Commissioning Policy: Prescribing of liothyronine (tri-iodothyronine) either alone or in combination with levothyroxine for the treatment of hypothyroidism

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Document Control Sheet

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Consultation with stakeholders:	SaTH Endocrinology Team, SaTH Lead Pharmacist for Medicines Utilisation and Deputy Chief Pharmacist, Area Prescribing Committee *NB: Policy based on Regional Medicines Optimisation Committee Guidance*		
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Document Amendment History

Version No.	Date	Brief Description
Version 2	04/10/2022	Amended to reflect ongoing prescribing responsibility following a robust trial with NHS Consultant specialist will sit with Primary Care and should be undertaken via shared care and change from CCG to ICB.

Contents

Commissioning Statement

NHS Shropshire, Telford and Wrekin do not routinely commission the prescribing of liothyronine for the treatment of hypothyroidism.
The ICB will consider the limited use of liothyronine in combination with levothyroxine for patients with confirmed Hypothyroidism who meet the clinical criteria specified in this policy.
In line with the British Thyroid Association advice, it would be expected that liothyronine treatment should only be required in a very limited number of patients that despite biochemical control of their hypothyroidism (euthyroid) they continue to experience a number of symptoms including deficits in cognition and mood, their ability to focus, and their general mental well-being and where alternative causes have been excluded.
Liothyronine monotherapy is not recommended in Hypothyroidism and will not routinely be commissioned. Use will only be considered under exceptional circumstances detailed by this policy below; this will be considered on an individual case by case basis by the relevant ICB.
Requests to initiate a liothyronine trial and subsequently continue liothyronine prescribing following a carefully audited trial or structured review as outlined by this policy, should be submitted via Blueteq as appropriate.

Introduction

The replacement therapy of choice for hypothyroidism is levothyroxine (T4). Levothyroxine is given once a day and is converted to triiodothyronine in peripheral tissues, providing stable and physiological quantities. Liothyronine (T3) has a much shorter half-life (1 day vs. 6 days) and steady state levels cannot be maintained with once daily dosing.[1] Before the 1970s, synthetic combinations of levothyroxine and liothyronine or desiccated animal thyroid containing varying amounts of thyroid hormones were used, but these have now been replaced with the use of levothyroxine monotherapy.
Armour® Thyroid tablets are made from desiccated porcine thyroid glands. The amount of hormone in the thyroid gland varies from animal to animal but Armour® Thyroid contains standard amounts of levothyroxine and liothyronine according to United States Pharmacopoeia (USP) standards and specifications. Armour® Thyroid is licensed in the US; there is no licensed product available in the UK although it can be ordered via importing companies.

Rationale for the decision

There is evidence to suggest that between 5 and 10% of patients that receive levothyroxine for hypothyroidism with normal serum TSH levels have persistent symptoms related to the condition. Rationale for these symptoms include: awareness of chronic disease, presence of associated autoimmune diseases, extra-thyroid autoimmunity (not related to thyroid function) and inadequacy of levothyroxine therapy to restore serum levothyroxine and liothyronine levels.[2]

A combination of levothyroxine and liothyronine, in both non- and physiological proportions, has not consistently been shown to be more beneficial than levothyroxine alone with respect to cognitive function, social functioning and wellbeing.[1]

The variation in hormonal content and large amounts of liothyronine may lead to increased serum concentrations of T3 due to rapid absorption and symptoms of thyro-toxicity, such as palpitations and tremor.[1]
Clinicians treating patients with hypothyroidism have an ethical obligation to avoid potential harmful therapies without proven benefits.
Whilst it is possible that some patients might benefit from the use of combination treatment, the parameters identifying such a patient group have yet to be clearly identified. Furthermore the majority of the trials conducted, used non-physiological ratios of levothyroxine to liothyronine, which can lead to over-replacement.
In 2015 the British Thyroid Association (BTA), issued a position statement *"There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism".*[3]

Summary of recommendations

In June 2019, NHS England updated their guidance on items which should not routinely be prescribed in Primary Care. Liothyronine continues to be listed by NHS England as a drug which should not be routinely prescribed as there is insufficient evidence of either clinical or cost-effectiveness to support its use.
NHS England:

- Advises that prescribers in primary care should not initiate liothyronine for any new patient.
- Advises that individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration given to switching to levothyroxine where clinically appropriate.
- Advises that a local decision, involving the Area Prescribing Committee (or equivalent) informed by National guidance (e.g. from NICE or the Regional Medicines Optimisation Committee), should be made regarding arrangements for on-going prescribing of liothyronine.

