APPLICATION TO THE MEDICAL SERVICES ADVISORY COMMITTEE

THE DIAGNOSTIC USE OF THYROGEN FOR PATIENTS WITH WELL-DIFFERENTIATED THYROID CANCER

October 2011

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List of abbreviations

^{131}I	Radioiodine 131
ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
ANZ	Australia and New Zealand
ATA	American Thyroid Association
CI	Confidence interval
CINSW	Cancer Institute of New South Wales
DAP	Decision analytic protocol
DPMQ	Dispensed price per maximum quantity
DTC	Differentiated thyroid cancer
dxWBS	Radioiodine diagnostic whole body scan
EANM	European Association of Nuclear Medicine
ESMO	European Society of Medical Oncology
ETA	European Thyroid Association
HTA	Health technology assessment
HRQOL	Health related quality of life
ICER	Incremental cost effectiveness ratio
MBS	Medicare Benefits Schedule
MCS	Mental component summary
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NPV	Negative predictive value
NSW	New South Wales
PASC	Protocol Advisory Sub-Committee
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCS	Physical component summary
POMS	Profile of Mood States
PPV	Positive predictive value
QALY	Quality adjusted life year
QoL	Quality of life
SF-36	Short form 36
T3	Liothyroxine sodium
T4	Thyroxine sodium
Tg	Thyroglobulin
TGA	Therapeutic Goods Administration
THT	Thyroid hormone therapy
TSH	Thyroid stimulating hormone
UK	United Kingdom
USA	United States of America
WBS	Whole body scan

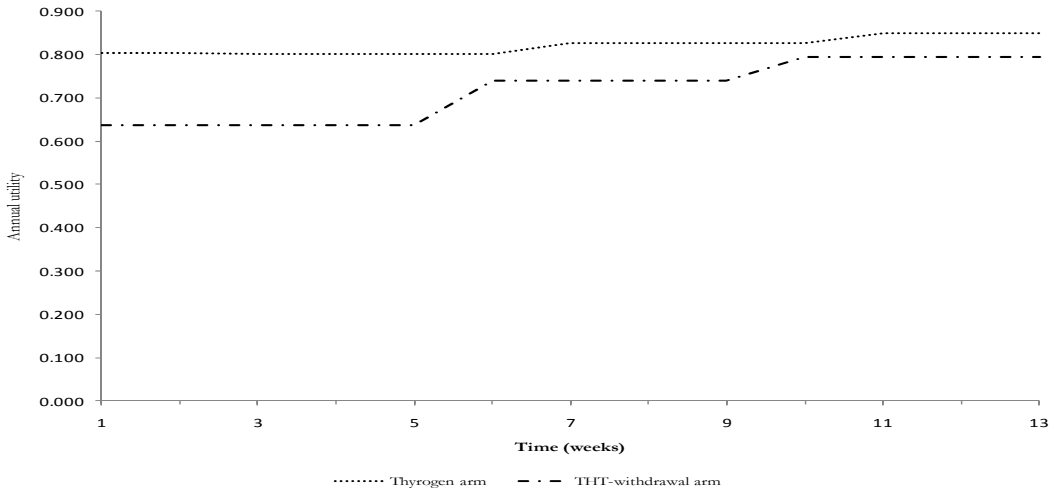
Issues raised in the decision analytic protocol (DAP)

The application for an expanded Medicare Benefits Schedule (MBS) listing for Thyrogen® was submitted to the Medical Services Advisory Committee (MSAC) in December 2010, at a time during which the MSAC submission process was undergoing significant reform. Genzyme Australasia received feedback on their application, via a decision analytic protocol (DAP). The issues that arose in the DAP, and where they have been addressed in this submission, are shown in **Table 1**. The Sponsor believes this updated version of the December 2010 MSAC application provides sufficient evidence to confirm the cost-effectiveness of Thyrogen for diagnostic use in this broader, but still small, eligible patient population with well-differentiated thyroid cancer.

Table 1 Summary of issues identified in the DAP and where they are addressed in the submission

