive and use machines, because levothyroxine is identical to the naturally occurring thyroid hormone.

Euthyrox contains lactose
Tell your doctor, if you have an intolerance to certain sugars, because Euthyrox contains lactose.

3. How to take Euthyrox

Always take Euthyrox exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist, if you are not sure.

Your doctor will determine your individual dose based on examinations and as well as on laboratory tests. In general, you start with a low dose, which is increased every 2 - 4 weeks, until your full individual dose is reached. During the initial weeks of treatment you will have appointments for laboratory tests in order to adjust the dose.
If your baby is born with hypothyroidism your doctor may recommend to start with a higher dose because a rapid replacement is important. The initial recommended dosage is 10 to 15 micrograms per kg body weight for the first 3 months. Thereafter, your doctor will adjust the dose individually.

The usual dose range is shown in the table below. A lower individualised dose may be sufficient,
- if you are an elderly patient,
- if you have heart problems,
- if you have severe or long-standing thyroid sub-function,
- if you have low weight or a large goitre.

Use of Euthyrox	*Recommended daily dose of Euthyrox*	
- to treat benign goitre in patients with normal thyroid function	75 - 200 microgram	
- to prevent recurrence of goitre after surgery	75 - 200 microgram	
- to replace natural thyroid hormones, when your thyroid gland does not produce enough - initial dose - maintenance dose	adults 25 - 50 microgram * 100 - 200 microgram	children 12.5 – 50 microgram * 100 – 150 microgram per m^2 of body surface
- to suppress tumour growth in patients with thyroid cancer	150 - 300 microgram	
- to balance thyroid hormone levels, when overproduction of hormones is treated with anti-thyroid medicines	50 - 100 microgram	
- to test thyroid function**	100 microgram: *** 200 microgram (2 tablets) starting 2 weeks before the test 150 microgram: **** Starting 4 weeks before the test 75 microgram (½ tablet) for two weeks, then 150 microgram (1 tablet) until the test 200 microgram: ***** 200 microgram (1 tablet) starting 2 weeks before the test	

** the following information will only be included in the package leaflets of Euthyrox 112 microgram, 125 microgram, 137 microgram, 150 microgram, 175 microgram or 200 microgram:*
Euthyrox 112 microgram, 125 microgram, 137 microgram, 150 microgram, 175 microgram or 200 microgram tablets are not suitable for the lower dose range listed here, but your doctor may prescribe a lower strength of Euthyrox tablets.

*** only applicable for the package leaflets of Euthyrox 100 microgram, 150 microgram or 200 microgram.*
**** the respective information will only be included in the package leaflet of Euthyrox 100 microgram.*
***** the respective information will only be included in the package leaflet of Euthyrox 150 microgram.*
****** the respective information will only be included in the package leaflet of Euthyrox 200 microgram.*

Administration
Euthyrox is meant for oral use. Take a single daily dose on an empty stomach in the morninig (at least half an hour before breakfast), preferably with a little liquid, for example with half a glass of water.
Infants may receive the entire daily dose of Euthyrox at least half an hour before the first meal of the day. Immediately before use, crush the tablet and mix it with some water and give it to the child with some more liquid. Always prepare the mixture freshly.

Duration of treatment
Duration of treatment may vary depending on the condition for which you use Euthyrox. Your doctor will therefore discuss with you how long you need to take it. Most patients need to take Euthyrox for their lifetime.

If you take more Euthyrox than you should
If you have taken a higher dose than prescribed, you may experience symptoms such as rapid heart beat, anxiety, agitation or unintended movements. In patients with a disorder affecting the neurological system such as epilepsy, seizures may occur in isolated cases. In patients at risk of psychotic disorders, symptoms of acute psychosis may occur. If any of this happens, contact your doctor.

If you forget to take Euthyrox
Do not take a double dose to make up for a forgotten tablet, but take the normal dose the following day.

If you have any further questions on the use of Euthyrox, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Euthyrox can cause side effects, although not everybody gets them.