The British Thyroid Association (BTA) advises 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.[3]

NICE Guidance NG145 states "Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain." [4]
Based on the available evidence and current list price, NICE are unable to recommend liothyronine either alone or in combination treatment however the guidance does recognise further research is required in this area as some people who remain unwell with levothyroxine monotherapy may demonstrate greater benefit with liothyronine. Current NICE guidance refers to the Regional Medicines Optimisation Committee guidance.[5]

"There is insufficient evidence at present to specify the quality of life measures to be adopted during a trial of combination levothyroxine and liothyronine, or during a trial titration from liothyronine to levothyroxine. Further work is ongoing to develop a validated quality of life measurement tool. In the interim, NHS consultant endocrinologists should document the range and severity of hypothyroid symptoms experienced by the patient prior to and during the assessment period.[5]"

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 from the centre undertaking the treatment and not be routinely obtained from primary care prescribers.

Patient safety considerations

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

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

The manufacturer's summary of product characteristics[6] (SPC) and the most current edition of the British National Formulary[7] should be consulted for full information on contraindications, warnings, side effects and drug interactions.

Clinical criteria for liothyronine prescribing

New Patients: Criteria for initiation of a trial of liothyronine in combination with levothyroxine (by NHS Consultant Endocrinologist)

A trial of liothyronine in combination with levothyroxine should only be considered for patients that meet all of the following:

1) Patients with a confirmed diagnosis of Primary Hypothyroidism. For patients where diagnosis is unclear, a retrospective review of the original diagnosis should be undertaken.
   NB: Patients who are pregnant or have cardiac arrhythmias are unsuitable for combination thyroid hormone treatment

2) Patients prescribed levothyroxine that has been fully titrated, that have demonstrated full compliance with their treatment for a minimum of 6 months

3) Patients that remain symptomatic despite a serum TSH within the reference range for 6 months or more and have been prescribed levothyroxine in line with the MHRA recommendations;
   - have been prescribed a specific levothyroxine product known to be well tolerated by the patient

- or where symptoms or poor control of thyroid function persist despite adhering to a specific product, levothyroxine in an oral solution formulation has been prescribed

4) Patients experiencing persistent symptoms despite being euthyroid; they should be investigated and patients thoroughly evaluated for other potentially modifiable conditions (appendix 1) before considering a trial of liothyronine.

5) Patients must have received adequate chronic disease support; including psychological support[2] where the clinician has identified this would be indicated.

6) Patients must fully understand the uncertain benefits, likely risks of over-replacement and lack of long-term safety data associated with liothyronine use. A prior initiation agreement should be fully documented which acknowledges the uncertain benefits and risks and makes it clear treatment will be discontinued following the trial if there is insufficient evidence to demonstrate ongoing clinical benefit. Clinicians treating patients with hypothyroidism have an ethical obligation to avoid potential harmful therapies without proven benefits.

In exceptional circumstances, where patients have met the above criteria and the NHS Consultant Endocrinologist deems a trial of liothyronine is warranted, prescribing responsibility should remain with the Endocrinologist. There should be a formal assessment of the safety and benefit of treatment within 6 months of starting therapy, evidenced by quality of life improvements and biochemical markers.

This prescribing will not be funded by the ICB, in line with the ICB's policy on experimental and unproven treatments.

New Patients: Criteria for ongoing treatment with liothyronine

Ongoing treatment with liothyronine should only be considered for patients that meet all of the following:

1) Patients must have completed a minimum of 3 months trial (NHS Endocrinologist-led)

2) Patients are required to demonstrate full compliance with their treatment

3) Evidence of clinical benefit should be formally assessed by the Consultant Endocrinologist. The European Thyroid Association advises improvement should be demonstrated after 3 months otherwise treatment should be discontinued.

