Improving T3 Prescription in the UK – a Joint Campaign on behalf of Thyroid Patients

by

ITT (Improve Thyroid Treatment Campaign Group), Thyroid UK, Midlands Thyroid Support Group and Thyroid Patient Advocacy

27th March 2018
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To:

Simon Stevens, Chief Executive NHS England
Professor Sir Malcolm Grant CBE, Chair of Board of NHS England

Key messages:

1. Thyroid disease affects approximately 2% - 4% of the UK population – 1,200,000 – 2,400,000 people\(^1\). The symptoms are serious and require daily medication. The standard medications are levothyroxine (T4) and liothyronine (T3) to replace thyroid hormones normally produced naturally within the body. Patients require either of these medicines in isolation or in combination depending on the specific nature of the disease.

   In the United Kingdom, the annual incidence of primary hypothyroidism in women is approximately 3.5 per 1000 and in men, 0.6 per 1000.\(^2\)

   However, in recent years Clinical Commissioning Groups (CCGs) have been withdrawing T3 (liothyronine) treatment due to a 6,000% increase in the cost of the drug by the manufacturer Concordia, who were subsequently referred to the Competition and Markets Authority (CMA) by the Department of Health.\(^3\)

2. Following the NHS England 2017 consultation, “Items which should not routinely be prescribed in primary care: a consultation on guidance for CCGs”, the NHS England Board decided to continue NHS prescription of liothyronine for those patients who cannot be adequately treated by levothyroxine but stated that it should only be prescribed in secondary care,\(^4\) even though, prior to the NHS consultation, liothyronine was prescribed by many doctors in primary care without any problems.

   There is, however, abundant evidence that some CCGs are effecting a blanket policy banning liothyronine in both primary and secondary care, possibly due to the fact that the NHS England Board decision is an ambiguously worded statement, open to misinterpretation. This is having a serious impact on the health of patients. Divisions are emerging between those areas where prescription is continuing - a postcode lottery (see Appendix A - CCG Policy on Liothyronine).

   Divisions also exist between wealthy patients who can afford private prescriptions or can travel abroad where it is readily available and those poorer patients who lack the means and therefore remain ill.

3. Procurement of liothyronine is not being well-managed by the by the various NHS bodies responsible as the cost of this medication in Europe is 25p per tablet compared with £9 in the UK (see Appendix B – Cost of Liothyronine in other EU countries).
4. This situation threatens good medical practice as clinical recommendations and opinion are being superseded by what appear to be poorly researched and managed purchasing decisions.

**Recommendations:**

1. The cost of liothyronine is reduced by proper management of procurement. Either, it is sourced from existing EU sources at reasonable competitive prices or lower pricing is negotiated using The Health Service Medical Supplies (Costs) Act.

   There should be comparable costs of liothyronine tablets in the UK to that of EU prices. Poor budgetary management should not be an excuse for a forced change in clinical decision-making.

2. CCGs are given clearer guidelines by NHS England that are unambiguous and that takes into account the position statement of the BTA which includes the statement “The BTA position statement on hypothyroidism should not be interpreted as a recommendation to not use Liothyronine or as an endorsement for its discontinuation.”

3. CCGs are asked to comply with NHS England guidance to prevent the risk of postcode lottery:
   
   a. Liothyronine prescribing, once instigated in secondary care, is then passed back to primary care thus sharing the costs across both sectors.
   b. Patients who are clinically well on liothyronine continue to benefit from it without threat of removal; these patients will have already tried levothyroxine without successful resolution of their symptoms.
   c. New patients, where there is clear indication that levothyroxine is not restoring them to a euthyroid state, are referred to an endocrinologist as soon as possible so that a trial of liothyronine can be started.
   d. Patients who have been well for many years on liothyronine and previously unwell on levothyroxine should be allowed to continue without referral as this is putting undue pressure on secondary care.

4. CCGs, Hospital Trusts and Health Boards should comply with NHS decisions and restore the prescribing of liothyronine to ensure good health for thyroid patients. Cost should not be put before patient health and good health should not depend on where a patient lives.

5. CCGs, Hospital Trusts and Health Boards should, in the meantime, authorise clinicians to prescribe licenced liothyronine products from Europe on a named-patient basis, as has happened in the past due to supply issues, until the cost of UK liothyronine products are reduced to a level that is comparable with the EU market place as would be expected for a country (currently) within the EU.

We look forward to your reply.

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Background

1. Many patients do well on levothyroxine but there is a subgroup of patients who have remaining symptoms. Inaccuracies about being published about the use of liothyronine as a treatment and testing of T3 is very rarely done (see Appendix C – Thyroid Patient Care and Treatment Options).

2. In 2017 liothyronine was included in an NHS consultation “Items which should not routinely be prescribed in primary care: a consultation on guidance for CCGs” because of its cost.(4) Graham Jackson (NHSCC chair) and Julie Wood (Chief Executive NHSCC) at the NHS Consultation Face to Face meeting, held in London 5th September 2017. “There is no question about the clinical effectiveness of T3 (liothyronine), there is also no real question either whether people may need T3. The reason it is on the list is the whole commercial situation… If the loophole is closed and the price is dropped then we’re on 17 drugs then, aren’t we?”