You may experience one or more of the following side effects if you take more Euthyrox than prescribed, or if you do not tolerate your prescribed dose (e.g. when the dose is increased quickly):

Irregular or rapid heart beat, chest pain, headache, muscle weakness or cramps, flushing (warmth and redness of the face), fever, vomiting, disorders of menstruation, pseudotumor cerebri (increased pressure in the head), trembling, restlessness, sleep disturbances, sweating, weight loss, diarrhoea.

If you experience any of these side effects, contact your doctor. Your doctor may decide to interrrupt the therapy for several days or to reduce the daily dose until the side effects have disappeared.

Allergic reactions to any of the ingredients of Euthyrox are possible (see section 6. 'What Euthyrox contains'). Allergic reactions may include swelling of the face or throat (angio-oedema). If this happens, contact your doctor immediately.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Euthyrox

Keep this medicine out of the sight and reach of children.

Do not use Euthyrox after the expiry date, which is stated on the blister or bottle and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25° C. Keep the blisters or the bottle in the outer carton, in order to protect from light.

After first opening of the bottle, the tablets can be used for a maximum of 3 months.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Euthyrox <strength> microgram contains

- The active substance is levothyroxine. Each tablet contains 25 microgram, 50 microgram, 75 microgram, 88 microgram, 100 microgram, 112 microgram, 125 microgram, 137 microgram, 150 microgram, 175 microgram, or 200 microgram levothyroxine sodium.

- The other ingredients are maize starch, croscarmellose sodium, gelatine, lactose monohydrate, and magnesium stearate.

What Euthyrox <strength> microgram looks like and contents of the pack

Euthyrox <strength> microgram tablets are white, round, flat on both sides, with a bevelled edge, a dividing score and an inscription EM 25, EM 50, EM 75, EM 88, EM 100, EM 112, EM 125, EM 137, EM 150, EM 175 or EM 200 on top:

Euthyrox is available in packs of 20, 25, 30, 50, 60, 90, 100 or 500 tablets or in calendar packs of 28 or 84 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
[To be completed nationally]

Manufacturer

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Euthyrox
Denmark: Euthyrox
Germany: Euthyrox
Greece: Euthyrox
Iceland: Euthyrox
Croatia: Euthyrox
Norway: Euthyrox
Portugal: Eutirox
Spain: Eutirox
Sweden: Euthyrox

This leaflet was last revised in XX/2017.

[To be completed nationally]

Annex 3 - Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Austria	Approved	02/08/2001	01/06/1978	Euthyrox	MRP
Belgium	Approved	10/03/1978	01/12/1988	Euthyrox	National
Bulgaria	Approved	22/06/2006	01/01/2006	Euthyrox	National
Croatia	Approved	31/10/2014	06/03/2015	Euthyrox	MRP
Cyprus	Approved	25/11/2002	Marketed	Euthyrox	National
Czech Republic	Approved	10/06/1980	01/10/1992	Euthyrox	National
Denmark	Approved	20/06/2001	28/12/2009	Euthyrox	MRP
France	Approved	02/06/1980	09/12/1980	Levothyrox	National
Germany	Approved	01/03/2000	01/10/1978	Euthyrox	MRP
Greece	Approved	06/06/2007	01/01/2009	Euthyrox	MRP
Hungary	Approved	01/01/1992	01/01/1993	Euthyrox	National
Iceland	Approved	20/09/2001	01/04/2002	Euthyrox	MRP
Italy	Approved	04/12/2014	28/02/1999	Eutirox	National
Latvia	Approved	12/09/1996	01/01/2002	Euthyrox	National
Luxembourg	Approved	07/11/1979	Marketed	Euthyrox	National
Netherlands	Approved	15/12/1982	01/12/1982	Euthyrox	National
Norway	Approved	30/11/2001	01/02/2008	Euthyrox	MRP
Poland	Approved	27/04/2004	01/12/2004	Euthyrox	National
Portugal	Approved	15/09/2001	01/01/2006	Eutirox	MRP
Romania	Approved	12/08/1992	12/08/1992	Euthyrox	National
Slovakia	Approved	16/12/1992	01/01/1993	Euthyrox	National
Slovenia	Approved	12/09/2002	01/07/2003	Euthyrox	National
Spain	Approved	12/09/2013	01/07/2009	Eutirox	MRP
Sweden	Approved	20/07/2001	01/07/2001	Euthyrox	MRP