   This should be evidenced by improvement of quality of life indicators and biochemical markers.[5]
   - ✓ monitoring of chief symptom (eg depression, fatigue, aches, oedema)

- ✓ + 1 objective measure, from: weight loss, sick days/reduction in work absence, laboratory markers (cholesterol)
  Treatment continuation should only be considered if both measures show improvement.[8]

4) Patients should not experience any adverse effects associated with commencing the therapy during the treatment trial

5) Use of Liothyronine in primary care should be supported by having an agreed integrated care protocol in place

6) Patient should be in agreement to report any adverse effects to the GP and specialist and must continue to attend regular outpatient appointments with their specialist.

Only if all of the above criteria have been met will the patient be considered for continued prescribing. Requests to continue liothyronine prescribing following a carefully audited trial should be submitted via a continuation form on Blueteq as appropriate. Only once Bluteq authorisation has been received should prescribing responsibility be transferred into Primary Care. An integrated care protocol should be issued and agreed with the GP before prescribing is transferred to Primary Care.

The recommended dose ratio of levothyroxine/liothyronine is 13:1 to 20:1 by weight. Available combination preparations (e.g. Armour®, ERFA Thyroid) contain dose ratios lower than 13:1 therefore prescribing is not recommended or supported by the NHS.

Criteria for continuation in existing patients currently prescribed liothyronine (monotherapy or combination)

1) Only liothyronine prescribed in combination with levothyroxine will usually be considered for continuation in line with this policy.

   Liothyronine monotherapy is not recommended in hypothyroidism; prescribing would be in exceptional circumstances only, such as clearly distinguishable specific levothyroxine medication intolerance including extremely rare cases of levothyroxine induced liver injury. Or potentially for patients who do not effectively metabolise levothyroxine to liothyronine, if a specialist assessing the patient according to this policy agrees. Use will only be considered under exceptional circumstances; this will be considered on an individual case by case basis by the ICB.

2) Individuals currently prescribed liothyronine monotherapy or in combination with levothyroxine for hypothyroidism should be referred to a consultant NHS endocrinologist by the local agreed process (appendix 2) to consider transition to levothyroxine through a trial titration where clinically appropriate.

3) For individuals already prescribed liothyronine in combination with levothroxine, a trial titration for gradual transition to levothyroxine (under a consultant NHS endocrinologist) should be undertaken unless there is clear and full documentation of clinically validated benefit of treatment with liothyronine.

This should include all of the following:

- Confirmed diagnosis of Primary Hypothyroidism

- Evidence patient has received and demonstrated full compliance with fully titrated levothyroxine therapy for a minimum of 6 months and patients with persistent symptoms have been prescribed levothyroxine in line with MHRA recommendations.

- Record of persistent symptoms despite a serum TSH within the reference range for 6 months or more

- Patients experiencing persistent symptoms despite being euthyroid should have been fully investigated and thoroughly evaluated for other potentially modifiable conditions before a trial of liothyronine was considered.

- Patient must have received adequate chronic disease support, including psychological support prior to initiating liothyronine[2] where the clinician has identified this is indicated.

- Patients must fully understand the uncertain benefits, likely risks of over-replacement and lack of long-term safety data associated with liothyronine use. An agreement should be in place which fully documents the uncertain benefits and risks and makes it clear treatment will be discontinued if there is insufficient evidence to demonstrate ongoing clinical benefit.

- Evidence of clinical benefit should have previously been/ should be formally assessed by the Consultant Endocrinologist.

