Prescribing Framework for Liothyronine

Patient's Name:……... NHS Number: ……

Patient's Address:……...……(Use addressograph sticker)

GP's Name:……..

Communication

We agree to treat this patient within this Prescribing Framework

Specialist Prescriber's Name…… Prof Reg. No. ……

Specialist Prescriber's Signature…… Date:……

Where prescriber is <u>not</u> a consultant:

Consultant's Name: …… GMC No ……..

Consultant's Signature ……..... …… Date:……

GP's Signature:…… Date:……..

GP's Name (if different from listed above)……..

The front page of this form should be completed by the specialist and the form sent to the patient's general practitioner.

The patient's GP should sign and **<u>send back to specialist</u>**, to confirm agreement to enter into shared care arrangement. If the General Practitioner is **<u>unwilling</u>** to accept prescribing responsibility for the above patient the specialist should be informed within two weeks of receipt of this framework and specialist's letter.

Full copy of framework can also be found at: http://www.hey.nhs.uk/amber.htm

1. Background

Recommendation

The Hull and East Riding Prescribing Committee (HERPC) and the Department of Diabetes, Endocrinology and Metabolism, Hull University Teaching Hospitals NHS Trust

- **DO NOT** recommends the prescribing of liothyronine or liothyronine containing products for the treatment of primary hypothyroidism.
- **DO** recommend prescribing of thyroid hormones in line with Royal College of Physicians guidance[1].
- **Exceptions and Further Recommendations:**

  The British Thyroid Association (BTA) advise that a small proportion of patients treated with levothyroxine continue to suffer with symptoms despite adequate biochemical correction.

  In these circumstances, where levothyroxine has failed and in line with BTA guidance, endocrinologists providing NHS services may recommend liothyronine for individual patients after a carefully audited trial of at least 3 months duration of liothyronine.

  (Liothyronine is used for patients with thyroid cancer, in preparation for radioiodine ablation, iodine scanning, or stimulated thyroglobulin test. In these situations it is appropriate for patients to obtain their prescriptions).
- **This SCF applies** to those situations where alternative treatments have been found to be inadequate, and in line with RMOC Guidance for prescribing liothyronine[8].

This document should be read in conjunction with the guidance "Responsibility for prescribing between Primary & Secondary/Tertiary Care" https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

Rationale

- Levothyroxine (T4) is a prodrug. It is converted to liothyronine (T3) in the body. Prior to the 1970s, synthetic combinations of levothyroxine and liothyronine or desiccated animal thyroid extracts containing varying amounts of thyroid hormones were used. These have now been replaced with the use of levothyroxine monotherapy.[2]
- **Levothyroxine** is the thyroid hormone of choice.
- Levothyroxine is cost-effective, suitable for once daily dosing and provides stable and physiological quantities of thyroid hormones for patients requiring replacement.[2]
- There is overwhelming evidence in support of the safety and effectiveness of levothyroxine alone in treatment of hypothyroidism.[1]
- **Liothyronine** is not routinely recommended for prescribing as it has a much shorter half-life. Steady state levels cannot be maintained with once daily dosing.[2] Multiple doses can lead to supraphysiological peaks and may not be able to avoid sub-therapeutic troughs.

- The variation in hormonal content and large amounts of liothyronine may lead to increased serum concentrations of T3 and subsequent symptoms of thyroid excess, e.g. palpitations and tremor.[2] Over-replacement with any thyroid hormone (T3 or T4 alone and T4+T3) may be associated with osteoporosis and may increase the risk of atrial fibrillation.[3,4]

- There is currently insufficient clinical evidence of effectiveness and cost-effectiveness to support the use of liothyronine, either alone or in combination, for the treatment of hypothyroidism.[5,6]

- Combination of levothyroxine and liothyronine, in both physiological and non-physiological proportions, has not been shown to be more beneficial than levothyroxine monotherapy with respect to cognitive function, social functioning and wellbeing.[1,5,6]

- Liothyronine is available as licensed (and unlicensed) 20 microgram tablets and unlicensed 5 microgram tablets. Many other liothyronine-containing preparations are also unlicensed. Therefore, the safety and quality of these products cannot be assured.

- The amount of active ingredient in the liothyronine products from different suppliers may not be standardised. Variability in control means that there is batch-to-batch variation..

