Northern, Eastern and Western Devon
Clinical Commissioning Group

South Devon and Torbay
Clinical Commissioning Group

Protocol to initiate new patients on Liothyronine (L-T3)

Overview

Liothyronine (L-T3) is a very expensive treatment used in a small number of hypothyroid patients due to sub-optimal response to the usual treatment, levothyroxine (L-T4). The evidence to support use of L-T3 is very limited and is insufficient to justify the high financial cost currently incurred.

NHS England has advised CCGs (30th November 2017) that:

- There should be no new initiations of liothyronine in primary care
- Individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration given to switching to levothyroxine where clinically appropriate, **but that**:
- The British Thyroid Association (BTA) advice is 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.

https://www.england.nhs.uk/publication/items-which-should-not-be-routinely-prescribed-in-primary-care-guidance-for-ccgs/

Consultation has taken place between the Devon CCGs, specialist endocrinologists and primary care to agree the basis on which liothyronine may be initiated in new patients. This protocol describes that process and the responsibilities of the clinicians involved in caring for these patients. There is a separate but closely aligned protocol for review of existing patients on liothyronine. The South & West Devon Formulary (SWDF) section on liothyronine is included in Appendix 1.

Further guidance is available from the Regional Medicines Optimisation Committee (RMOC) https://www.sps.nhs.uk/articles/rmoc-guidance-prescribing-of-liothyronine/ The aim of this guidance is to inform CCGs and Area Prescribing Committees in local decision making, and support a consistent approach for the exceptional circumstances in which patients have an on-going need for liothyronine.

A. Primary Care Responsibilities:

1. There should be **no new initiations in primary care**
2. If considering a new initiation of Liothyronine (T3) before referrals to endocrinology ensure that L-T4 prescribing is optimal. Consider:
   a) A thorough evaluation of other potentially modifiable conditions (see **appendix 2**). Any relevant conditions should be corrected where possible before changing thyroid treatment.

b) Repeating Thyroid Function Tests (TFTs) 2-3 months after starting L-T4
c) If TFTs are not within the normal range adjust the dose of L-T4 and allow 2-3 months for symptoms to stabilise
d) Due to its long half-life, L-T4 25 microgram tablets may be given on alternate days for fine adjustment of dosage
e) If alternate day 25 microgram dosing is not successful try 12.5 microgram tablets daily for fine control if necessary (these are more expensive than the other strengths of L-T4 but much cheaper than L-T3)
f) Branded L-T4 (Eltroxin) may be considered as only marginally more expensive than generic. Although the BTA state" For the vast majority of patients on L-T4, brand or named supplier prescribing is not considered necessary (2/+00)", the MHRA has stated "Rarely, patients may require a specific brand of L-T4 to be prescribed due to intolerance of generic preparations."

3. Patients that genuinely do not have symptom improvement on L-T4, where the symptoms are felt to be compatible with the thyroid and have TFTs in the normal range can be considered for referral to the Endocrinology Clinic for assessment (see **appendix 3** for referral details required).
4. GPs should not refer patients to endocrinology unless they are prepared to continue prescribing of liothyronine should it be initiated in and recommended to continue by secondary care as per the process described below
5. For patients initiated by secondary care and continued on it as per the specialist advice below: refer to the review section of the existing patients protocol.
6. Strict control of the issue of liothyronine tablets will be necessary with a maximum of one pack of 28 x 20mcg tablets prescribed every 56 days. There should be no early or extra prescriptions provided (apart from appropriate quantities for holidays)

B. Secondary Care Responsibilities

1. Assessment by endocrinology to confirm a thorough evaluation of other potentially modifiable conditions has been done (see **appendix 2**). Any relevant conditions should be corrected where possible before changing thyroid treatment.
2. Before considering LT-3 ensure that L-T4 prescribing is optimal as in A) 2) above
3. Additionally, endocrinologists may wish to up titrate L-T4 even at expense of TSH being below reference range (but not < 0.1mU/L, as this carries a risk of serious cardiac effects, strokes and osteoporosis).
4. If symptoms persist despite all of the above, clearly document the main symptoms that the patient finds troublesome. There should be an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data for LT-3. Provide written information and if the patient still wishes to go ahead offer a trial of 2 months combination L-T4 /

L-T3 treatment (i.e.one pack of 28 x 20 micrograms L-T3) initiated by secondary care:

a) The licensed product of Liothyronine 20microgram tablets must be used. Lower strength tablets / capsules and all liquids are unlicensed specials. These can be even more expensive than the licensed tablets, are of unknown quality / stability and prescribers are not supported by a product licence.

b) Liothyronine 20 microgram tablets are scored allowing 10 microgram doses to be taken. 5 microgram doses can be taken by dividing the half tablet again and taking morning and evening on the same day.