  This should be evidenced by a demonstrated improvement of quality of life indicators and biochemical markers following treatment with liothyronine compared to levothyroxine alone.[5]
  - ✓ Improvement in chief symptom (eg depression, fatigue, aches, oedema)
  - ✓ + 1 objective measure, from: weight loss, sick days/reduction in work absence, laboratory markers (cholesterol)

  Treatment continuation should only be considered if both measures have shown improvement.[8]

- Patients should not experience any adverse effects associated with liothyronine

4) If any patient currently taking liothyronine should not undergo a trial titration to levothyroxine; this is to be communicated to the patients GP. If a previous trial titration has proved unsuccessful, the consultant endocrinologist should decide whether there is any good reason to consider a further review, and inform the GP accordingly. Ongoing prescribing responsibility of the liothyronine and

levothyroxine should be continued in Primary Care with liothyronine prescribed under an ICP.

5) For individuals who are established on liothyronine (monotherapy or combination) and are considered to be stable but warrant a trial titration to levothyroxine in line with the above criteria, a full discussion about change in therapy should be had with the patient prior to undertaking the trial.

6) The withdrawal of liothyronine should occur gradually in line with NHS consultant endocrinologist recommendations, and may take many months to complete (appendix 3). To ensure patient safety, prescribing of liothyronine and levothyroxine during this review and withdrawal should be undertaken in secondary care by the NHS consultant endocrinologist.

7) If ongoing treatment with liothyronine is required, an ICP should be issued and agreed with the GP before continuation in Primary Care. Prescribing should only be transferred into Primary Care once the patient is stabilised.

Private patients

In accordance with NHS guidance on 'Defining the Boundaries between NHS and Private Healthcare', patients who are currently obtaining supplies via private prescription or self-funding should not be offered NHS prescribing unless they meet the relevant criteria outlined in this commissioning policy. Patients who have been seen privately retain the option of being referred back to the private service for private prescription[5] or recommendation of an alternative treatment.

Liothyronine for alternative uses other than hypothyroidism

Oncology: thyroid disease
Liothyronine is recommended as part of the management of thyroid cancer in preparation for radioiodine remnant ablation (RRA) or radioiodine therapy (131I). The prescribing is considered for short term use as part of the endocrine management and therefore prescribing responsibilities should be retained by the specialist endocrine / oncology team involved with the management of the patient.
Short term use of liothyronine is sometimes also advised in preparation for a sestamibi parathyroid scan. Prescribing responsibilities should be retained by the specialist endocrine/oncology team involved with the management of the patient.

Thyroid cancer patients who have completed their treatment usually need to take levothyroxine for life, so should be managed in the same way as patients with hypothyroidism.[5]

Psychiatry: resistant depression
Liothyronine is sometimes used off-label in psychiatry as a treatment for resistant severe depression. NICE states: augmentation of an antidepressant with thyroid hormones under 'strategies that should not be used routinely as there is inconsistent evidence of effectiveness'.[5]

Where liothyronine is used off-label for resistant severe depression, this must be initiated and monitored by a consultant NHS psychiatrist and advice should be sought from NHS consultant endocrinologist. Prescribing should remain with the specialist, prescribing will not be accepted within primary care for this indication.

This prescribing for the above circumstances would remain with the recommending specialist and would not be funded by the ICB.

Related Documents

https://www.british-thyroid-association.org/current-bta-guidelines-
https://www.sps.nhs.uk/articles/what-clinical-evidence-is-there-to-support-the-use-of-desiccated-thyroid-extract/
https://static1.squarespace.com/static/53b1670ee4b0be242b013ed7/t/543ee743e4b05588d7c67389/1413408579862/RCP+Diagnosis+and+management+of+primary+hypothyroidism+2011.pdf
https://cks.nice.org.uk/hypothyroidism
https://www.sps.nhs.uk/articles/rmoc-guidance-prescribing-of-liothyronine/
https://www.british-thyroid-association.org/sandbox/bta2016/faq_for_patients_.pdf
https://www.prescqipp.info/our-resources/webkits/drop-list/low-value-medicines-lvm/patient-information-pdf-versions/-

Dissemination

These guidelines will be disseminated by the following methods:

- Staff - via Medicines Management newsletter
- Published to the Website
- Awareness raising by taking for information to Area Prescribing Committee
- Link included on Netformulary

Advice

For further advice on this document please contact:

Clare Stallard Senior Pharmaceutical Advisor, Primary Care and Place
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Review and Compliance Monitoring

Prescribing of liothyronine in Primary Care is monitored monthly by the Medicines Management Team via epact2. Ongoing prescribing will be monitored by Bluteq reports.

