PHARMAC
Pharmaceutical Management Agency

PHARMACEUTICAL SCHEDULE APPLICATION

From: Funding Application Advisor

Date: November 2018

Whole thyroid extract, normal and extended release T3 for hypothyroidism

SUMMARY OF PHARMACEUTICAL			
Brand Name		**Chemical Name**	Whole thyroid extract (combination triiodothyronine/thyroxine); T3 (Triiodothyronine); synthetic T3/T4 (triiodothyronine/thyroxine)
Indications	Treatment of hypothyroidism	**Presentation**	Compounded oral tablet. Varies.
Therapeutic Group	Thyroid and antithyroid agents (Hormone Preparations)	**Dosage**	Varies.
Supplier	Multiple	**Application Date**	January 2018 (consumer)
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Market Data	Year 1	Year 2	Year 3
Number of Patients	30,554	33,609	36,970
Subsidy (gross)	$13,500,000	$17,300,000	$19,000,000
Net Cost to Schedule	$12,800,000	$16,600,000	$18,200,000
Net Cost to DHBs	$12,800,000	$16,600,000	$18,200,000
Net Cost to DHBs (NPV)	$75,900,000		

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.

QUESTIONS TO PTAC

Health benefit

1. Does whole thyroid extract and T3 provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?
2. Which patient population would benefit most from whole thyroid extract and T3?
3. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from whole thyroid extract and T3?
4. Should whole thyroid extract and/or T3 be funded, are there any consequences to the health system that have not been noted in the application?

   4.1. Does the Committee consider that whole thyroid extract and/or T3 would result in reduced doctor consultation visits, lab testing, and avoidance of other illnesses (infertility, pregnancy complications, neuromuscular symptoms, cardiac disfunction, psychiatric illnesses)?

Need

5. Does whole thyroid extract and T3 have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule, in the requested indication? If so, which pharmaceutical (or therapeutic subgroup) and at what dose does it have the same or similar effect? Are there currently any problems with access to them, or their availability?
6. How severe is the health need of patients with hyperthyroidism?
7. What is the strength and quality of evidence in relation to health needs due to this indication?

Suitability

8. Are there any non-clinical features of the whole thyroid extract and T3 tablet formulation (e.g. size, shape) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

9. With which pharmaceuticals would whole thyroid extract and T3 be used in combination, and which pharmaceuticals would it replace, in treating the requested indication?
10. Would the use of whole thyroid extract and T3 create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?

General

11. Is there any data or information missing from the application, in particular clinical trial data and commentary?

Recommendations

12. Should whole thyroid extract and/or T3 be listed in the Pharmaceutical Schedule?]?
13. If listing is recommended, what priority rating would you give to this proposal? [low / medium / high / only if cost-neutral]?

14. If listing is recommended, should restrictions or Special Authority criteria be applied? If so, provide details.

15. Does the Committee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from PTAC regarding an application from the Thyroid Association of New Zealand Incorporated, a patient advocacy group, for the use of Whole Thyroid Extract, normal and extended release T3 for the treatment of hypothyroidism.

DISCUSSION

BACKGROUND

Previous consideration of treatments for hypothyroidism

Currently, levothyroxine (T4) 25mcg, 50mcg and 100mcg tablets are listed on the Pharmaceutical Schedule without restriction for use in hospital or the community.

Liothyronine sodium (synthetic T3) is listed in Section H of the Pharmaceutical Schedule as a 20 mcg injection and restricted to use in patients with thyroid cancer who are due to receive radioiodine therapy. The 25mcg tab presentation is also listed in Section H. There is no supplier listed for liothyronine as either the tablet or injection presentation.

Need

Description of the disease

Hypothyroidism is a condition of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. Hypothyroidism is caused by inadequate function of the gland itself (primary hypothyroidism), inadequate stimulation by thyroid-stimulating hormone from the pituitary gland (secondary hypothyroidism), or inadequate release of thyrotropin-releasing hormone from the brain's hypothalamus (tertiary hypothyroidism).