3. In 2016/17 NHS England spent more than £34 million(5) on liothyronine. In 2006 this was £600,000. In November 2017 the CMA provisionally found that Concordia, the monopoly supplier, abused its dominant position to overcharge the NHS by many millions of pounds for their product, liothyronine.(3) According to the CMA, the amount the NHS paid increased from about £4.46 per pack before de-branding in 2007 to £258.19 by July 2017 while production costs remained broadly stable. The NHS pays approximately £9 for a liothyronine tablet(6) In 2007 the cost of a liothyronine tablet was 16 pence or £15.92 for 100 tablets,(3) an increase of almost 6,000%.

4. 72% of respondents to the consultation supported the continued prescribing of liothyronine in primary care. However, the NHS England Board’s decision stated “the decision made by the NHS England Board [is] that liothyronine should only be prescribed in secondary care” rather than initiated there and then passed to primary care.(4)

5. Concordia have stated that the Department of Health and Social Care has at no time questioned the escalating costs of liothyronine.

6. Concordia have stated that the increase in the cost of liothyronine was due to a requirement by the MHRA for all batches of liothyronine produced to only be released after individual batch approval by the MHRA (see Appendix D – Extract of Correspondence with Concordia International Rx UK Ltd). Concordia state the MHRA requirements resulted in significant additional financial investment and this is the reason for the high cost of liothyronine. However, there appear to be no special measures on the new suppliers, Morningside and Teva.

7. In response to a Freedom of Information request, the MHRA has confirmed that, “Concordia, as with all manufacturers of medicinal products including liothyronine, must comply with Directive 2001/83/EC, the current European Quality guidelines, the
British Pharmacopeia (BP) monograph and current standards of Good Manufacturing Practice (GMP).” (7) The MHRA describes liothyronine as “… a well established, bio-identical and already approved drug manufactured across Europe” (8), in which case it would seem to follow that procurement geography could be extended to include EU territories because, for example, the EU Directive route entitles UK citizens to purchase healthcare in other European Economic Area countries and to apply for reimbursement from the NHS.

The underlying principles of this policy do not seem to support the narrow procurement management of the NHS in returning good value for money to the UK taxpayer.

It also raises the question about why the cost of liothyronine in the UK is significantly higher than in Europe. EU prices are about 2 pence to 26 pence per tablet whereas the NHS is paying over £9 per tablet. Why has the NHS been satisfied to pay this price for a “well established, bio-identical, already approved drug”?

It seems like a drastic oversight when the reaction is to restrict prescribing policy to the detriment of the health of thyroid patients in the UK.

8. The NHS has not taken measures to manage cost by importing liothyronine from the EU where similar standards are required at a fraction of the cost. Germany and France have similar high standards of manufacture. The NHS has not managed the cost of liothyronine through purchasing power to buy from Europe despite this option previously being used. The MHRA previously allowed doctors to prescribe liothyronine from Europe when there was a liothyronine supply problem in the UK. (9)

9. The NHS England Consultation Report of Findings states that the CCGs expressed the view that: “If prescribing is to be allowed to continue, there should be clear guidance in terms of the thyroid function test results and significant pressure on manufacturers to reduce the price to a reasonable level. At a lower cost there would be less need to pursue de-prescribing of a medication that some patients feel very strongly have (sic) had a positive effect on their quality of life.” (4)

10. To date the Department of Health and Social Care and the NHS have not utilised the powers available under The Health Service Medical Supplies (Costs) Act (enacted April 2017). (10) The Act allows the Secretary of State to require companies to reduce the price of an unbranded generic medicine or to impose other controls on that company’s unbranded generic medicines even if the company is in the voluntary scheme for their branded medicines.

11. The NHS England Board guidance is unfortunately ambiguous and this may be contributing to an inconsistency in CCG approach to thyroid patient treatment. “The Joint Clinical Working Group therefore recommended; the prescribing of liothyronine for any new patient should be initiated by a consultant endocrinologist in the NHS and that de-prescribing in ‘all’ patients is not appropriate as there are recognised exceptions. The recommendation would therefore be changed to advise prescribers to de-prescribe in all appropriate patients.” (4)

a. Firstly, many GPs have been prescribing liothyronine and the wording above implies that they, as prescribers, could de-prescribe rather than recommend a referral to secondary care.
b. Secondly, regarding the use of the word "appropriate", the response of Thyroid UK was: "Thyroid UK is not happy with the word "appropriate." They have not explained who would be "appropriate" to remain on liothyronine. The definition of "appropriate" is very subjective and NHS England should have gone further and explained that patients who do not do well on levothyroxine should be given a trial of liothyronine." (11)

12. CCGs are actively de-prescribing. Numerous CCG Governing Boards have set out the financial saving to budgets of the de-prescribing of liothyronine. 90% of CCGs responding to the NHS England Consultation felt that liothyronine should be removed from primary care.(4) A review of CCG formulary policy evidences that CCGs are not following the NHS England Board guidance, which requires a secondary care review by a specialist endocrinologist, and have removed access to liothyronine almost completely (see Appendix E - Outcome of the consultation, subsequent guidance and selective interpretation following consultation). This is creating postcode lottery treatment for patients.

