NHS Somerset

Shared Care Protocol
Liothyronine for primary hypothyroidism - new prescriptions
(For information regarding privately prescribed Liothyronine see Appendix 1)

This shared care protocol (SCP) sets out details for the sharing of care ***for patients initiated on liothyronine capsules (in combination with levothyroxine) by NHS Endocrinology services for the management of hypothyroidism.***

It should be read in conjunction with the latest Summary of Products Characteristics (SmPC) available at http://www.medicines.org.uk/emc/

As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.

This document provides information on drug treatment for the shared commitment between the specialist and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.

Introduction:

For further information please click on the links below or visit:

- https://bnf.nice.org.uk/drugs/liothyronine-sodium/
- https://www.medicines.org.uk/emc/search?q=liothyronine+capsules
- NICE NG145 Thyroid disease: assessment and management 2019 https://www.nice.org.uk/guidance/ng145
- Updated RMOC Guidance – Prescribing of Liothyronine – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

NHS England guidance states that 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.

As noted by the British Thyroid Association (BTA) Executive Committee, 'clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not prescribing potentially harmful therapies without proven advantages over existing treatments'. Also 'If a decision is made to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4 then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of L-T4/L-T3 combination therapy is warranted in these circumstances and their clinical judgement must be recognised as being valid given the current understanding of the science and evidence of the treatments'.

The Regional Medicines Optimisation Committee (RMOC) therefore 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.

Licensed indication: Hypothyroidism

Dose (posology & method of administration):
This Shared Care Protocol applies to Liothyronine CAPSULES only. All other forms of liothyronine are non-formulary.

5micrograms or 10micrograms a day (in 1-2 divided doses) in combination with levothyroxine. Oral.

Note: These doses are lower than the maximum licensed dose. The majority of side effects are extremely unlikely at the doses advised here. Furthermore, published side effects related to Liothyronine monotherapy, which will not be offered.

Contra-indications

- Known sensitivity to the drug or any of its excipients
- Thyrotoxicosis
- Cardiac arrythmias
- Ischaemic heart disease / Angina
- Pregnancy – In Somerset, liothyronine is not offered in pregnancy or those seeking to conceive. There is a risk of inadequate T4 to the foetus.

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

Cautions:

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.
- Breast feeding: an increase in monitoring of thyroid function tests may be required, discuss with specialist endocrinology team.
  Note: Liothyronine is not offered during breastfeeding in Somerset.

Special warnings and precautions:

- All hypo adrenal patients should have steroid levels replaced before starting thyroid hormone replacement.
- Liothyronine sodium treatment may result in an increase in insulin or anti-diabetic drug requirements. Care is required for patients with diabetes mellitus and diabetes insipidus.
- TSH levels should be monitored during treatment to reduce the risk of over- or under-treatment. The risks of over-treatment include atrial fibrillation, osteoporosis and bone fractures.

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

Drug interactions:

- Liothyronine sodium therapy may potentiate the action of anticoagulants. Phenytoin levels may be increased by liothyronine. Anticonvulsants, such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace thyroid hormones from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter liothyronine dose requirements.
- If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.

- Colestyramine and colestipol given concurrently reduces gastrointestinal absorption of liothyronine.
- Liothyronine raises blood sugar levels and this may upset the stability of patients receiving antidiabetic agents.
- Liothyronine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants. A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring patients on liothyronine therapy.
- Co-administration of oral contraceptives may result in an increased dosage requirement of liothyronine sodium.
- Amiodarone may inhibit the de-iodination of thyroxine to triiodothyronine resulting in a decreased concentration of triiodothyronine with a rise in the concentration of inactive reverse triiodothyronine.
- As with other thyroid hormones, Liothyronine may enhance effects of amitriptyline and effects of imipramine.
- Metabolism of thyroid hormones accelerated by barbiturates and primidone (may increase requirements for thyroid hormones in hypothyroidism).
- Requirements for thyroid hormones in hypothyroidism may be increased by oestrogens.