The clinical manifestations of hypothyroidism are highly variable, depending upon the age at onset and the duration and severity of thyroid hormone deficiency. Many of the manifestations of hypothyroidism reflect one of two changes induced by lack of thyroid hormone:

- A generalized slowing of metabolic processes. This can lead to abnormalities such as fatigue, slow movement and slow speech, cold intolerance, constipation, weight gain (but not morbid obesity), delayed relaxation of deep tendon reflexes, and bradycardia.

- Accumulation of matrix glycosaminoglycans in the interstitial spaces of many tissues. This can lead to coarse hair and skin, puffy faces, enlargement of the tongue, and

hoarseness. These changes are often more easily recognized in young patients, and they may be attributed to aging in older patients.

Epidemiology

The prevalence of overt hypothyroidism varies from 0.1 to 2 percent. The prevalence of subclinical hypothyroidism is higher, ranging from 4 to 10 percent of adults. Hypothyroidism is five to eight times more common in women than men, and more common in women with small body size at birth and during childhood. [Uptodate, Sept 2018]

The applicant considers that there are more than 148,000 diagnosed thyroid patients in New Zealand.

The health need of the person

In most patients, hypothyroidism is a permanent condition requiring lifelong treatment with thyroid hormone replacement. The goal of therapy is restoration of the euthyroid state, which can be readily accomplished in almost all patients by oral administration of synthetic thyroxine (levothyroxine, T4). Appropriate treatment reverses all the clinical manifestations of hypothyroidism.

The applicant notes that according to patient survey data, there is a subgroup of approximately 16% of patients with hypothyroidism that require the inclusion of triiodothyronine (T3) in their treatment regime in order to achieve complete symptom relief. The applicant notes that more than 10,000 patients in New Zealand are currently taking whole thyroid extract.

The applicant claims that this subgroup of patients do not respond to levothyroxine, due to patients having faulty deiodinase DIO1/DIO2 genes, which convert T4 to T3 (Panicker, et al., J Clin Endocrinol Metab. 2009;94(5):1623) or other issues that may affect T4 to T3 conversion. The applicant identifies this subgroup as patients with hyperthyroidism that meet one of the following:

1. Poor converters of T4 to T3
2. Have faulty DIO1 and/or DIO2 genes
3. Have Hashimotos and antibodies have not stabilised
4. Post-partum thyroiditis patients who do not respond to T4 only treatments
5. Have had thyroidectomy and do not respond to T4 only treatments
6. Patients who experience adverse reactions of no symptom relief or partial symptom relief when on T4 treatments.

Approximately, 5%-10% of patients who normalise thyroid-stimulating hormone levels with LT4 monotherapy may have persistent symptoms that patients and clinicians may attribute to hypothyroidism. Uptodate suggests that candidates for combined therapy may include

patients who have not felt well on T4 monotherapy since thyroidectomy, ablative therapy with radioiodine, or who have serum T3 at or below the lower end of the T3 reference range.

The availability and suitability of existing medicines, medical devices and treatments

Levothyroxine (T4) is listed on the Pharmaceutical Schedule for the treatment of hypothyroidism in 25 mcg, 50 mcg and 100 mcg tablets. The currently listed brands of levothyroxine are Synthroid, Eltroxin and Mercury Pharma. T4 is a prohormone with very little intrinsic activity and it is deiodinated in peripheral tissues to form T3, the active thyroid hormone.

Liothyronine sodium (synthetic T3) is listed in Section H of the Pharmaceutical Schedule and restricted to a maximum of 14 days treatment for patients with thyroid cancer who are due to receive radioiodine therapy.

There are no medications that contain triiodothyronine or liothyronine (T3) listed in Schedule B of the Pharmaceutical Schedule.

The health need of family, whānau, and wider society

PHARMAC acknowledge that there may be a health need for other people as a result for caring for patients with hypothyroidism whose symptoms are not completely managed by taking levothyroxine.

The impact on the Māori health areas of focus and Māori health outcomes

Hypothyroidism is not identified as one of the Māori health areas of focus for PHARMAC. Prevalence rates are likely to be similar to the total NZ population.