Patients have reported that:

a. Their liothyronine has been withdrawn without a secondary care review by a specialist endocrinologist.

b. As new patients they have been refused access to secondary care to have specialist treatment considered by their CCG and/or local hospital trust on cost grounds.

c. Endocrinologists have rejected referrals unless GPs confirm that, if liothyronine is deemed necessary, primary care would support the prescription.

d. They have been referred to and assessed by secondary care and their need for liothyronine confirmed but they have been denied an NHS prescription on the grounds of cost.

13. Some CCGs have offered incentives for doctors to change patients from liothyronine to levothyroxine. (12)

14. There is evidence that in some CCGs, hospital trusts and health boards both primary and secondary care policies ban the prescribing of liothyronine.

For example, Brighton and Sussex University Hospitals NHS Trust. (13) “We are sorry to inform you that T3 (lithyronine) treatment for hypothyroidism (either alone or in combination with T4 [levothyroxine]) is no longer available through the NHS. This is a local policy which applies to prescriptions from GPs and from NHS endocrinology clinics. It is supported by national NHS recommendations. It does not apply to patients treated in the private sector. The only option for patients wishing to continue T3 therapy is through the private sector: your GP will need to refer you to a private endocrinologist.”

Although CCGs only need to “have regard” for recommendations made by the NHS, the NHS should be ensuring the guidance provided is being followed. Currently there are many patients throughout the country whose health is being seriously affected by
the non-compliance with NHS guidance. This is not the first time CCGs have disregarded NHS England guidance.\(^{(14)}\) \(^{(15)}\)

15. An outdated guideline from the British Thyroid Association (BTA) on thyroid treatment has been used by the NHS England consultation and the CCG prescribing policy. It was a statement referring only to primary hypothyroidism and it did not cover all types of thyroid disorder. The BTA issued updated statements. In 2016, the BTA stated that patients who are doing well on liothyronine should not have their liothyronine stopped and warned of potential unintended consequences, including additional costs to the NHS. This statement has not been incorporated into NHS England or CCG guidance.\(^{(16)}\)

16. In October 2017 the BTA stressed that; “The BTA position statement on hypothyroidism should not be interpreted as a recommendation to not use Liothyronine or as an endorsement for its discontinuation”.\(^{(17)}\)

The updated 2016 and 2017 statements are not referred to by NHS England or CCGs who continue to refer to the older BTA 2015 statement.\(^{(18)}\)

17. In a letter from the Lord O’Shaughnessy to Thyroid UK he states that decisions about what medicines to prescribe are made by the doctor or healthcare professional responsible for that part of the patient’s care and should not be made based entirely on the cost of the medicine and he also confirmed that prescribers are allowed to prescribe a non-UK branded medicine on their own personal responsibility.

He also stated that, “…there is no action that can be taken under the contract if GPs do not comply with local prescribing initiatives.”

These comments from the Lord O’Shaughnessy show that since the needs of the patient requiring liothyronine is not being met (due to cost) their GP should not only be able to prescribe a European brand but should be informed that he can do this with impunity (see Appendix F – Letter from the Lord O’Shaughnessy dated 23\(^{rd}\) November 2017).

18. In a letter received from a GP he explains to his patient that, “This practice holds a General Medical Services Contract, which is a nationally determined contract. We are required to prescribe to patients that which they clinically, reasonably require, either in my opinion or upon the advice of a consultant, at NHS cost, any medication which appears in the Drug Tariff which can be found at [www.drugtariff.nhsbsa.nhs.uk](http://www.drugtariff.nhsbsa.nhs.uk). The Drug Tariff is published every month.

Liothyronine appears in the Drug Tariff and therefore is perceivable at NHS expense when this has been suggested or advised by a Consultant Endocrinologist. You fall into that category and therefore it does not matter what the CCG says, to them this is a “they would like us to do”. My contract and the National Terms of Service trumps the CCG’s desires. Whilst ever the Liothyronine is recommended by Dr….. or another endocrinologist and whilst ever it appears in the Drug Tariff, you should stop worrying about whether we will prescribe this for you or not. Unless, and until the Secretary of State stands up in Parliament and removes it from the Drug Tariff, you will continue to get this medication.”
19. Experts in thyroid treatment have also argued against the removal of liothyronine because of costs. Recently Sir Anthony Toft, the BTA president 1996 to 2009 and former physician to Her Majesty The Queen, published a paper supporting the prescription of liothyronine and stated, “Experience of managing more patients with thyroid disease than most over a period of some 40 years is being trumped by inflexible guidelines; truly a remarkable state of affairs. Others hide behind guidelines to avoid the cost of prescribing liothyronine, which in the UK is exorbitantly priced by the sole supplier at some £250 for two month’s supply of 10 μg daily, when well-travelled patients can obtain supplies for a few euros in Italy and Greece and beyond.”

