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.