The impact on the health outcomes of population groups experiencing health disparities

The supplier notes that pregnant women and the elderly are groups that are the most vulnerable to hypothyroidism.

Health Benefit

Details of the pharmaceutical under consideration

Clinical Pharmacology and Mechanism of Action

Thyroid hormones, namely T3 and T4, are released by the thyroid gland and are primarily responsible for regulating processes related to metabolism. T4 is the major thyroid hormone in the blood and is converted to the active T3 (triiodothyronine) by deiodinase enzymes, which are further broken down to form T1a and T0a. T4 has a longer half-live than T3 and therefore can be taken once daily.

Whole Thyroid Extract is obtained from domesticated animals (usually pigs) and contains T1, T2, T3 and T4 as well as calcitonin.

Liothyronine is a synthetic form of T3.

New Zealand Registration

Whole thyroid extract and normal and extended release T3 are supplements and are not registered by Medsafe for use in New Zealand.

Whole thyroid is available as a compounded medicine and can be provided by a number of pharmacies in New Zealand through Pharmaceutical Compounding NZ Limited or Optimus Healthcare Limited NZ.

Recommended Dosage

Varies from person to person. Currently the treatments are compounded according to patient's requirements.

Proposed Treatment Paradigm

The applicant suggests that most patients are first trialled on oral combination T3/T4 therapy. While treatment may vary from patient to patient, a significant number of patients require lifelong treatment.

International Recommendations

The American Thyroid Association and European Thyroid Association guidelines state that levothyroxine should remain the standard of care for treating hypothyroidism and note that they found no consistently strong evidence for the superiority of alternative preparations (e.g., levothyroxine-liothyronine combination therapy, or thyroid extract therapy, or others) over monotherapy with levothyroxine, in improving health outcomes.

The health benefits to the person, family, whānau and wider society

Evidence Summary

The applicant, the Thyroid Association of New Zealand Incorporated, has provided accounts of health benefits from their members with hypothyroidism taking T3 containing treatments and other literature, which PHARMAC staff consider to mostly provide poor quality evidence regarding efficacy.

PHARMAC staff have identified the following studies as relevant to this application.

Table 2: Relevant publications

Study	Citation
Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials	Grozinsky-Glasberg, et al. J Clin Endocrinol Metab. 2006;91(7):2592
Systematic review of all the published controlled studies comparing treatment with levothyroxine alone with combinations of levothyroxine plus liothyronine in hypothyroid patients	Escobar-Morreale et al. J Clin Endocrinol Metab. 2005;90(8):4946
Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study	Hoang, et al. J Clin Endocrinol Metab. 2013;98(5):1982-90
Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy.	Hennessey, et al. Int J Clin Pract. 2018;72(2). doi: 10.1111/ijcp.13062
Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients	Panicker, et al., J Clin Endocrinol Metab. 2009;94(5):1623
Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3'-triiodothyronine therapy	Appelhof, et al. J Clin Endocrinol Metab. 2005;90(11):6296
No Effect of the Thr92Ala Polymorphism of Deiodinase-2 on Thyroid Hormone Parameters, Health-Related Quality of Life, and Cognitive Functioning in a Large Population-Based Cohort Study	Wouters, et al. Thyroid. 2017;27(2):147

A metanalysis of 11 studies of T4-T3 combination therapy compared to T4 monotherapy for hypothyroidism, in which 1216 patients were randomized, did not find any difference in the effectiveness of combination therapy compared to T4 therapy for managing symptoms (Grozinsky-Glasberg, 2006).

A systematic review of nine randomized trials that compared T4 therapy alone with T3-T4 combination therapy in patients with hypothyroidism (Escobar-Morreale, 2005) revealed that only one trial reported beneficial effects of combination T4-T3 therapy on mood, quality of life, and psychometric performance when compared with T4 therapy alone.

A randomized, double-blind, crossover study of hypothyroid patients receiving either dessicated thyroid extract or T4 therapy found no differences in symptoms or neurocognitive measurements between the two treatments (Hoang, 2013). Dessicated thyroid extract caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for dessicated thyroid extract over T4 therapy.