20. Thyroid health is important because of the number of medical issues that can result, including cardiac conditions, diabetes, and adverse mental health.

21. A Thyroid UK “Hypothyroid Experiences Survey” concluded that the proportion of people that don’t respond to levothyroxine is 12.5% rather than the 5%-10% reported in other studies. It is likely that 12.5% of thyroid patients will remain untreated on levothyroxine. Other clinical studies quote up to 20% of patients remaining symptomatic.

22. The Department of Health confirmed on February 8th 2018, that the potential cost of secondary specialist care versus monitored use of liothyronine has not yet been calculated and compared. If 12.5% of thyroid patients require a secondary care review there will be a consequential cost of increasing volume of GP and secondary consultant appointments.

Simon Pearce, Professor of Endocrinology at Newcastle University, has quantified the additional workload on secondary care endocrinologists as “preposterous”.

He stated, “During 2016 there were 75,000 prescriptions for liothyronine in England. Assuming a prescription lasts for one month that amounts to 6,000 patients. Assuming 50% are referred to secondary care that is an extra 3,000 new outpatient appointments. Assuming each endocrinologist sees 300 new appointments a year then you need 10 new endocrinologists. Where are they coming from and who is paying for this?” (BBC interview).

There similarly appears to be no consideration of the cost of removing liothyronine on the ability of thyroid patients to work. Ineffective thyroid treatment is harmful to patients who require more NHS support and due to continuing symptoms are often at risk of unnecessary medication, referrals and investigations for their continued symptoms. An ITT survey of patients concluded that a majority had taken years to obtain effective treatment and had needed time off work during that time.

23. NHS England has published data that confirms 85% of patients who require liothyronine are women.

24. Under the NHS Five Year Forward View, the NHS state how they want to become better at helping people to manage their own health. NHS England state, “This involves scaling up support for people living with LTCs to manage and make decisions about their own health and wellbeing. Patient activation is a core enabler for this programme.”
a. The Patient Activation Measure (PAM) is an NHS tool that enables healthcare professionals to understand a patient’s activation level in respect of their knowledge, skills and confidence in managing their own health and care particularly those with long term conditions.

b. Many thyroid patients already have the knowledge, skills and confidence in managing their own health but are not being encouraged to take part in shared-decision making and are being ignored when they tell their clinician that they do not feel well on levothyroxine alone.

c. Thyroid patients should be listened to in respect of how they want to manage their own thyroid health. This includes being involved in shared-decision making and giving them a trial of liothyronine if their symptoms are not resolved on levothyroxine alone. CCG’s should not be making the decision for them and their GP.

25. The NHS England Board’s guidance, “Responsibility for prescribing between Primary and Secondary/Tertiary Care” states: “However, when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs. If the GP considers him- or herself unable to take on this responsibility, then this should be discussed between the relevant parties so that additional information or support can be made available, or alternative arrangements made.”

a. If a GP feels they are clinically competent to prescribe liothyronine it would support PAM and be a more cost-efficient delivery of care to a patient than referral to secondary care.

b. The impact of the high cost of liothyronine on financial budgets may hinder shared care agreements and the transfer of clinical prescribing responsibility between primary and secondary care. Patient experience evidences that, in some areas, disagreement about where the prescribing cost of liothyronine is incurred has them being caught in the middle and left without the medication they need.
Recommendations

1. The cost of liothyronine is reduced by proper management of procurement. Either, it is sourced from existing EU sources at reasonable competitive prices or lower pricing is negotiated using The Health Service Medical Supplies (Costs) Act.

There should be comparable costs of liothyronine tablets in the UK to that of EU prices. Poor budgetary management should not be an excuse for a forced change in clinical decision-making.

2. CCGs are given clearer guidelines by NHS England that are unambiguous and that takes into account the position statement of the BTA which includes the statement “The BTA position statement on hypothyroidism should not be interpreted as a recommendation to not use Liothyronine or as an endorsement for its discontinuation.”

3. CCGs are asked to comply with NHS England guidance to prevent the risk of postcode lottery:

   a. Liothyronine prescribing, once instigated in secondary care, is then passed back to primary care thus sharing the costs across both sectors.
   b. Patients who are clinically well on liothyronine continue to benefit from it without threat of removal; these patients will have already tried levothyroxine without successful resolution of their symptoms.
   c. New patients, where there is clear indication that levothyroxine is not restoring them to a euthyroid state, are referred to an endocrinologist as soon as possible so that a trial of liothyronine can be started.
   d. Patients who have been well for many years on liothyronine and previously unwell on levothyroxine should be allowed to continue without referral as this is putting undue pressure on secondary care.