Audits of compliance of prescribing in line with the criteria outlined in this guidance may be requested by NHS STW Medicines Management team.

This document will be reviewed every three years unless superseded by National Guidance or new evidence becomes available.

References

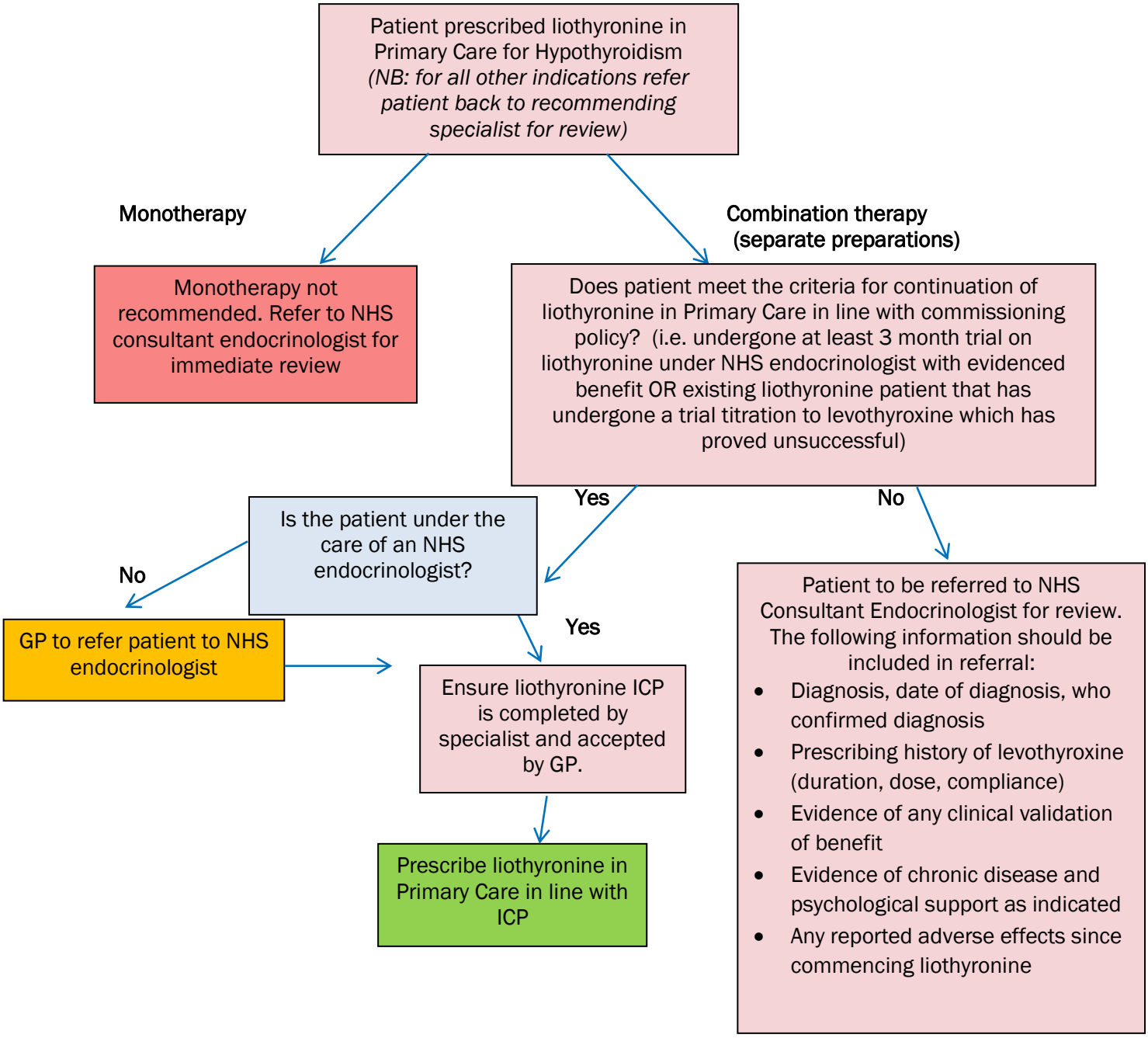
1. What is the rationale for using a combination of levothyroxine and liothyronine (such as Armour® Thyroid) to treat hypothyroidism. UK Medicines Information service November 2011
2. Okosieme et al., "Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee," *Clinical Endocrinology ,* vol. 0, pp. 1 - 10, 2015. Available at: http://www.btf-thyroid.org/images/documents/BTA_Hypothyroidism_Statement.pdf [Accessed 12/09/19]
3. https://www.england.nhs.uk/wp-content/uploads/2019/08/items-which-should-not-routinely-be-prescribed-in-primary-care-v2.1.pdf
4. NICE NG 145, Thyroid Disease: Assessment and Management. November 2019. Available at https://www.nice.org.uk/guidance/ng145/chapter/Recommendations [Accessed 21/08/20]
5. https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf
6. Liothyronine Summary of Product Characteristics (SPC) Advanz Pharma October 2018 Available at: https://www.medicines.org.uk/emc/product/5905/smpc [Accessed 12/09/19]
7. Liothyronine BNF online Available at: https://bnf.nice.org.uk/drug/liothyronine-sodium.html [Accessed 12/09/19]
8. The Dudley Group of Hospitals ESCA Liothyronine January 2018 available at: http://www.dudleyformulary.nhs.uk/download/540/shared-care-esca-liothyronine.
9. British Thyroid Association Executive Committee Information for Members on Prescribing Liothyronine (L-T3). British Thyroid Association December 2016. Available at: https://www.british-thyroid-association.org/sandbox/bta2016/information_for_endocrinologists.pdf [Accessed 30/08/19]