1 Enter the date of the most recent change to the licence status: e.g. date of approval or date of suspension

A3.2 Licensing status in the rest of the world

Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Albania	Approved	04/02/2016	Not Marketed	Euthyrox	
Algeria	Approved	16/08/1998	Marketed	Levothyrox	
Angola	Approved	25/02/2015	Marketed	Eutirox	
Argentina	Approved	26/10/2001	6/1/1998	Euthyrox	
Armenia	Approved	10/06/2014	4/22/2004	Euthyrox	
Aruba	Approved	03/12/2003	Marketed	Eutirox	
Azerbaijan	Approved	26/12/2012	Marketed	Euthyrox	
Bahamas	Approved	N/A	Marketed	Eutirox	
Bahrain	Approved	20/04/2005	1/1/2005	Euthyrox	
Barbados	Approved	N/A	Marketed	Eutirox	
Belarus	Approved	07/10/2013	9/30/1994	Euthyrox	
Belize	Approved	N/A	Marketed	Eutirox	
Benin	Approved	06/03/2006	Not Marketed	Euthyrox	
Bolivia	Approved	01/10/2002	Marketed	Eutirox	
Bolivia	Withdrawn	15/01/2008	Not Marketed	L-Thyroxin Merck	
Bolivia	Approved	12/03/2015	Not Marketed	Euthyrox	
Bosnia and Herzegovina	Approved	15/06/2015	2/18/2016	Euthyrox	
Botswana	Approved	24/04/2013	Not marketed	Euthyrox	
Brazil	Approved	01/03/1996	9/1/1997	Euthyrox	
Brazil	Withdrawn	13/08/2004	Not Marketed	L-Thyroxin Merck	
Brazil	Approved	01/06/2009	7/1/2009	Levotiroxina Sodica	
Brunei Darussalam	Approved	31/10/2011	Marketed	Euthyrox	
Burkina Faso	Approved	09/12/2009	Marketed	Levothyrox	
Cameroon	Approved	23/06/2016	Marketed	Euthyrox	
Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Canada	Approved	19/05/2005	Not Marketed	Euthyrox	
Chile	Withdrawn	15/05/2000	Not Marketed	L-Thyroxin Merck	
Chile	Approved	27/07/2005	12/1/2000	Eutirox	
China	Approved	01/07/1997	1/1/1998	You Jia Le	
Colombia	Withdrawn	17/05/1991	Not Marketed	L-Thyroxin Merck	
Colombia	Approved	05/07/2007	Marketed	Eutirox	
Congo	Approved	23/01/2001	Marketed	Levothyrox	

Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Costa Rica	Approved	19/10/1999	1/1/1998	Eutirox	
Cote D'Ivoire	Approved	10/11/1981	Marketed	Levothyrox	
Cuba	Approved	12/12/2008	Marketed	Eutirox	
Curacao	Approved	08/10/2003	Marketed	Eutirox	
Djibouti	N/A	N/A	Marketed	Levothyrox	
Dominican Republic	Approved	31/01/2000	1/1/2003	Eutirox	
Ecuador	Withdrawn	23/01/2004	Not Marketed	L-Thyroxin Merck	
Ecuador	Approved	09/06/2014	4/20/2007	Eutirox	
Egypt	Approved	25/10/2005	5/1/2006	Euthyrox	
El Salvador	Approved	13/08/2014	Marketed	Eutirox	
Gabon	Approved	29/06/2001	Marketed	Levothyrox	
Georgia	Approved	27/05/2014	5/27/2014	Euthyrox	
Guatemala	Approved	13/05/1998	3/1/1998	Eutirox	
Haiti	Approved	N/A	Marketed	Eutirox	
Honduras	Approved	17/03/2000	Marketed	Eutirox	
India	Approved	17/07/2015	Marketed	Euthyrox	
Indonesia	Approved	09/02/2006	8/1/1997	Euthyrox	
Iran, Islamic Republic Of	Approved	05/09/2007	5/1/2008	Euthyrox	
Israel	Approved	27/02/2012	9/14/2011	Euthyrox	
Jamaica	Approved	28/08/2003	Marketed	Eutirox	
Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Jordan	Approved	05/02/1997	1/1/1998	Euthyrox	
Kazakhstan	Approved	08/12/2014	12/8/2014	Euthyrox	
Kenya	Approved	10/10/2015	3/14/2016	Euthyrox	
Kuwait	Approved	27/11/2004	2/1/2006	Euthyrox	
Kyrgyzstan	Approved	31/07/2015	9/9/2005	Euthyrox	
Lebanon	Approved	17/01/2003	5/1/2002	Euthyrox	
Macedonia, The Former Yugoslav Republic Of	Approved	20/04/2016	Marketed	Euthyrox	
Madagascar	Approved	01/08/1989	Marketed	Levothyrox	
Malaysia	Approved	28/05/1998	6/1/2007	Euthyrox	
Mali	Approved	09/11/2009	Marketed	Levothyrox	
Mauritania	Approved	31/12/2010	1/1/2006	Levothyrox	
Mauritius	Approved	17/03/2004	Marketed	Levothyrox	
Mexico	Approved	11/07/1999	Marketed	Eutirox	
Moldova, Republic Of	Approved	17/11/2011	Marketed	Euthyrox	

Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Montenegro	Approved	12/02/2015	Marketed	Euthyrox	
Morocco	Approved	18/02/1988	Marketed	Levothyrox	
Mozambique	Approved	21/04/2014	Marketed	Euthyrox	
Namibia	Approved	16/06/2011	Marketed	Euthyrox	
Nicaragua	Approved	22/05/1998	1/1/1998	Eutirox	
Nigeria	Approved	28/04/2007	Not Marketed	Euthyrox	
Oman	Approved	28/09/2005	Marketed	Euthyrox	
Palestinian Territory, Occupied	Approved	02/12/2014	Not Marketed	Euthyrox	
Panama	Approved	05/06/2001	Marketed	Eutirox	
Peru	Withdrawn	26/12/2007	Not Marketed	L-Thyroxin Merck	
Peru	Approved	06/09/2013	Marketed	Eutirox	
Peru	Approved	04/02/2015	Marketed	Levotiroxina Sodica	
Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Philippines	Withdrawn	20/09/2004	Not Marketed	L-Thyroxin Merck	
Philippines	Approved	25/05/2014	1/3/2005	Euthyrox	
Qatar	Approved	21/09/2003	Marketed	Euthyrox	
Russian Federation	Approved	21/10/2008	9/1/2005	Euthyrox	
Saudi Arabia	Approved	14/06/2006	Marketed	Euthyrox	
Senegal	Approved	N/A	Marketed	Levothyrox	
Serbia	Withdrawn	N/A	Not Marketed	L-Thyroxin Merck	
Serbia	Approved	20/06/2013	1/1/2005	Euthyrox	
Singapore	Approved	06/05/1998	Marketed	Euthyrox	
South Africa	Approved	17/04/2009	Marketed	Euthyrox	
Sudan	Approved	13/01/2005	1/13/2005	Euthyrox	
Switzerland	Approved	28/09/1999	3/1/2000	Euthyrox	
Syrian Arab Republic	Approved	20/11/2011	Not Marketed	Euthyrox	
Tajikistan	Approved	29/10/2013	10/16/2008	Euthyrox	
Tanzania, United Republic of	Approved	19/09/2013	3/14/2016	Euthyrox	
Thailand	Approved	30/11/2001	Marketed	Euthyrox	
Togo	Approved	03/09/2014	Marketed	Levothyrox	
Trinidad and Tobago	Approved	11/06/2003	Marketed	Eutirox	
Tunisia	Approved	24/12/1987	Marketed	Levothyrox	
Turkey	Approved	10/05/2005	10/21/2005	Euthyrox	

Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Turkmenistan	Approved	13/04/2014	4/14/2004	Euthyrox	
Uganda	Approved	28/05/2014	3/14/2016	Euthyrox	
Ukraine	Approved	24/03/1998	Marketed	Euthyrox	
United Arab Emirates	Approved	27/11/2005	11/1/2006	Euthyrox	
United States	Approved	31/05/2002	Not Marketed	Novothyrox	
Uzbekistan	Approved	06/02/2012	2/9/2007	Euthyrox	
Venezuela	Withdrawn	N/A	Not Marketed	L-Thyroxin Merck	
Country	Current licence status	Date of licence action[1]	Date first marketed in country	Brand name(s)	Comments
Venezuela	Approved	11/03/1997	3/11/1997	Euthyrox	
Vietnam	Withdrawn	15/04/2002	Not Marketed	L-Thyroxin Merck	
Vietnam	Approved	02/06/2014	5/1/2001	Levothyrox	
Yemen	Approved	05/09/2011	Marketed	Euthyrox	

1 Enter the date of the most recent change to the licence status: e.g. date of approval or date of suspension

Annex 4 Synopsis of on-going and completed clinical trial program

Study ID	Phase	Country	Study Title/Study Design	Dosing regimen	Study population	First patient first visit	Planned enrolment	Subjects Exposed
EMR200125-001	I	Germany	An open-label, single-dose, randomized, two-period, two-sequence crossover, single-center trial to assess bioequivalence of 600 µg levothyroxine new formulation versus old formulation administered orally as 3 white tablets of 200 µg in healthy volunteers.	Single dose administration of 3 tablets of 200µg levothyroxine; washout period of 35 days between crossover	Healthy volunteers	Q3/ 2013	216 (108 subjects per sequence)	43
EMR200125-002	I	Germany	An open-label, single-dose, randomized, two-period, two-sequence crossover, single-center trial to assess bioequivalence of 600 µg levothyroxine new formulation versus old formulation administered orally as 3 white tablets of 200 µg in healthy volunteers.	600 µg levothyroxine new formulation administered orally as either 12 white tablets of 50 µg or 6 white tablets of 100 µg or 3 white tablets of 200 µg	Healthy volunteers	Q3/ 2013	42 (7 subjects per sequence)	42
EMR200125-003	I	Germany	An open-label, single-dose, randomized, three-period, six sequence crossover, single-center trial to assess dosage form proportionality of 600 µg levothyroxine new formulation administered orally as either 12 white tablets of 50 µg or 6 white tablets of 100 µg or 3 white tablets of 200 µg in healthy volunteers.	600 µg levothyroxine new formulation versus Synthroid® administered orally as 3 tablets of 200 µg	Healthy volunteers	Q1/ 2014	26 (13 subjects per sequence)	26

Study ID	Phase	Country	Study Title/Study Design	Dosing regimen	Study population	First patient first visit	Planned enrolment	Subjects Exposed
EMR200125-507	IV	China	A single-centre intervention study conducted in a single centre in China, to verify clinical utility of the quantitative and the qualitative POC TSH test kits compared with the third generation TSH test kit.	No active treatment	Patients after thyroidectomy for benign thyroid nodules		274	unk

Cut off date is 08 March 2011

Abbreviations:

QW = every week

QOW = every other week

BIW = twice a week

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period	Number of persons (in each group or of cases and controls) and person time (if appropriate)
EMR200007_504 DEuTSH Non-randomized, non-comparative, multi-center Observational	Descriptive study on individually titrated levothyroxine in the management of South African hypothyroid patients	South Africa	24 months	290
EMR200007_502 ORCHIDEE Open-label, non-randomized, non-comparative Observational	Observation of medical care of initial hypothyroidism in France	France	5 months	1285
EMR200007_606 BRAZIL Open-label, non-randomized, non-comparative, multi-center Observational	Evaluation of the treatment of primary hypothyroidism in different regions in Brazil	Brazil	26.5 months	2500