This list is not exhaustive. The manufacturer's summary of product characteristics (SmPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Pregnancy and lactation:

Pregnancy

Safety during pregnancy is not known. The risk of foetal congenital abnormalities should be weighed against the risk to the foetus of untreated maternal hypothyroidism.

Should pregnancy occur during treatment with T3 – seek urgent endocrine consultant advice regarding switching from T3 to T4, T4 dosage and TFT monitoring while waiting for specialist review

Lactation

Liothyronine sodium is excreted into breast milk in low concentrations.
This may interfere with neonatal screening programmes.

Fertility

There are no fertility data available.

Adverse effects & management:

- Adverse effects are less likely at the doses and for the indication listed in this document.
- Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse effect	Action to be taken by GP
Angina, cardiac arrythmia	Stop liothyronine, check TSH level and discuss with Endocrinologist via A&G
Palpitations, restlessness, tremor, diarrhoea, headache, muscle cramps	Continue liothyronine, check TSH level If required, discuss with Endocrinology via A&G

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme www.mhra.gov.uk/yellowcard

Shared Care Responsibilities

- Abbreviations: T3 – Liothyronine
  T4 - Levothyroxine
- For guidelines for patients who are already taking T3 who desire an NHS prescription, see Appendix 1
- NHS clinicians should not feel obliged to start or continue T3 medication provided by other health care practitioners or accessed without medical advice, if they judge this not to be in the patient's best interest

GP responsibilities for patients on T4 monotherapy desiring a trial of T3/T4 combination therapy

Prior to referring a patient to the NHS Endocrinology clinic:

- Patient must have demonstrable hypothyroidism as evidenced by a previous documented rise in TSH >10mU/L. If this is not available, a brief trial of T4 reduction should be instigated to demonstrate this prior to consideration of referral. If the TSH rises to >10mU/L on reducing the T4, the dose should be increased again pending the appointment with Endocrinology

- Other causes of 'thyroid-type symptoms' have been considered and tested for if appropriate (see Appendix 2). Screening for sleep apnoea should be performed. These other conditions should be optimised before referral is considered. If these conditions are the source of symptoms, treatment with T3 will not alleviate them.

- The following tests should have been checked: U&Es, LFTs, ferritin, HbA1c, Coeliac screen, B12, calcium, vitamin D

- Patient should have been taking T4 for at least 12 months with a TSH consistently in the lower half of the reference range

- Patient should be given an NHS Somerset T3 Patient Information Leaflet (see Appendix 4) Link to printable pdf version here.

- Once the above is completed, the patient can be referred to their local NHS Endocrine clinic (these slots are limited and will be offered on a first come, first served basis). Patients must be registered with an NHS Somerset GP practice. Only patients from these practices will fall under these guidelines.

Consultant responsibilities:

- When meeting the Endocrinologist the following will take place:
    - History of thyroid disease and other medical conditions
    - Assessment of persistent symptoms, including a formal assessment of mood using GHQ12 (Appendix 3)
    - Consideration of whether a trial of mild TSH suppression (beneath lower limit of reference range but >0.1mU/L) to be considered
    - Patient will be advised of the possible risks of T3 therapy (unknown long-term safety, risk of arrhythmia, possible risk of osteoporosis and stroke, adverse effect on mental health)
    - Patient will be given an NHS Somerset T3 Patient Information Leaflet (if not already done)
    - If agreed by **both** the patient and Endocrinologist, a trial of T3/T4 will be considered at a maximum of T3 10microgams daily (either as a once daily dose or in divided doses) in combination with T4

- Consultant to prescribe first three months' supply
- TSH, psychological and clinical assessment at 3 months (may be virtual)
- If there is a significant improvement at 3 months, GP will be asked to take over prescribing.
- Assessment is repeated at 12 months and a decision is made whether to continue the treatment longer term
- If there is not a significant improvement at 3 months or the improvement has been lost by 12 months, the combination therapy will be converted back to T4 monotherapy.
- At 12 months, or earlier if T3 treatment trial fails, patient will be discharged back to their GP for annual TSH assessment, aiming for TSH in the lower half of the reference range.