4. CCGs, Hospital Trusts and Health Boards should comply with NHS decisions and restore the prescribing of liothyronine to ensure good health for thyroid patients. Cost should not be put before patient health and good health should not depend on where a patient lives.

5. CCGs, Hospital Trusts and Health Boards should, in the meantime, authorise clinicians to prescribe licenced liothyronine products from Europe on a named-patient basis, as has happened in the past due to supply issues, until the cost of UK liothyronine products are reduced to a level that is comparable with the EU market place as would be expected for a country (currently) within the EU.
References

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9. Liothyronine 20 microgram tablets: continuity of supply and potential need for patient monitoring. Recent interruption to the supply of liothyronine 20 microgram tablets from Amdipharm Mercury. Published 29 May 2013. From: Medicines and Healthcare products Regulatory Agency
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    http://www.thyroiduk.org/tuk/newspage.html#decision


21. Thyroid disease https://www.diabetes.co.uk/conditions/thyroid-disease.html


27. Thyroid drug to remain available on the NHS  
Interview with Simon Pearce, professor of endocrinology at Newcastle University - 30 November 2017.  
http://www.bbc.co.uk/news/health-42179765


29. Patient activation - People's ability to manage their own health and wellbeing  

30. Responsibility for prescribing between Primary and Secondary/Tertiary Care  
Appendices

A. CCG policy on liothyronine (Illustrative only, not all CCGs have been documented)

B. Cost of liothyronine

C. Thyroid Patient Care and Treatment Options and Why Patient Thyroid Health is Important.

D. Extract of Correspondence with Concordia International Rx UK Ltd

E. Outcome of the consultation, subsequent guidance and selective interpretation following consultation.

F. Letter from the Lord O'Shaughnessy dated 23rd November 2017
Appendix A

CCG Policies on Liothyronine – a Postcode Lottery

The action of CCGs and Health Boards to withdraw liothyronine without any consultation with the patient, nor reassessing clinical need with an endocrinologist, goes against the specialist medical guidance and also breaches overarching NHS guidelines, which state:

“The safety and well-being of patients is paramount…”.

“The NHS is expected to act in the best interest of the patients at all times and work together in the spirit of partnership.”

The withdrawal of liothyronine due to cost violates the following key principles of the NHS constitution, which are meant to guide the NHS in all it does:

“Access to NHS services is based on clinical need, not an individual’s ability to pay”

“The patient will be at the heart of everything the NHS does” (DH, 2015, p.3).

“You have the right to receive care and treatment that is appropriate to you, meets your needs and reflects your preferences” (DH, 2015, p.6)

The prescribing approach of a number of CCGs is set out below. This is not an exhaustive list but shows a range of formulary policy. In many cases this is contrary to the NHS Board guidance on liothyronine. Many patients have reported to thyroid groups that their experience is different to formulary policy.

1. In the Brighton & Hove CCG area, a patient reported receiving, together with a de-prescription letter from the GP, a printed patient information leaflet from the local hospital trust, and as set out on their website. The leaflet begins with the following statement:

“We are sorry to inform you that T3 (Liothyronine) treatment for hypothyroidism (either alone or in combination with T4 [Levothyroxine]) is no longer available through the NHS. This is a local policy, which applies to prescriptions from GPs and from NHS endocrinology clinics.

*It is supported by national NHS recommendations. It does not apply to patients treated in the private sector.*

*The only option for patients wishing to continue T3 therapy is through the private sector: your GP will need to refer you to a private endocrinologist.”*


2. The Greater Manchester Joint Formulary Group’s (encompassing 11 CCGs and Secondary Care) policy is to prescribe liothyronine:

“All for use in hypothyroid crisis and short-term post thyroid surgery”.

The effective policy instruction is not to prescribe at either primary or secondary levels across a very large area.

3. In Herefordshire, the CCG formulary policy in respect of liothyronine is:

“Requests from private consultants and other NHS consultants (other than NHS psychiatry or NHS endocrinology) should NOT be accepted for NHS prescribing… New patients who have been seen should be referred back to the private service for private prescription of Liothyronine or recommendation of an alternative treatment.”

4. The Berkshire West CCG formulary policy restricts the use of liothyronine, which is not in line with NHS Board guidance.

“Restricted for the treatment of myxoedema (hypothyroid) coma, this may precipitate cardiac arrhythmia.”

5. Nottinghamshire Area Prescribing Committee policy is:

“Liothyronine (oral) is not supported by local NHS endocrinologists and it is not included in the recommendations for the treatment of hypothyroidism from the Royal College of Physicians.”

6. The position in Scotland is no different to England. In Scotland, thyroid treatment was debated in the Scottish Parliament on 22 November 2017. In that debate, The Minister for Public Health and Sport (Aileen Campbell) confirmed:

“She [Jackie Baillie] described concern that T3 will be removed from the prescribed medicines list. NHS England might be considering that, but there is no question of such an approach being taken in Scotland.”