PT Code	PT Name	HLT Name	MedDRA Version	MedDRA Type Code	MedDRA Type
10000381	Accidental overdose	Maladministrations	v.18.1	5	Medication Error
10013659	Drug administered at inappropriate site	Maladministrations	v.18.1	5	Medication Error
10021597	Inappropriate schedule of drug administration	Maladministrations	v.18.1	5	Medication Error
10027091	Medication error	Medication errors NEC	v.18.1	5	Medication Error
10048055	Wrong drug administered	Maladministrations	v.18.1	5	Medication Error
10048056	Wrong patient received medication	Maladministrations	v.18.1	5	Medication Error
10057362	Underdose	Underdoses NEC	v.18.1	5	Medication Error
10058121	Poor quality drug administered	Maladministrations	v.18.1	5	Medication Error
10063972	Vaccination error	Medication errors NEC	v.18.1	5	Medication Error
10064294	Drug dose omission	Maladministrations	v.18.1	5	Medication Error
10064295	Drug administration error	Maladministrations	v.18.1	5	Medication Error
10064296	Drug prescribing error	Medication errors NEC	v.18.1	5	Medication Error
10064298	Counterfeit drug administered	Maladministrations	v.18.1	5	Medication Error
10064304	Incorrect route of drug administration	Maladministrations	v.18.1	5	Medication Error
10064305	Incorrect drug dosage form administered	Maladministrations	v.18.1	5	Medication Error
10064306	Incorrect drug administration rate	Maladministrations	v.18.1	5	Medication Error
10064307	Incorrect drug administration duration	Maladministrations	v.18.1	5	Medication Error
10064354	Drug dispensing error	Medication errors NEC	v.18.1	5	Medication Error
10064355	Incorrect dose administered	Maladministrations	v.18.1	5	Medication Error
10064366	Extra dose administered	Maladministrations	v.18.1	5	Medication Error
10064373	Labelled drug-drug interaction medication error	Medication monitoring errors	v.18.1	5	Medication Error
10064374	Labelled drug-food interaction medication error	Medication monitoring errors	v.18.1	5	Medication Error
10064381	Labelled drug-disease interaction medication error	Medication monitoring errors	v.18.1	5	Medication Error
10064382	Intercepted medication error	Medication errors NEC	v.18.1	5	Medication Error
10064385	Circumstance or information capable of leading to medication error	Medication errors NEC	v.18.1	5	Medication Error
10065634	Drug dispensed to wrong patient	Medication errors NEC	v.18.1	5	Medication Error
10065638	Intercepted drug dispensing error	Medication errors NEC	v.18.1	5	Medication Error
10065639	Intercepted drug administration error	Maladministrations	v.18.1	5	Medication Error
10065645	Intercepted wrong patient selected	Medication errors NEC	v.18.1	5	Medication Error
10068518	Radiation overdose	Maladministrations	v.18.1	5	Medication Error
10068519	Radiation underdose	Maladministrations	v.18.1	5	Medication Error
10068945	Incorrect dose administered by device	Maladministrations	v.18.1	5	Medication Error

PT Code	PT Name	HLT Name	MedDRA Version	MedDRA Type Code	MedDRA Type
10069273	Product label confusion	Medication errors NEC	v.18.1	5	Medication Error
10069328	Incorrect product storage	Medication errors NEC	v.18.1	5	Medication Error
10069332	Product name confusion	Medication errors NEC	v.18.1	5	Medication Error
10070470	Drug administered in wrong device	Maladministrations	v.18.1	5	Medication Error
10071062	Drug administered to patient of inappropriate age	Product use issues NEC	v.18.1	5	Medication Error
10071587	Product dosage form confusion	Medication errors NEC	v.18.1	5	Medication Error
10072103	Incomplete course of vaccination	Maladministrations	v.18.1	5	Medication Error
10072342	Multiple use of single-use product	Maladministrations	v.18.1	5	Medication Error
10072393	Intercepted drug prescribing error	Medication errors NEC	v.18.1	5	Medication Error
10072608	Inadequate aseptic technique in use of product	Maladministrations	v.18.1	5	Medication Error
10073085	Prescribed underdose	Underdoses NEC	v.18.1	5	Medication Error
10073205	Booster dose missed	Maladministrations	v.18.1	5	Medication Error
10073317	Accidental exposure to product	Accidental exposures to product	v.18.1	5	Medication Error
10073318	Accidental exposure to product by child	Accidental exposures to product	v.18.1	5	Medication Error
10073594	Expired device used	Maladministrations	v.18.1	5	Medication Error
10073702	Therapeutic drug monitoring analysis not performed	Medication monitoring errors	v.18.1	5	Medication Error
10073703	Therapeutic drug monitoring analysis incorrectly performed	Medication monitoring errors	v.18.1	5	Medication Error
10073752	Lack of injection site rotation	Maladministrations	v.18.1	5	Medication Error
10073758	Accidental use of placebo	Maladministrations	v.18.1	5	Medication Error
10073768	Incorrect dosage administered	Maladministrations	v.18.1	5	Medication Error
10073954	Intentional underdose	Underdoses NEC	v.18.1	5	Medication Error
10074433	Medication monitoring error	Medication monitoring errors	v.18.1	5	Medication Error
10074776	Product packaging confusion	Medication errors NEC	v.18.1	5	Medication Error
10074853	Drug titration error	Medication errors NEC	v.18.1	5	Medication Error
10074899	Contraindicated drug administered	Product use issues NEC	v.18.1	5	Medication Error
10074902	Expired product administered	Maladministrations	v.18.1	5	Medication Error
10074904	Accidental underdose	Maladministrations	v.18.1	5	Medication Error
10074906	Drug dose titration not performed	Medication errors NEC	v.18.1	5	Medication Error
10074946	Incorrect product formulation administered	Maladministrations	v.18.1	5	Medication Error
10075225	Dietary supplement prescribing error	Medication errors NEC	v.18.1	5	Medication Error
10075353	Paravenous drug administration	Maladministrations	v.18.1	5	Medication Error
10075461	Drug monitoring procedure incorrectly performed	Medication monitoring errors	v.18.1	5	Medication Error