General Practitioner responsibilities:

- If T3 combination treatment is to be continued for more than 3 months, GP to take over prescribing T3 as per NHS Endocrinologist recommendations.
- If T3 is to continue after 12 months, GP, to arrange annual TSH assessment, aiming for TSH in the lower half of the reference range.
- At least once every three years GP should consider discussing converting T3/T4 combination therapy to T4 monotherapy:
    - For each 10 micrograms T3 the patient is taking, replace with 50 micrograms T4. If on T3/T4 combination therapy, add this extra T4 to the dose of T4 they are already taking. Total T4 dose should be rounded to closest practical dose. TSH should be checked at 6 weeks and the dose adjusted, aiming for a TSH in the lower half of the reference range. Patients should be counselled that it

can take some months for the body to readjust. It is worth waiting for 3-6 months after the TSH stabilises for stabilisation of symptoms. Advantages of converting to T4 monotherapy are ease (once a day medication), more stable thyroid hormone levels, reduced risk of arrythmias and reduced cost.

- Endocrine consultant support and advice can be sought via A&G – see also 'Adverse effects & management'.

Patient / carer responsibilities:

- After counselling, to be willing to take / administer prescribed medication as directed at home.
- To report any significant signs or symptoms relating to their condition, including side effects or concordance issues to the GP.
- To undergo medication review at least every three years to consider if converting to T4 monotherapy is appropriate
- Inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

Further support

• Medicines Information department, Musgrove Park Hospital: 01823 342253

• Medicines Information department, Yeovil District Hospital: 01935 384327

• Prescribing & Medicines Management Team, NHS Somerset: 01935 384123

• Medicines Management Team, Somerset NHS Foundation Trust: 01823 368265

Version:	1.3	Date
Version 1.0 drawn up by:	Dr Julia Thomas, Consultant Endocrinologist After discussion at the Somerset Endocrine meeting (YDH and MPH)	6/6/22
Approved by:	Somerset Prescribing Forum, NHS Somerset	
	Drug & Therapeutics Committee, Somerset NHS FT	18/11/22
	MH Drug & Therapeutics Committee, Somerset NHS FT	N/A
	Somerset Prescribing & Medicines Management Committee	18/01/23
Updated by:	Dr Julia Thomas (Consultant Endocrinologist) & Hels Bennett (NHS Somerset ICB Medicines Manager) Updated to reflect comments by PAMM committee	21/02/23
Review by: Dr Julia Thomas		April 24

References

1. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee (british-thyroid-association.org)
2. Updated RMOC Guidance – Prescribing of Liothyronine – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice May-2021-DSU-PDF.pdf (publishing.service.gov.uk)
3. Use of Liothyronine (T3) in hypothyroidism: joint British Thyroid Association/Society for Endocrinology consensus draft statement
4. https://bnf.nice.org.uk/
5. http://www.medicines.org.uk/emc/
6. NICE NG145 Thyroid disease: assessment and management 2019 https://www.nice.org.uk/guidance/ng145

Appendix 1

Guidelines for patients already taking Liothyronine provided by other health care practitioners or accessed without medical advice

NHS clinicians should not feel obliged to start or continue T3 medication provided by other health care practitioners or accessed without medical advice, if they judge this not to be in the patient's best interest.

Patients already established on T3 can be managed within the GP setting. The service described in the above shared care part of this document is specifically for patients who are considering a new trial of T3/T4.