Whether a combination of T4 and T3 is beneficial in a subset of hypothyroid patients with a polymorphism in the type 2 deiodinase, which converts T4 to T3, has been studied in a number of trials. One analysis found that patients with a polymorphism in the *DIO2 gene* had worse baseline quality-of-life scores and showed greater improvement after T4-T3 therapy compared with T4 alone (Panicker, 2009). A difference in response to combined T4-T3 therapy based on *DIO2* genotype was not found in other studies (Appelhof, 2005; Wouters, 2017).

Consequences for the health system

The applicant notes that patients that receive symptom relief with T3 treatment will have reduced doctor consultation visits, lab testing, and avoidance of other illnesses (infertility, pregnancy complications, neuromuscular symptoms, cardiac disfunction, psychiatric illnesses) that would impact health system services. We seek the Committee's view on these points.

Suitability

The features of the medicine or medical device that impact on use

Currently whole thyroid extract is available as a compounded medicine.

Costs and Savings

Costs and savings to pharmaceutical expenditure

Cost per patient

The applicant attached a notification from Pharmaceutical Compounding NZ (PCNZ) regarding the price increases for whole thyroid extract (WTE). The GST-exclusive prices are listed in the table below.

Pharmaceutical Strength	Price (GST exclusive) per 100 capsules

15 mg	$52.28
60 mg	$70.55
90 mg	$82.88
120 mg	$95.20
210 mg	$135.58

The prices of liothyronine (T3) and synthetic T3/T4 therapy have not been provided.

The dose of WTE varies considerably depending on tolerance and response to treatment. Patients may be initiated on a dose of 15mg twice daily, with the dose adjusted every 2-3 weeks depending on response. Based on a maintenance dose of 120 mg per day (60 mg capsule twice daily), the annual cost of treatment is estimated to be $515.02. The cost of treatment in year 1 is estimated to be $404.46 based on an initial dose of 30mg and dose adjustments of 15 mg every 2 weeks for 12 weeks. For further dosage recommendations, see Hoang et al. 2013 or https://www.drugs.com/ppa/thyroid-desiccated.html

Estimated Incremental Total Cost of Listing

The applicant considers that 16% of hypothyroid patients who are either currently taking T4-only treatment or self-funding WTE would benefit from WTE. The estimated number of people taking T4-treatment is 128,463 and a further 10,000 self-funding WTE. The estimated patient uptake is 22,154. We note that it is likely that nearly all patients self-funding WTE would switch to funded treatment, therefore uptake is likely to be closer to 30,000. The gross cost per year (based on a higher uptake) is estimated to be $13,500,000 in year 1, increasing to $17,300,000 in year 2. Assuming around 70% of patients switch from levothyroxine (at an annual cost of around $33 per patient, depending on dose), the net budget impact is estimated to be approximately $12,800,000.

Costs and savings to the rest of the health system

The applicant claims that the funding of WTE and T3 would result in savings to the health sector from reduced doctor consultations, referrals to specialists, laboratory tests and hospital visits. They claim that currently this subgroup of hypothyroid patients require multiple tests and doctors visits before the underlying cause of hypothyroidism is determined. We seek the Committee's view on this.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

PHARMAC staff will assess the cost-effectiveness of whole thyroid extract following a positive recommendation from PTAC.

APPENDICES

Appendix 1:

Grozinsky-Glasberg, et al. J Clin Endocrinol Metab. 2006;91(7):2592

Escobar-Morreale et al. J Clin Endocrinol Metab. 2005;90(8):4946

Hoang, et al. J Clin Endocrinol Metab. 2013;98(5):1982-90

Hennessey, et al. Int J Clin Pract. 2018;72(2). doi: 10.1111/ijcp.13062

Panicker, et al., J Clin Endocrinol Metab. 2009;94(5):1623

Appelhof, et al. J Clin Endocrinol Metab. 2005;90(11):6296

The Factors for Consideration

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system