PT Code	PT Name	HLT Name	MedDRA Version	MedDRA Type Code	MedDRA Type
10075462	Drug monitoring procedure not performed	Medication monitoring errors	v.18.1	5	Medication Error
10076087	Lack of administration site rotation	Maladministrations	v.18.1	5	Medication Error
10076088	Lack of application site rotation	Maladministrations	v.18.1	5	Medication Error
10076089	Lack of infusion site rotation	Maladministrations	v.18.1	5	Medication Error
10076090	Lack of vaccination site rotation	Maladministrations	v.18.1	5	Medication Error
10076245	Transcription medication error	Medication errors NEC	v.18.1	5	Medication Error
10076308	Intentional product use issue	Product use issues NEC	v.18.1	5	Medication Error
10076309	Product use issue	Product use issues NEC	v.18.1	5	Medication Error
10076470	Documented hypersensitivity to administered product	Medication monitoring errors	v.18.1	5	Medication Error
10076542	Product selection error	Medication errors NEC	v.18.1	5	Medication Error
10076544	Intercepted product selection error	Medication errors NEC	v.18.1	5	Medication Error
10076573	Wrong technique in product usage process	Maladministrations	v.18.1	5	Medication Error
10076639	Prescription drug used without a prescription	Product use issues NEC	v.18.1	5	Medication Error
10076869	Product preparation error	Medication errors NEC	v.18.1	5	Medication Error
10076874	Dose calculation error	Medication errors NEC	v.18.1	5	Medication Error

PT Code	PT Name	HLT Name	SMQ Code	SMQ Name	SMQ Count	MedDRA Version	MedDRA Type Code	MedDRA Type
10000381	Accidental overdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10000383	Accidental poisoning		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10010833	Contraindication to medical treatment		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10010835	Contraindication to vaccination		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10012802	Difficulty removing drug implant		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10013659	Drug administered at inappropriate site		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10021597	Inappropriate schedule of drug administration		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10027091	Medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10030020	Occupational exposure to radiation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10033295	Overdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10048055	Wrong drug administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10048056	Wrong patient received medication		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10051076	Prescribed overdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10057362	Underdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10058121	Poor quality drug administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10063972	Vaccination error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064294	Drug dose omission		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064295	Drug administration error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064296	Drug prescribing error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064304	Incorrect route of drug administration		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064305	Incorrect drug dosage form administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064306	Incorrect drug administration rate		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064307	Incorrect drug administration duration		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064354	Drug dispensing error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064355	Incorrect dose administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064366	Extra dose administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064373	Labelled drug-drug interaction medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064374	Labelled drug-food interaction medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064381	Labelled drug-disease interaction medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064382	Intercepted medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10064385	Circumstance or information capable of leading to medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10065066	Device connection issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error