Patients already on T3 (mono or combination) therapy should be:

- Reviewed by their GP
- If no evidence of a previously raised TSH is available, the GP may consider reducing T4 for 6-12 weeks to demonstrate evidence of a TSH >10 to confirm the diagnosis of hypothyroidism prior to discussion of prescription
- Advised of the possible risks of T3 therapy (unknown long term safety, risk of arrhythmia, possible risk of osteoporosis and stroke, adverse effect on mental health)
- Given an NHS Somerset T3 Patient Information Leaflet (see Appendix 4). Link to printable pdf version here.
- Offered the chance to convert to T4 monotherapy:
    - For each 10 micrograms T3 the patient is taking, replace with 50 micrograms T4. If on T3/T4 combination therapy, add this extra T4 to the dose of T4 they are already taking. Total T4 dose should be rounded to closest practical dose. TSH should be checked at 6 weeks and the dose adjusted, aiming for a TSH in the lower half of the reference range. Patients should be counselled that it can take some months for the body to readjust. It is worth waiting for 3-6 months after the TSH stabilises for stabilisation of symptoms. Advantages of converting to T4 monotherapy are ease (once a day medication), more stable thyroid hormone levels, reduced risk of arrythmias and reduced cost.
- If patient keen to continue on T3, the GP can prescribe if they believe it is clinically indicated and to be of benefit to the patient. The GP is not obliged to continue the prescription, see above.
- If choosing to continue the T3 prescription, the GP can prescribe a maximum dose of T3 10micrograms od, or 5micrograms bd, in combination with T4 (higher doses of T3 will need to partially be converted to T4 as per the advice above)
- Have TSH measured 6-8 weeks after any change and three months later

- TSH should be maintained in the lower half of the reference range.
- Once the TSH stable on two measurements 3 months apart, it should be measured annually
- At least once every three years GP should consider discussing converting T3/T4 combination therapy to T4 monotherapy:
    - For each 10 micrograms T3 the patient is taking, replace with 50 micrograms T4. If on T3/T4 combination therapy, add this extra T4 to the dose of T4 they are already taking. Total T4 dose should be rounded to closest practical dose. TSH should be checked at 6 weeks and the dose adjusted, aiming for a TSH in the lower half of the reference range. Patients should be counselled that it can take some months for the body to readjust. It is worth waiting for 3-6 months after the TSH stabilises for stabilisation of symptoms. Advantages of converting to T4 monotherapy are ease (once a day medication), more stable thyroid hormone levels, reduced risk of arrythmias and reduced cost.
- Endocrine consultant support and advice can be sought via A&G

Appendix 2 Possible causes of persistent symptoms in euthyroid patients on T4

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

Appendix 3

Short General Health Questionnaire (GHQ 12)

Have you recently?

1. Been able to concentrate on what you're doing?	Better than usual	Same as usual	Less than usual	Much less than usual
2. Lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
3. Felt you were playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
4. Felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
5. Felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
6. Felt you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
7. Been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
8. Been able to face up to your problems?	More so than usual	Same as usual	Less so than usual	Much less able
9. Been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
10. Been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
11. Been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
12. Been feeling reasonably happy, all things considered	More so than usual	About same as usual	Less so than usual	Much less than usual;

Appendix 4

Copy of NHS Somerset T3 Patient Information Leaflet

A normal functioning thyroid gland releases both T4 (thyroxine) and T3 (triiodothyronine); the body converts T4 into T3 to meet its requirements.

EVIDENCE FOR T3 USE IS WEAK

Good evidence exists that treating with synthetic T4 alone is sufficient for maintaining good health in most people. Combined analysis of 11 studies in more than 1200 subjects concluded that there was no evidence to suggest that the combination of synthetic T4/T3* is better than using only synthetic T4 in terms of quality of life or metabolic parameters. We know that a once daily synthetic T4 tablet can achieve similar physiological levels of T4 in the blood that would be measured in a person with a healthy thyroid.

**synthetic T3 (liothyronine)*
**synthetic T4 (levothyroxine)*

MONITORING T3 TREATMENT

With synthetic T4 treatment we can use a simple blood test of the Thyroid Stimulating Hormone (TSH) level to adjust dose and monitor treatment. Using TSH to monitor synthetic T3 treatment may not be accurate. This is because T4 lasts several days in the body and the levels are very stable, whilst T3 lasts a day and the levels vary throughout the day. Therefore, levels of TSH or T3 at one time point may not be a good reflection of thyroid hormone sufficiency.