However, in their Report to Aberdeenshire Integration Joint Board on 14th February 2018, Aberdeenshire Health & Social Care Partnership state, “Liothyronine – hypothyroidism not supported by NHSG. Convert to levothyroxine which is cheaper.”


7. However, some CCG’s are prescribing in line with NHS England recommendations:

Pan Mersey Area Prescribing Committee:

“Existing stable patients in primary care may continue to be prescribed liothyronine by the GP where they are satisfied the patient is benefiting specifically from the use of liothyronine.”

Wirral CCG also has a policy in line with NHS recommendations and states:

“Advice on Switching from Liothyronine (T3) to Levothyroxine (T4): Patients who are stable on T3 or T4/T3 combination who have clearly not tolerated or benefited from T4 (despite adequate length trial of T4) These patients should not be switched to T4, unless the clinician believes a re-trial of T4 is justified (if clinical circumstances have changed).”
Cost of Liothyronine (T3) in other EU countries

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<th>Country</th>
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Source: Paul Robinson 8/5/17 patient based information.
Appendix C

Thyroid Patient Care and Treatment Options

1. Patients initially diagnosed with hypothyroidism are routinely prescribed levothyroxine. Many patients are well on levothyroxine. Liothyronine in combination with levothyroxine, or on its own, is only prescribed following clear signs that levothyroxine alone is not working. In many cases patients report this only after years of levothyroxine only treatment. Liothyronine is only prescribed when patients have attempted treatment with levothyroxine and remain symptomatic.

In 2015 Thyroid UK ran their Hypothyroid Experiences Survey in which 5,159 people took part. The survey concluded “Based on the respondents’ answers regarding responses to levothyroxine, we would suggest that the proportion of people that don’t respond to levothyroxine is 12.5% rather than the 5% - 10% reported in other studies.” - http://www.thyroiduk.org.uk/tuk/TUK_PDFs/patient-experience-survey/Hypothyroid%20Patient%20Experiences%20Survey%20-%20V1.pdf

2. NHS England and CCGs promote levothyroxine as an effective alternative to liothyronine. This is not the case, they are fundamentally different thyroid hormones, biologically and chemically. In promoting levothyroxine (synthetic T4) as a valid alternative the CCGs and NHS are ignoring known causes that leave thyroid patients unable to convert the inactive thyroid hormone (thyroxine) T4, to the active thyroid hormone (triiodothyronine) T3 (including DIO2 and DIO1 genetic defects).

3. Thyroid Patient Advocacy undertook a survey and found that there are many patients who do not respond well to levothyroxine only therapy. http://tpauk.com/main/wp-content/uploads/2016/01/Survey-Finds-Thousands-of-Patient-Counterexamples-to-L-T4-Monotherapy.pdf

4. The BTA guidelines recommend the testing of T3 levels as part of the thyroid blood panel tests on the thyroid. Currently TSH and only sometimes T4 is tested. However, the NHS (based on the existing NICE Clinical Knowledge Summaries, which are currently under review) does not routinely test T3 levels. Because T3 levels are not routinely tested it is possible that the number of patients who have below range T3 may well be understated.

5. The thyroid affects nearly every bodily function. In healthy patients the thyroid produces both thyroxine (T4) and triiodothyronine (T3). In order to provide more T3 than the 20% produced by the thyroid, the body converts T4 into the active, useable, hormone T3. This active T3 hormone is required by all cells in the body to function correctly. For those with conversion issues the inactive T4 hormone is not converted into the active hormone T3. Shortage of T3 can result in a wide range of symptoms. This is not an exhaustive list but it demonstrates the range of health issues for hypothyroid patients if not properly treated.

   a. Psychological and cognitive e.g. brain fog, peripheral brain neuropathy, anxiety, depression and increased risk of developing dementia or Alzheimer’s disease.

   b. Gastro complications e.g. constipation, bloating, bowel obstruction, gallstones
c. **General symptoms**: Slow metabolism and associated weight gain, hair loss, negative impact on adrenal cortex, eyebrow thinning, reactive hypoglycaemia, type 2 diabetes, breathing difficulties, dry skin, chronic autoimmune urticaria, angioedema, gum and dental issues, lower energy levels and general weakness, migraine, tinnitus and vertigo.

d. **Musculoskeletal** e.g. fibromyalgia, carpal tunnel and arthritis

e. **Cardiovascular** e.g. blood pressure abnormalities, cholesterol abnormalities, and heart abnormalities such as dilated cardiomyopathy.

f. **Gynaecological** e.g. Infertility including miscarriage, PCOS, endometriosis and menstrual changes

g. **Liver and kidney function** including chronic kidney disease.
Appendix D

Extract of Correspondence with Concordia International Rx UK Ltd

Questions posed to Concordia:

1) When will the “significant reduction” in cost of liothyronine, be put into action? Are we talking weeks, months or years, or a specific date?