- It is recognised that some patients on levothyroxine remain symptomatic despite treatment. The reasons for this are poorly understood. Thyroid symptoms are non-specific. Symptoms may be due to a non-thyroidal illness and/or may have a psychological dimension.

Royal College of Physicians Recommendations[1]

- Patients with suspected primary hypothyroidism should only be diagnosed with blood tests including measurement of serum TSH.

- Patients with primary hypothyroidism should be treated with T4, using levothyroxine tablets (listed in the British National Formulary) alone.

- There is no indication for the prescription of levothyroxine or any preparation containing thyroid hormones to patients without an established diagnosis of thyroid disease and thyroid blood tests within the reference ranges.

- In patients with suspected primary hypothyroidism there is no indication for the prescription of levothyroxine or any preparation containing thyroid hormones to patients with thyroid blood tests initially within the normal range. Thus patients with normal levels of T4 and TSH do not have primary hypothyroidism, and even if they have symptoms which might suggest this, they should not be given thyroid hormone replacement therapy.

- The RCP does not support the use of thyroid extracts or T4 and T3 combinations without further validated research published in peer-reviewed journals. Therefore, the inclusion of T3 in the treatment of hypothyroidism should be reserved for use by accredited endocrinologists in individual patients.

- Laboratories which measure thyroid function in other bodily fluids besides blood need to provide analytical and clinical validation to demonstrate their efficacy.

RMOC Guidance – Prescribing Liothyronine Recommendations[8]

NHS England guidance states that prescribers in primary care should not initiate liothyronine (L-T3) for any new patient, and that individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration given to switching to levothyroxine (L-T4) where clinically appropriate. Prescriptions for individuals receiving liothyronine should continue until that review has taken place.

The majority of patients suffering from hypothyroidism can be treated effectively with levothyroxine alone, but liothyronine is perceived to be an important medicine for a small proportion of patients in order to maintain health and wellbeing. The prescribing of liothyronine is only supported if initiated by, or considered appropriate following a review by, an NHS consultant endocrinologist. The withdrawal or adjustment of liothyronine treatment should also only be undertaken by, or with the oversight of, an NHS consultant endocrinologist. Where General Practitioners (GPs) are involved in such treatment changes this should be with NHS consultant endocrinologist support. This advice applies to both liothyronine monotherapy and combination therapy with levothyroxine.

The RMOC guidance for prescribing liothyronine recommends that strict criteria are applied to ensure that liothyronine is only prescribed in the situations where alternative treatments have been found to be inadequate. In such circumstances, an ongoing shared care arrangement may be appropriate if agreed by local commissioners. If a patient is initiated on treatment, prescribing responsibility should remain with the hospital consultant for at least 3 months.

Clinical and biochemical monitoring of treatment and for potential side-effects is to be undertaken by the clinician supervising the treatment. TSH levels should be monitored, and free L-T4 / free L-T3 levels measured where clinically appropriate. The risks of over-treatment with thyroid hormones include atrial fibrillation, osteoporosis and bone fractures, and the risks of under treatment are also significant.

2. Indication

Liothyronine is only prescribed as part of a combination treatment with levothyroxine

- Where symptoms of hypothyroidism persist despite optimal dosage with levothyroxine (TSH 0.4-1.5mU/L).
- Where alternative causes of symptoms have been considered as per box below

Endocrine /autoimmune	Diabetes mellitus, Adrenal insufficiency, Hypopituitarism, Coeliac disease, Pernicious anaemia
Haematological	Anaemia, Multiple myeloma
End organ damage	Chronic liver disease, Chronic kidney disease, Congestive cardiac failure
Nutritional	Deficiency of any of the following: Vitamin B12, Folate, Vitamin D, Iron
Metabolic	Obesity, Hypercalcaemia, Electrolyte imbalance
Drugs	Beta-blockers, Statins, Opiates
Lifestyle	Stressful life events, Poor sleep pattern, Work-related exhaustion, Alcohol excess
Other	Obstructive sleep apnoea, Viral and postviral syndromes, Chronic fatigue syndrome, Carbon monoxide poisoning, Depression and anxiety, Polymyalgia rheumatic, Fibromyalgia

Exclusions

- Patients with thyroid cancer who need liothyronine as part of their investigation and treatment will remain under the specialist care.
- Women who are planning pregnancy who are taking liothyronine should remain under specialist care as it is not recommended in pregnancy.
- In rare cases where liothyronine is used for resistant depression, therapy should be supervised by a consultant psychiatrist. This is off licence and not approved locally.