c) Combination L-T4 / L-T3 regimens should aim for a microgram dose ratio of 10:1 L-T4: L-T3 with a maximum dose of 10mcg daily L-T3 prescribed taken either once daily or in two divided doses.

d) Initial monitoring of TFTs should occur after 6-8 weeks and after each medication change to ensure TSH does not become suppressed. There should be a formal assessment as close to 3 months as possible to ensure there has been an improvement in the agreed symptoms which were important to the patient (and thought to be relevant to the thyroid).

e) If there is no evidence of ongoing clinical benefit then combination Levothyroxine and Liothyronine (T4/T3) is to be discontinued and converted back to L-T4 monotherapy.

f) The first prescription for liothyronine should be for one pack of 28 x 20mcg tablets at a dose of 10 mcg daily i.e. 56 days' supply. Note: the budget for this prescribing to be transferred from primary care. After the formal assessment if prescribing is to continue it will be provided by primary care**.

g) Secondary care to ensure full liaison with primary care regarding the outcome of the trial of T4/T3 and whether prescribing is to continue.

5. L-T4/L-T3 combination therapy or L-T3 monotherapy is contraindicated in pregnancy
6. Once stable, offer discharge back to primary care (if GP in agreement) with phone / email advice about dosing if helpful.

**note: this will require the formulary entry for liothyronine to be amended (as per appendix 1).

Appendix 1

Devon Formulary entry for Liothyronine

The South & West Devon Formulary and Referral classifies Liothyronine as an amber (specialist initiated) drug and requires that

1) Prescribing is for the licensed product (20 microgram tablets) only.
2) **Indications:**
    a. Hypothyroidism that has not responded adequately to levothyroxine therapy or patients who have persistent symptoms felt to be secondary to thyroid hormone deficiency despite seemingly adequate replacement therapy with levothyroxine
    b. Preparation for radioiodine remnant ablation (RRA) in patients with thyroid cancer (secondary care only)
3) **Dose:** Hypothyroidism: Oral, maximum 10 micrograms daily as a single or 2 divided doses, in combination with a reduced dose of levothyroxine. Elderly- smaller initial doses
4) **Notes:**
    a. Liothyronine (LT-3) is not appropriate for initiation by GPs. Liothyronine may be suitable for a small number of patients whose symptoms have not resolved despite optimal treatment with levothyroxine (L-T4). Liothyronine is restricted to a maximum dose of 10 mcg daily as dual therapy with levothyroxine initiated by an endocrinologist.
    b. 10 micrograms L-T3 is approximately equivalent to 50 micrograms L-T4
    c. Secondary care to carry out the initial assessment, monitoring and dose adjustment, and prescribe an initial supply of one pack of 28 x 20mcg (56 days' supply). GPs will be asked to prescribe following this and will be informed if the treatment is to continue or not beyond the 3 month formal assessment. GP to review the benefits of L-T3 and consider a trial off L-T3 every 3 years to ensure it is still clinically beneficial.
    d. There is no convincing evidence to support routine use of thyroid extracts, liothyronine monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism
    e. Liothyronine for RRA should be prescribed from the centre undertaking the treatment, and should **not** be routinely prescribed in primary care

Appendix 2

Some possible causes of persistent symptoms in euthyroid patients on L-T4 to be considered by primary care prior to referral to secondary care

Ref: Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee, Clinical Endocrinology 2015.

Endocrine/autoimmune

Diabetes mellitus	Adrenal insufficiency	Hypopituitarism	Coeliac disease
Pernicious anaemia			

Haematological

Anaemia	Multiple myeloma

End-organ damage

Chronic kidney disease	Chronic liver disease	Congestive cardiac failure

Nutritional

Vitamin B12 deficiency	Folate deficiency	Vitamin D deficiency
Iron deficiency		

Metabolic

Obesity	Hypercalcaemia	Electrolyte imbalance

Drugs

Beta-blockers	Statins	Opiates

Lifestyle

Stressful life events	Poor sleep pattern	Work-related exhaustion
Alcohol excess		

Others

Obstructive sleep apnoea	Viral and post viral syndromes	Chronic fatigue syndrome
Carbon monoxide poisoning	Depression and anxiety	Polymyalgia rheumatica
Fibromyalgia		

Appendix 3

Patient not responding / tolerating levothyroxine:

Referral details required

- Initial diagnostic TFTs (was TSH ever raised)?
- Current dose levothyroxine
- Start date
- Started by whom
- Reasons for starting
- Relevant endocrinological history prior to and after starting T4 including relevant monitoring and TSH results
- Current ongoing problem
- Relevant past medical history
- Current other medication (any relevant past medication history)