2) What specifically in the manufacturing method makes your UK price of T3 5,000% more expensive than most non-UK suppliers?

“Dear (name withheld)

Thank you for your email.

First of all let me apologise for the delay in responding to the remaining parts of your enquiry. We have checked and have received confirmation that NHS has never banned or black listed Liothyronine. Whilst the recently issued guidelines from NHS stated that “prescribers in primary care should not initiate Liothyronine for any new patient” it went onto clarify that “prescribing of Liothyronine for any new patient can be initiated by a consultant endocrinologist in the NHS”. We were also pleased that, following its recent consultation in the autumn, NHS issued its view on the de-prescribing of Liothyronine in existing patients stating in the guidelines that “de-prescribing in all patients was not appropriate”. This latest NHS recommendation is consistent with the existing clinical guidelines issued by NICE which states “Combination therapy with LT4 and LT3 may be considered by endocrinology specialists as an experimental approach in people who have persistent symptoms despite compliance with LT4 treatment and a TSH value in the normal range”.

Therefore, in terms of your key concerns about ongoing supply, please be assured that Liothyronine tablets are still available as a reimbursed prescription medicine in the UK market. Your doctor and/or specialist would be best suited to advise your treatment options, and to explain the prescription and reimbursement system, and we strongly recommend for you to speak to them directly.

In terms of the questions that you have raised about the complexity and cost of Liothyronine:

Liothyronine 20mcg is a very old and complex product and due to its potency, requires only a very small quantity of active ingredient in each tablet. This makes manufacturing the medicine, and in particular achieving consistency between tablets, complex and difficult. The MHRA have been particularly interested in these issues in recent years and in 2012 the MHRA declared special interest in both Levothyroxine and Liothyronine, following the suspension by the MHRA of a Levothyroxine marketing authorisation of a major supplier in the UK. Since that date, we have been working closely with the MHRA on the manufacturing process. In addition, all our batches of Liothyronine produced have only been released after individual batch approval by the MHRA with a Batch Specific Variation (BSV). This requires compilation of analytical results and preparation of quality and medical expert statements, which are submitted, to the MHRA to justify the release of every batch. These have meant significant additional time and financial investment.
As part of this work, the MHRA requested that we modernise the manufacturing process and update the analytical tests in accordance with their new standards. This remains an expensive, complex and time-consuming process. It has involved us revisiting the manufacturing process in detail and working with our contract manufacturer, which has arranged a 5-year project to build a completely new facility in order to meet these modern quality and manufacturing standards. Liothyronine will be among the first wave of products transferred to this new facility once it is complete. All this has had a significant effect on our prices, which are now at a level broadly similar to the price of branded Liothyronine (Cytomel®) in North America.

We have therefore been investing significantly in recent years in keeping Liothyronine (and Levothyroxine) available for UK patients. As a responsible manufacturer we have worked closely with the UK’s MHRA and have invested heavily in seeking to manufacture in the way that they want us to do. As far as we are aware, the special focus on Liothyronine specifications and manufacturing that has been required by the MHRA in the UK is above and beyond the regulatory requirements elsewhere in Europe and the rest of the world.

In terms of prices in the UK, the UK’s Department of Health have created one of the most effective generics markets where competition drives down selling prices and where generic medicines are estimated to save the NHS over £13billion each year. Indeed, NHS spending on medicines from generic manufacturers, such as Concordia, represents only 1% of the NHS’ total annual expenditure (£122.6billion in 2016/17). In terms of our Concordia medicines, the average price in the UK is only £6. There are now three suppliers of Liothyronine tablets in the UK and in the few months since their introduction we have seen our selling prices fall. We assume that this will flow through to a reduction in the reimbursement price for Liothyronine (which is the price paid by the NHS). However, as the Department of Health controls reimbursement prices through the Drug Tariff system, we are not able to speculate on exactly how or when the price paid by the NHS will change.

With regards to your comment on the cost of Liothyronine in the rest of Europe, and as mentioned above, as far as we are aware, the special focus on Liothyronine specifications and manufacturing that has been required by the MHRA in the UK is above and beyond the position elsewhere in Europe and the rest of the world. We understand that it is for that reason that the MHRA has not permitted those medicines to be licensed and sold here.

Lastly, we confirm that the DoH have never approached Concordia with any concerns about Liothyronine prices. The increase in Liothyronine prices have occurred openly and transparently over the past ten years as the costs of keeping this medicine available for UK patients have increased. Each price application has been submitted in advance to the DoH and prices were not increased until we had received acceptance back. As you can imagine, this remains one of the points of strong discussion with the Competition and Markets Authority (CMA).

I hope this answers your questions. Please feel free to contact me for further information.

Thank you.

Regards,

Medical Affairs Team"
Appendix E

Outcome of the Consultation, Subsequent Guidance and Selective Interpretation following Consultation.