Appendix 1 - Other potentially modifiable conditions

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

Integrated Care System
Shropshire, Telford and Wrekin

Appendix 2- Process for referral to NHS consultant endocrinologist to consider transition to levothyroxine



Appendix 3- Guidance on Switching from Liothyronine (T3) to Levothyroxine (T4) under the instruction of an NHS Consultant Endocrinologist:

Patients undergoing a trial of switching from liothyronine to levothyroxine should remain under the full care of the NHS consultant endocrinologist during this period. Prescribing responsibility for both liothyronine and levothyroxine should remain with Secondary Care during this period. This must be communicated to the GP to prevent duplication.

Once a discussion with the patient has taken place and agreement reached to begin the switch, the transition to levothyroxine should "be made cautiously and gradually aiming to avoid under or over-replacement with thyroid hormones. The final levothyroxine requirement is likely to be around 1.6µg/kg. Any information about previous levothyroxine dosage that achieved a serum TSH within the reference range will be a useful guide that predicts the individual requirement.[8]"

Patients taking T3 should be switched to levothyroxine monotherapy over a period of approximately 6 months by titration over a 2 month period, this should then be followed by 4 months at a stable state, a patient information leaflet should be provided.

"There is no defined conversion factor, and conversion of patients from liothyronine to levothyroxine monotherapy will require a reduction in the dose of liothyronine and an increase in levothyroxine. A reduction of dose of liothyronine by 10 micrograms will probably require an increase in dose of levothyroxine of 50 micrograms.

Once on levothyroxine monotherapy, patients will need to have adjustment in the dose as per standard practice by monitoring of the TSH on a 6 weekly basis. Blood tests should not be undertaken more often than 6 weekly because the TSH will not have reached steady state until 6 weeks after any change. Free T4 / free T3 levels should also be measured where clinically appropriate.[4]"

If ongoing treatment with liothyronine in combination with levothyroxine is required, an ICP should be issued and agreed with the GP before continuation in Primary Care. Prescribing should only be transferred into Primary Care once the patient is stabilised.

Where patients no longer require liothyronine and have successfully moved to levothyroxine monotherapy, prescribing responsibility of levothyroxine can be returned to primary care without the need for an ICP.