Although we know severe hypothyroidism is associated with low body temperatures, using temperature monitoring to assess long term thyroid treatment has no scientific basis and is not an accepted practice.

T3 TREATMENT: SAFE OR UNSAFE?

Unlike synthetic T4 treatment where there is plenty of data to demonstrate it is safe, there is only 1 observational study which suggests long term safety of combination T4 and T3 therapy. We know from people with overactive thyroids that too much thyroid hormone over long periods may cause serious complications. Oral synthetic T3 dosing can give peaks of T3 in the blood that are much higher than would be seen in a healthy patient or in a person treated with synthetic T4

The transient rise in serum T3 associated with synthetic T3 therapy may provoke abnormal heart rhythms in susceptible individuals and would be advised against in patients with heart disease. There are also concerns about too much thyroid replacement increasing the risk of osteoporosis (thin and fragile bones) in the long term.

Due to the risks of causing harm, better evidence is needed before routine synthetic T3 use can be routinely recommended.

GENETIC VARIABLITY DATA AND T3

There is some evidence that a minority of individuals handle T4 to T3 hormone conversion differently due to genetic differences. In one study some of the patients who had a particular rare genetic variation reported symptom improvement on a combination of synthetic T3 and T4. The numbers involved were small and this finding is yet to be replicated in other trials. The study authors do not recommend using this genetic test (which is not available in routine clinical practice) to determine who should be treated with T3. This is because further studies are required to confirm this finding and the actual genetic cause.

NATURAL T3 - ARMOUR THYROID

Armour thyroid (also known as natural desiccated thyroid, NDT) is a dried animal thyroid extract product that is not licensed in the UK. It contains higher amounts of T3 in relation to T4 than are normally present in humans. Furthermore, the proportions of T3 and T4 in each brand can vary. It is not licensed medication and has not undergone the same

safety testing that other medications have. It cannot be prescribed on the NHS.

The British Thyroid Association does not recommend its use as it may be unsafe in the long term.

WHAT DO THE THYROID ASSOCIATIONS SAY ABOUT TREATMENT WITH T3 – LIOTHYRONINE?

The British Thyroid Association does not recommend T4/T3 routinely. If it is clear that all other options have been explored then a trial, supervised by endocrinologists, of T4/T3 may be considered after discussing the risks and benefits. However, an endocrinologist's clinical judgement may mean that this is not recommended.

The European Thyroid Association says that there is insufficient evidence to suggest T4/T3 combination is superior to T4 alone. It suggests that if other associated conditions have been ruled out, optimal biochemical control is achieved and there are persistent symptoms, then a trial of combination may be considered.

The American Thyroid Association says that T4 treatment alone should be used (as lack of evidence of benefit of combination and no long term data) and combination treatment should be considered only in a clinical trial setting.

COMPARATIVE COST

Synthetic T3 as Liothyronine 10mcg twice daily costs approximately £1,700 per patient per year*. Synthetic T4 as Levothyroxine 100mcg once daily costs approximately £22 per patient per year*. **Somerset NHS FT pharmacy data 2022*

SOMERSET SERVICES

Some patients who experience persistent symptoms while taking T4 ask to trial taking combined T3/T4 therapy. Patients who have proven primary hypothyroidism (TSH >10 mu/l), have taken an appropriate dose of T4 for more than 1 year and in whom the symptoms are not explained by other medical conditions may be referred to be seen in a dedicated Endocrinology Thyroid clinic. Availability of these clinics is limited. When a patient is referred and their case accepted, they will be added to a waiting list. When seen, they will be assessed to see if a trial of T3/T4 is appropriate.

Further reading

http://www.btf-thyroid.org/resources/news-archive/241-bta-statement-on-the-management-of-primary-hypothyroidism-2015

NHS Somerset

Information for Patients

Hypothyroidism

The current evidence for T3 hormone replacement