1. Views of respondents to the NHS Consultation showed a preference to keep liothyronine and enable prescribing in primary care when clinical need has been established. The results of the consultation were:

- 84% of respondents believed that liothyronine should be available to new patients in primary care
- 72% of respondents did not agree with the de-prescription of liothyronine
- 51% supported the recommendation that, in exceptional circumstances, if there is a clinical need for liothyronine to be prescribed in primary care this should be undertaken in a co-operation arrangement with a multidisciplinary team and/or other healthcare professional - https://www.england.nhs.uk/wpcontent/uploads/2017/11/items-which-should-not-be-routinely-precscribed-in-pc-consultation-report.pdf

2. Following the consultation the NHS England Board gave advice to CCGs:

“Advise CCGs that prescribers in primary care should not initiate liothyronine for any new patient.”

“Advise CCGs that individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration given to switching to levothyroxine where clinically appropriate.”

“Advise CCGs 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. This should be for individuals who, in exceptional circumstances, have an on-going need for liothyronine as confirmed by a consultant NHS endocrinologist.”
Appendix F - Letter from the Lord O'Shaughnessy

From the Lord O'Shaughnessy
Parliamentary Under Secretary of State for Health (Lords)

Richmond House
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SW1A 2NS
020 7210 4850

23 NOV 2017

Ms Lyn Mynott
Chair and Chief Executive
Thyroid UK
32 Darcy Road
St Osyth
Clacton-on-Sea CO16 8QF

Thank you for your letters of 19 October to Jeremy Hunt and Philip Dunne about liothyronine.

I appreciate your concerns and am grateful to you for raising this important issue.

I would like to apologise if the incorrect guidance from the Royal College of Physicians was quoted in this and other correspondence. We will ensure that we quote from the right guidance in the future and ensure our standard responses are changed accordingly. I would therefore like to thank you for bringing this to our attention and for the opportunity to address the points raised in your letter.

As you will be aware, the Human Medicines Regulations 2012 requires that licensed medicines meet specified standards of safety, quality and efficacy. Each batch of medicine must be tested before it is released for sale. The manufacturers and distributors must be licensed by the Medicines and Healthcare products Regulatory Agency and must comply with good practice standards.

Decisions about what medicines to prescribe are made by the doctor or healthcare professional responsible for that part of the patient’s care, and should not be made based entirely on the cost of the medicine. The cost of a medicine has to be balanced against the importance of meeting the individual treatment needs of patients and potential additional costs to the NHS if supply is interrupted. For example, adverse reactions when treatment is stopped could give rise to such costs.
As you know, prescribers are allowed to prescribe a non-UK branded medicine on their own personal responsibility. However, this is only where the needs of the patient cannot be met by an available UK licensed medicine. Such needs must be clinical in nature, and may include product shortages, the absence of a similar UK licensed product, or intolerance to available UK licensed products.

With regard to your concerns that there are targets for switching T3 patients onto levothyroxine, I am afraid the Department does not hold that information, as this is held by individual clinical commissioning groups (CCGs). You would therefore need to contact them to find out more. Contact details can be found on the NHS Choices website, www.nhs.uk, by searching for ‘A- Z List of All NHS Clinical Commissioning Groups in England’.

With regard to concerns raised about the price of liothyronine, it is exactly those concerns that made us refer the manufacturer, Concordia, to the Competition and Markets Authority (CMA). The CMA has provisionally found that Concordia abused its dominant position to overcharge the NHS by millions for liothyronine tablets. The CMA has been investigating how much the pharmaceutical company was charging for liothyronine tablets and it has found that, in 2016, the NHS spent more than £34 million on the drug, an increase from around £600,000 in 2006. The amount that the NHS paid per pack rose from around £4.46, before it was de-branded in 2007, to £258.19 by July this year, an increase of almost 6,000 per cent, while production costs remained broadly stable.

Furthermore, I am aware that Marketing Authorisations for liothyronine have now been granted to other companies, including Morningside Healthcare. As a result of this competition, I certainly expect that prices will come down, but this may not happen immediately. The Department will monitor the situation and inform the CMA if there are signs that competition is not working as it should or use my own powers to intervene, for which we are currently consulting on supporting regulations.

With regard to your question on what would happen to a GP if they went against their CCG’s prescribing policy, there is no action that can be taken under the contract if GPs do not comply with local prescribing initiatives. GPs may have agreed locally that they will work under the local prescribing policies, in which case the CCGs are entitled to expect them to do so. However, there would be no legal sanction if they did not. If the CCG is running a prescribing incentive scheme, then of course they will not get the relevant incentive payment.

Following on from this, if an Individual Funding Request (IFR) is rejected by the CCG, the IFR panel should provide written reason for the decision not to fund that treatment. Where the IFR panel has not funded the treatment, the patient or requesting clinician will be entitled to ask for a review of the process which led to
that decision. However, if the panel does not accept reason for requesting a review, then the clinician must accept this as the final decision.

I hope this reply is helpful.

JAMES O'SHAUGHNESSY