2. Dose

When liothyronine is commenced a reduction in levothyroxine dose will be required. Specialists should individualise approach to dose changes, however typically, for every 10microgram of liothyronine (half tablet of 20microgram preparation) the levothyroxine dose should be reduced by 50micrograms. (E.g. levothyroxine 125microgram each morning would become 75microgram levothyroxine each morning and 10microgram liothyronine each morning). Response is assessed via pre and post symptom scoring or quality of life questionnaire.

3. Duration of treatment

To be determined by the specialist team

5. Contraindications and cautions

Liothyronine is contraindicated in known hypersensitivity to the drug or any of its excipients, thyrotoxicosis, cardiac arrhythmias and angina.

Use with caution in patients with:

- Ischaemic heart disease: any new presentation or significant worsening of existing ischaemic heart disease should be discussed with the specialist endocrinology team.
- Pregnancy
- Breast feeding: an increase in monitoring of thyroid function tests may be required, discuss with specialist endocrinology team.

6. Adverse effects

Most serious toxicity is seen with long-term use and may therefore present first to GPs.

- Angina, arrhythmia
- Other symptoms of excessive dose: Palpitations, restlessness, tremor, diarrhoea, headache, muscle cramps

7. Interactions

Amiodarone, Carbamazepine, Digoxin, Fosphenytoin, Hormone replacement therapy, Lanthanum, Phenobarbital, Phenytoin, Primidone.

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

8. Monitoring

Initial biochemical monitoring will be undertaken by the specialist until a regimen is established.
The aim of the treatment is to maintain TSH of 0.4-2.5mU/L with theT3 and T4 in the normal range.

TSH Level	Action for GPs
More than 5 mU/L	Increase levothyroxine dose by 25microgram
0.4 – 5.0 mU/L	No change required
Less than 0.4 mU/L	Seek specialist advice, may need a lower levothyroxine dose. Some patients may not feel well unless the TSH is <0.02 mU/L. In that case, the responsible specialist should discuss potential risks with the patient and define the tolerated parameters.

- Monitoring is by TSH levels measured from blood tests taken prior to the morning medication.
- Initially and following a dose change a repeat test will be required at 6-8weeks.

After dose stabilisation, monitoring should only be required annually unless there is a change in symptoms that may warrant the checking of TSH levels.

9. Information to patient

- Increases in serum free T3 levels arising from liothyronine administration may provoke cardiac arrhythmias in susceptible individuals, and it is contraindicated in patients with angina of effort or cardiovascular disease.

- TSH levels should be monitored during treatment, and also free T3 and free T4 levels where clinically appropriate in order to reduce the risk of over- or under-treatment. The risks of over-treatment include atrial fibrillation, osteoporosis and bone fractures, and the risks of under treatment are also significant.

- The current number of market authorisation holders may change. Patients should be informed that this is a rarely used product and there is the potential for instability in supply.

- Liothyronine is available as licensed (and unlicensed) 20 microgram tablets and unlicensed 5 microgram tablets. Many other liothyronine-containing preparations are also unlicensed. Therefore, the safety and quality of these products cannot be assured.

- For doses lower than 20 micrograms use the unlicensed 5 micrograms preparation or dissolve/disperse the 20 micrograms tablet in 20 mL of water for 10 minutes. Then using a suitable oral syringe to withdraw the amount of liquid corresponding to the dose prescribed (5mL for a 5mcg dose; 10 mL for a 10mcg dose).

