GUIDANCE ON THE PRESCRIBING OF LIOTHYRONINE (T3) AND LIOTHYRONINE-CONTAINING PRODUCTS FOR THE MANAGEMENT OF PRIMARY HYPOTHYROIDISM

Recommendation

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

- **DO NOT** recommend 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

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.\textsuperscript{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}\textsuperscript{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.
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. The equivalent doses are tabulated below for ease of use:

<table>
<thead>
<tr>
<th>Liothyronine (micrograms)</th>
<th>Equivalent dose of levothyroxine (micrograms)</th>
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<tbody>
<tr>
<td>5</td>
<td>25</td>
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<tr>
<td>10</td>
<td>50</td>
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<tr>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>
Liothyronine (micrograms) | Equivalent dose of levothyroxine (micrograms)
--- | ---
20 | 100
30 | 150
40 | 200
60 | 300
80 | 400
100 | 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.

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