VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Levothyroxine is an essential medicine for the treatment of underactive thyroid conditions and is very widely prescribed. In 2010, the MHRA estimates that approximately 1,300,000 people took levothyroxine in the UK (source: IMS MIDAS).

The use of thyroid extracts (containing the hormones levothyroxine and liothyronine) as a treatment for hypothyroidism, dates back to 1891. A more pure, synthetic form of levothyroxine was introduced in the 1950s. Despite experiments with liothyronine (T3), alone or in combination with levothyroxine (T4), the latter remains the dominant choice of clinicians and is the current standard thyroid hormone replacement in the UK for the treatment of hypothyroidism.

Once diagnosed, patients normally start the estimated full or just below the full replacement dose immediately unless they are over 50, have severe hypothyroidism or have cardiac problems, in which case, the levothyroxine dose is gradually increased from an initial daily dose of 25 - 50 mcg levothyroxine. This is then increased by 25 – 50 mcg/day at 3-4 weekly intervals until a normal metabolic state is attained.

Thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland, plays a pivotal role in the control of the thyroid axis and serves as the most useful marker of thyroid status. Careful monitoring of serum levels of TSH is necessary until an appropriate dose of levothyroxine is reached. The treatment target is a TSH level within the normal range (0.4 - 4.5 mU/L). TSH is monitored during chronic treatment, usually on an annual basis as chronic under-treatment or over-treatment may be associated with adverse symptoms and undesirable clinical outcomes.

The need for particularly careful dosage titration predominantly applies to thyroid cancer patients who have evidence of residual cancer, elderly patients with underlying cardiovascular disease, pregnant women (where optimal replacement is particularly important in the first trimester to support foetal development) and certain hypothyroid patients who are sensitive to minor fluctuations (either increases or decreases) in their thyroxine levels. For these groups of patients, the content of levothyroxine in the tablet (assay or potency) and bioequivalence (or interchangeability) is extremely important.

If a drug product of significantly lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of significantly greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia.

VI.2.2 Summary of treatment benefits

Not Applicable

VI.2.3 Unknowns relating to treatment benefits

None identified

VI.2.4 Summary of safety concerns

Important identified risks

Table 6

Risk	What is known	Preventability
Hypersensitivity	Hypersensitivity to any ingredients allergic reactions particularly of the skin and the respiratory tract may occur.	Patients with known hypersensitivity to levothyroxine or any of the excipients in this product should not take this product.
Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis	Thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids.	Patient with untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis should not take this product.
Use in patient with acute myocardial infarction, acute myocarditis, and acute pancarditis	Higher potential for adverse effects from levothyroxine therapy.	Patient with acute myocardial infarction, acute myocarditis, and acute pancarditis should not take this product.
Hyperthyroidism or hypothyroidism from treatment imbalance	Even slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. 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	Frequent checks of thyroid hormone parameters must be made in these cases. If necessary replacement treatment of a compensated adrenal insufficiency must be commenced.

Risk	What is known	Preventability
	levothyroxine should be avoided. Levothyroxine should not be given in a hyperthyroid metabolic state, except as supportive therapy in thyrostatic treatment of hyperthyroidism.	
Interaction with antithyroid agents (during pregnancy)	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.	This product must not be used at the same time with medicines against an overactive thyroid gland (thyrostatics).
Interactions with anti-diabetic agents	Levothyroxine may reduce the effect of anti-diabetic agents.	Blood glucose levels should be checked frequently at the start of thyroid hormone therapy and the dosage of the anti-diabetic agent has to be adapted, if necessary.
Interaction with Coumarin derivates	The effect of anti-coagulant therapy can be increased by concomitant treatments with levothyroxine.	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.
Use in patient with known history of epilepsy	Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.	Care is required when levothyroxine is administered to patient with known history of epilepsy.
Use in patients with Cardiac Arrhythmias (including tachycardia and palpitation)	Slight drug-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac arrhythmias. Arrhythmia, angina pectoris, cardiotoxicity, myocardial ischemia, myocardial infarction cardiac arrest, cardiac failure, tachycardia, palpitations may occur with excessive doses of levothyroxine sodium.	More frequent monitoring of thyroid hormone parameters must be performed in patients with cardiac issues.
Substitution of a drug with greater or lesser potency (switching)	Levothyroxine is not a drug as such but is a naturally occurring thyroid hormone. Therefore, as levothyroxine exists naturally in the body, it can be difficult to establish whether levothyroxine products made by different manufacturers	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.

Risk	What is known	Preventability
	have the same clinical effect (therapeutic equivalence). There is evidence that some groups of patients (for example those with thyroid cancer, those with heart disease and those who are pregnant) may be particularly sensitive to changes in thyroid hormone and may require close monitoring by their doctors. While most patients seem to tolerate slight changes in levothyroxine dose, or slight changes in their circulating hormone levels without any ill effects, there is literature evidence that in some patients, this may alter their sense of well-being and possibly require their dose of levothyroxine to be altered.	A Dear Healthcare Professional letter will be dispatched to Healthcare Professionals in Finland to highlight the differences in quantity of levothyroxine in the Medithyrox medicinal products and in the medicinal products already marketed in Finland.
Off Label use for weight reduction	Thyroid hormones, including Levothyroxine sodium, either alone or with other therapeutic agents, should not be used for weight reduction. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.	Medicine is available as a Prescription only medicine. Specific warnings on the PIL regarding taking additional thyroid hormones for the use of weight reduction.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Not Applicable	

Missing information

Risk	What is known
Not Applicable	

VI.2.5 Summary of risk minimisation 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 minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this product can be found in the Netherland's EPAR page

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Netherland's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Substitution of a drug with greater or lesser potency (switching)

Risk minimisation measure(s) Dear Healthcare Professional Letter for Finland
Objective and rationale
• Summary description of main additional risk minimisation measures *HCPs in Finland will be made aware of the differences in quantity of levothyroxine in the Medithyrox medicinal products and in the medicinal products already marketed in Finland via a DHPC letter.* *When/if switching the HCP should ensure that the thyroid function blood tests (including TSH levels) are obtained*
Direct HCP communication prior to launch ('Dear HCP' letter).

VI.2.6 Planned post authorisation development plan

There are no studies in the post authorisation developments plan.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not Applicable for initial RMP.