10. Responsibilities of clinicians involved

Stage of Treatment	Specialist	General Practitioner
Initiation	To ensure the patient fulfils the criteria for treatment. To ensure that all alternative causes of symptoms have been excluded. To prescribe, monitor and assess response biochemically and assess physical and psychological wellbeing after at least 3 months of treatment and until treatment dose is stabilised. Inform GP of response after 3months and if treatment is to continue, ask GP to prescribe (send prescribing framework to GP).	Respond to specialist informing if willing to continue treatment past 3 month.
Maintenance	Annual review Provide adequate advice and support for the GP Advice on switching or discontinuation when appropriate	Prescribing once maintenance doses established. Ensure no drug interactions with concomitant medicines that are added at a later time. Monitor biochemistry periodically as recommended by the specialist and action as per section 8. Report to and seek advice from the specialist on any aspect of patient care, which is of concern and may affect treatment. Monitor for side effects: - Angina, arrhythmia: stop Liothyronine, check TSH - Palpitations, restlessness, tremor, diarrhoea, headache, muscle cramps: continue liothyronine, check TSH Update specialist on any changes in medical condition or prescribed concomitant medication

11. Primary Care Advice on Switching from Liothyronine (T3) to Levothyroxine (T4)

- In line with RCP guidance, secondary care endocrinologists do not recommend routine prescribing of liothyronine and seldom initiate therapy of liothyronine on its own or in combination of liothyronine and levothyroxine.
- In exceptional situations, where T3 or T4+T3 therapy is initiated in secondary care, the rationale for treatment should be specified by the endocrinologist. Treatment should not be stopped or altered in those patients without first consulting the secondary care specialist.
- For those who are on combination therapy without secondary care initiation, attempt should be made to convert to the appropriate equivalent dose of levothyroxine monotherapy in agreement with the patient.
    - Face-to-face consultation with the GP before conversion of therapy is recommended to avoid or minimise patient dissatisfaction.
    - The patients should be made aware of non-specific nature of many thyroid complaints.

- Emphasis should be on the risks of non-physiological over-replacement. Osteoporosis and atrial fibrillation may be asymptomatic. A fracture or a thrombotic event may be the first manifestation of those conditions.

- Consider reviewing the diagnosis and ensure that the patient is being treated for genuine hypothyroidism (i.e. confirmed biochemically in a test performed in an NHS accredited lab). If uncertain, stop the thyroid replacement and allow a rise in TSH in about 8-12 weeks.
- Switch from liothyronine (including liothyronine containing products) to the equivalent dose of levothyroxine. This should take into account any other levothyroxine that the patient is also co-prescribed if on combination therapy.
- For the purposes of this guidance, it is assumed that 100 micrograms of levothyroxine is equivalent to 20 micrograms of liothyronine.2,7 The equivalent doses are tabulated below for ease of use:

Liothyronine (micrograms)	5	10	15	20	30	40	60	80	100
Equivalent dose of levothyroxine (micrograms)	25	50	75	100	150	200	300	400	500

- Thyroid function tests (TSH and T4) should be repeated in 8 weeks after switching to determine the appropriateness of the new dose.
- If unsure of the dose, switch to a standard dose of levothyroxine and then titrate as usual. For most adult patients with normal body weight, standard maintenance dose is 100-125 micrograms. Otherwise, the estimated maintenance dose of levothyroxine (in micrograms) is 1.5 x body weight (kg). The prescription should be rounded to the nearest 25 micrograms.

12. References

1. Royal College of Physicians: The diagnosis and management of hypothyroidism. 2014.
2. UK Medicines Information Service (UKMi): What is the rationale for using a combination of levothyroxine and liothyronine (such as Armour® Thyroid) to treat hypothyroidism? 2011. http://www.medicinesresources.nhs.uk/upload/NHSE_Armour_Thyroid_56_5final[1].doc
3. Kung AW, Pun KK. Bone mineral density in premenopausal women receiving long-term physiological doses of levothyroxine. JAMA 1991;265:2688-91.
4. Bauer DC, Ettinger B, Nevitt MC, Stone KL, Study of Osteoporotic Fractures Research G. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001;134:561-8.
5. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014;24:1670-751.
6. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. Eur Thyroid J 2012;1:55-71.
7. British National Formulary (BNF71). March 2016.
8. Updated RMOC Guidance – Prescribing of Liothyronine. Published 15th July 2019, updated 19th July 2019.

Contact Details:

During Office hours: Consultant Endocrinologist, as specified on clinic letter.
Out of hours: Endocrinology registrar on call – via switchboard.

Diabetes and Endocrinology Specialist Pharmacist: Prashanth Takkallapally – 01482 674043

APPROVAL PROCESS

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