PT Code	PT Name	HLT Name	SMQ Code	SMQ Name	SMQ Count	MedDRA Version	MedDRA Type Code	MedDRA Type
10065634	Drug dispensed to wrong patient		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10065638	Intercepted drug dispensing error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10065639	Intercepted drug administration error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10065645	Intercepted wrong patient selected		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10066374	Failure of child resistant mechanism for pharmaceutical product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10068515	Exposure to contaminated device		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10068518	Radiation overdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10068519	Radiation underdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10068945	Incorrect dose administered by device		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069216	Device adhesion issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069217	Needle issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069218	Syringe issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069225	Product reconstitution issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069232	Product dosage form issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069266	Product lot number issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069267	Product identification number issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069268	Product label on wrong product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069269	Product barcode issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069271	Product expiration date issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069273	Product label confusion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069289	Product label issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069294	Product dropper issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069328	Incorrect product storage		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069329	Product compounding quality issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069332	Product name confusion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069405	Product packaging issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069803	Injury associated with device		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069845	Device-device incompatibility		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069853	Device difficult to use		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10069889	Product adhesion issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10070468	Wrong device used		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10070469	Wrong device dispensed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error

PT Code	PT Name	HLT Name	SMQ Code	SMQ Name	SMQ Count	MedDRA Version	MedDRA Type Code	MedDRA Type
10070470	Drug administered in wrong device		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10070574	Interchange of vaccine products		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10070617	Device infusion issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10071062	Drug administered to patient of inappropriate age		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10071411	Exposure via direct contact		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10071412	Exposure via partner		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10071430	Exposure via skin contact		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10071587	Product dosage form confusion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072103	Incomplete course of vaccination		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072342	Multiple use of single-use product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072393	Intercepted drug prescribing error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072608	Inadequate aseptic technique in use of product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072878	Device use error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072931	Unintentional medical device removal		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072950	Accidental device ingestion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10072951	Accidental device ingestion by a child		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073085	Prescribed underdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073205	Booster dose missed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073301	Exposure via contaminated device		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073302	Exposure via ingestion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073303	Exposure via inhalation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073311	Occupational exposure to product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073317	Accidental exposure to product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073318	Accidental exposure to product by child		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073336	Exposure via eye contact		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073594	Expired device used		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073702	Therapeutic drug monitoring analysis not performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073703	Therapeutic drug monitoring analysis incorrectly performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073752	Lack of injection site rotation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073758	Accidental use of placebo		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10073768	Incorrect dosage administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074266	Circumstance or information capable of leading to device use error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error

PT Code	PT Name	HLT Name	SMQ Code	SMQ Name	SMQ Count	MedDRA Version	MedDRA Type Code	MedDRA Type
10074433	Medication monitoring error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074776	Product packaging confusion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074853	Drug titration error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074902	Expired product administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074904	Accidental underdose		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074906	Drug dose titration not performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10074946	Incorrect product formulation administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10075225	Dietary supplement prescribing error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10075353	Paravenous drug administration		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10075461	Drug monitoring procedure incorrectly performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10075462	Drug monitoring procedure not performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076087	Lack of administration site rotation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076088	Lack of application site rotation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076089	Lack of infusion site rotation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076090	Lack of vaccination site rotation		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076245	Transcription medication error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076309	Product use issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076470	Documented hypersensitivity to administered product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076542	Product selection error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076544	Intercepted product selection error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076573	Wrong technique in product usage process		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076589	Unintentional use for unapproved indication		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076869	Product preparation error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10076874	Dose calculation error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077659	Accidental exposure to product packaging		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077660	Accidental exposure to product packaging by child		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077672	Medical device monitoring error		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077678	Contraindicated device used		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077720	Device monitoring procedure not performed		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10077812	Device use issue		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10078390	Incorrect disposal of product		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error
10078504	Contraindicated product administered		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medicatio n Error

PT Code	PT Name	HLT Name	SMQ Code	SMQ Name	SMQ Count	MedDRA Version	MedDRA Type Code	MedDRA Type
10078668	Poor quality device used		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medication Error
10078731	Complication of drug implant insertion		20000224	Medication errors (SMQ)	NA	v.19.1	05	Medication Error