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TO: Sheila Turner, Chair, Thyroid Patient Advocacy

Many thanks again for your comments on the Liothyronine bulletin.

Firstly, we would like to clarify the role of PrescQIPP. We are an independent organisation funded by NHS commissioners to produce advice and guidance on medicines. Commissioners are free to implement whichever of our projects are priorities to them locally and we do not enforce our guidance at a local level. We are not funded by the pharmaceutical industry for any of our projects but do invite both the pharmaceutical industry and patient organisations to comment on our resources as part of our quality assurance process. Organisations need to register with us if they want to do this.

Also as a point of clarification the acronym DROP stands for **D**rugs to **R**eview for **O**ptimised **P**rescribing - it does not mean that all treatments should be stopped and it is not a suggested ban on all products within the list. Our subscribers who have worked with us a long time and are used to our resources understand that this is not a list of products to ban from the NHS and we are not saying these products can no longer be prescribed. Within every bulletin we state that individual circumstances should be considered when reviewing treatment.

In response to your rebuttal, we would like to firstly point out that although you have stated that the rebuttal is against Bulletin 121 - Liothyronine in primary hypothyroidism, your comments are all based on the original DROP-List bulletin (B117) and not the bulletin on liothyronine (B121). B121 was updated when the RCP statement was superseded by the BTA statement in 2015. The BTA statement is the document that has been referenced in B121. There are also more than four references cited in B121. For our DROP-List items we aim to produce a supporting bulletin, which is more in depth information on a particular item and in this case B121 supersedes the advice in B117 on liothyronine.

Before writing a bulletin we identify any relevant guidance that has been produced by professional bodies such as NICE, and in the case of the liothyronine bulletin the British Thyroid Association. Our resources support the implementation of national guidance such as these. When considering evidence, we do use the hierarchy of clinical evidence to decide whether to include particular studies in our review or not. The most robust evidence is from large randomized controlled double-blinded studies and systemic reviews or meta analysis. Cohort studies and individual patient experiences do have a role to play, but it is difficult to draw conclusions from these and also difficult to apply findings to the wider population. We do not consider test tube and animal studies for our resources as it is also difficult to draw conclusions about how results are applicable to the human population. If there are national

guidelines or a higher level of evidence already available then test tube and animal studies become irrelevant to the recommendations.

As mentioned above, you have commented on B117 and not B121, which states that it is a review of therapy in primary hypothyroidism (in line with the BTA's amended statement). The first recommendation in the bulletin is to ensure prescribing of thyroid hormones is in line with the BTA recommendations. http://onlinelibrary.wiley.com/doi/10.1111/cen.12824/full

The BTA statement is endorsed by several professional bodies which are: Association of Clinical Biochemistry, (ACB), British Thyroid Foundation, (BTF), Royal College of Physicians (RCP) and Society for Endocrinology (SFE). The PrescQIPP bulletin is therefore supporting the recommendations made by a professional body of experts.

The BTA has considered the evidence around L-T3 therapy, both alone and in combination with L-T4. The BTA advise that some patients, who have unambiguously not benefited from L-T4, may benefit from a trial of L-T4/L-T3 combination therapy. These patients should be supervised by accredited endocrinologists with documentation of agreement after being fully informed and have understood discussion of the uncertain benefits of treatment, likely risks of over-replacements, potential adverse consequences and lack of safety data. PrescQIPP's bulletin B121 highlights this statement as it is important that patients on a trial of combination therapy should be fully aware of the risks verses potential benefits of the treatment.

The BTA statement goes on to say that many clinicians may not agree that a trial of L-T4/L-T3 combination may be warranted in these circumstances and their clinical judgement must be recognised as being valid, given the current understanding of the science and evidence of treatments.

The BTA do not recommend the use of L-T3 (liothyronine) therapy alone as there are no longer-term controlled clinical trials available which provide evidence to support this treatment. Within the bulletin PrescQIPP have signposted to the set of questions and answers relating to the BTA statement that may help support discussion with patients: http://www.btf-thyroid.org/images/documents/FAQ_for_BTA_Hypothyroidism_Statement.pdf

The statement in the European Thyroid association's guidelines on the use of L-T3 and L-T4 combination therapy supports this position:
http://www.karger.com/Article/FullText/339444

"There is insufficient evidence that L-T4 + L-T3 combination therapy is better than L-T4 monotherapy, and it is recommended that L-T4 monotherapy remains the standard treatment of hypothyroidism. L-T4 + L-T3 combination therapy might be considered as an experimental approach in compliant L-T4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously received support to deal with the chronic nature of their disease, and associated autoimmune diseases have been excluded. Treatment should only be instituted by accredited internists/endocrinologists, and discontinued if no improvement is experienced after 3 months".

PrescQIPP have not written the BTA (or the ETA) guidelines, but we are seeking to support the implementation of them. Any concerns you have with the BTA guidelines need to be addressed to the BTA and not PrescQIPP. If the BTA update their advice, we will update our bulletin in line with this advice.

Both guidelines suggest that further research is needed and this research needs to be in the form of blinded placebo controlled trials as this where evidence is lacking in this treatment area.

In the BTA Q and A there is also a statement, which says:

"Patients with persistent symptoms despite a normal TSH sometimes ask whether a combination of T4 and T3, or an animal derived "natural thyroid extract" would be helpful. There have been over 20 clinical studies of comparing T4 to mixed T4+T3 preparations, and almost all of them have shown that if the study included a placebo that looks exactly the same as the thyroid hormone tablet, patients cannot tell which was which and the patients on the T4 alone improve as much as those on the combination. In three studies, patients seemed to prefer the combination, and this seems to have particularly been when higher dose were used. This raises the possibility that the combination is acting as a "drug" – since T3 is highly active – than as "hormone replacement", similar to the case with over-replacement with testosterone in male athletes."

As Thyroid Patient Advocacy correctly highlight, the cost of the drug has risen significantly over the last few years and there is work going on nationally to address this issue. PrescQIPP does not set the prices of drug treatments and we are unable to influence the prices that are set. We do point out and identify areas to commissioners where prices have risen and together we have been supporting raising the issue at a national level. We wholeheartedly support the fact that this area of practice is being investigated and hope that the cost of treatment does come down in future. However, regardless of the cost of treatment, the advice in the BTA statement, which also considers the safety and effectiveness of the treatment, still stands.

We are happy to update the DROP-List and reference the BTA guidelines rather than the RCP. We will add in a statement that our recommendations apply to primary hypothyroidism only and that if a clinician feels that combination therapy with L-T3 and L-T4 is appropriate, that this must be managed by a specialist in endocrinology after a discussion around the risks verses the benefits has been had with the patient.

A copy of the updated bulletin is attached for your information.

Finally, we would like to thank you for taking the time to engage with us and hope that you are reassured that we are not seeking a ban on the prescribing of liothyronine on the NHS.

Yours sincerely

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Director of Medicines Optimisation

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