Issue raised during development of the DAP	Sponsor's response	Location in submission
Issue 1 (p. 4): It is likely that MSAC would only consider extending the current listing if a systematic review of the evidence confirmed that the diagnostic accuracy associated with thyrotropin alfa-rch is no worse than that associated with withdrawal from THT (see p.6)	Evidence that has emerged since the 2001 MSAC review of Thyrogen adds to that already considered by MSAC to support the equivalent diagnostic performance of Thyrogen-stimulated testing with THT withdrawal stimulated testing. This has been acknowledged through leading clinical guidelines including the ETA, ATA and ESMO. This is reflected in high levels of concordance between test results seen across all clinical studies. Differences in results must be considered in the light of an imperfect reference standard. A perfect reference standard test is one which correctly identifies the patient's true disease status in all cases. In many clinical circumstances there is no perfect reference standard that can unequivocally determine a patient's disease state. This is the case for patients undergoing monitoring for well differentiated thyroid cancer. The previous MSAC evaluation report used THT-withdrawal stimulated testing (i.e. the comparator) as a proxy for a perfect reference standard, despite the fact it is not 100% accurate at determining the true disease state of the patient. Therefore, by definition, in these analyses, THT-withdrawal stimulated testing will appear to have 100% diagnostic accuracy. Furthermore, any other testing method that is compared to this test will appear to have less than perfect diagnostic accuracy. Consequently, the diagnostic accuracy results from the MSAC Evaluation Report, which indicated that Thyrogen-stimulated testing had a slightly lower sensitivity and specificity than THT-withdrawal-stimulated testing, represent a worst case scenario for Thyrogen. Indeed, the reverse could well be the case. A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation preparatory methods is that they have similar diagnostic accuracy. This is reflected by the high level of concordance seen between THT-withdrawal and Thyrogen-stimulation reported in the literature (Haugen *et al* 1999: 87% for serum Tg alone and 89.4% for dxWBS alone). In the event that these tests do not agree, the patient's true disease state will be best reflected by Thyrogen-stimulated testing in some cases and by THT-withdrawal stimulation in others (seen in Haugen *et al* 1999, **Section 12.1** refers). A systematic review was conducted to identify studies that described the diagnostic accuracy of Thyrogen-stimulated testing in identifying patients with well-differentiated thyroid cancer. The results of the systematic review showed that THT-withdrawal and Thyrogen-stimulation preparatory methods have similar diagnostic accuracy. This was also the conclusion drawn in the only systematic review of Thyrogen published since the 2002 MSAC review (Eustatia-Rutten *et al* 2004) and is further supported by the leading clinical practice guidelines for the management of thyroid cancer published around the world (Pacini *et al*, 2006a, Cooper *et al* 2006/2009, Pacini *et al* 2010). These expert groups recommended Thyrogen as an alternative to THT-withdrawal and these recommendations are based on a careful analysis of all available data, as well as expert clinical opinion. In addition, a wealth of published data supports that Thyrogen is as accurate as THT-withdrawal in diagnostic follow-up (Giusti *et al* 2003, David *et al* 2005, Kohlfuerst *et al* 2005, Crocetti *et al* 2008, Wong *et al* 2009).	Section 9.1, p. 63
Issue 2 (p. 4): The comparison of the administration of thyrotropin alfa-rch	A clinician survey (Appendix 1) was conducted to determine to what extent, if any, Thyrogen-stimulated testing would replace unstimulated ultrasensitive Tg testing (Appendix 1). The clinician survey found that while an increasing	Appendix 1, p.179

Issue raised during development of the DAP	Sponsor's response	Location in submission
followed by Tg assessment (i.e. stimulated Tg assessment) with unstimulated Tg assessment should be conducted using the current standard for Tg assay i.e. assays that have a detection threshold of 0.1ng/mL (see p.9)	proportion of clinicians are using unstimulated ultrasensitive Tg testing, 0% (0/264 patients) would have this testing modality replaced with Thyrogen-stimulated testing. In comparison, 98.5% (67/68) of patients that are currently undergoing THT-withdrawal stimulated diagnostic testing would have this testing modality replaced with Thyrogen. This clearly shows that the main comparator for Thyrogen (i.e. the test that the new testing modality is most likely to replace in practice) is THT-withdrawal not unstimulated ultrasensitive Tg testing. This is likely to reflect the fact that unstimulated ultrasensitive Tg testing is used later in the diagnostic follow up algorithm after patients have tested negative to a series of stimulated tests and are designated at low risk of disease recurrence. Furthermore, it should be noted that the diagnostic performance of unstimulated Tg testing has never been assessed by the MSAC, and based on current clinical evidence; international clinical practice guidelines (e.g. ATA) do not support the use of the ultra-sensitive Tg assay as the standard assay for use in clinical practice.	
Issue 3 (p. 4): There is uncertainty around the application's assumptions with respect to duration of hypothyroidism when a patient prepares for stimulated Tg assessment by withdrawing from THT; the economic evaluation presented to MSAC should permit sensitivity analysis around the duration of symptomatic hypothyroidism (see p.9)	The reader is reminded that the economic model does not assume that utility is severely impaired over the entire 13-weeks of the hypothyroid period. Instead, as shown in **Figure i**, utility initially starts low in the THT-withdrawal arm for a period of 5-weeks (annual utility weight = 0.637) and then increases at weeks 6–9 (annual utility weight = 0.740) and then again in weeks 10-13 (annual utility weight = 0.795) before returning to normal. This total period of hypothyroidism (i.e. 13-weeks) is the same as that applied in the successful PBAC submission for Thyrogen use in ablation. Therefore, the sponsor maintains that this is an appropriate estimate of the duration of symptomatic hypothyroidism in the patient population of interest and, therefore, this estimate is maintained in the base case analysis. However, the impact of altering this period is explored in sensitivity analysis. Specifically, when the duration of incremental benefit of rhTSH in the second-post test period is removed, by setting the second post-test utility in THT arm to parity with Thyrogen arm, the ICER increases to $41,330 per QALY.	Section 11.6.15.6, p. 115

Issue raised during development of the DAP	Sponsor's response	Location in submission
	 **Figure i:** Annual utility weight applied by week over diagnostic testing period	
Issue 4 (p.4): It is possible that there could be increased use of stimulated Tg assessment for monitoring of patients with at least two successive negative assessments if thyrotropin alfa-rch were made available on the MBS (in patients who would otherwise be managed by unstimulated Tg assessment); both the economic and financial analyses should allow for sensitivity analysis around increased use of stimulated Tg assessment in these patients (see p.9). Furthermore, as the data demonstrating benefit from repeated TSH-stimulated Tg assessment in patients with two or more successive negative stimulated Tg assessments is likely to be limited; sensitivity analysis	The use of Thyrogen in patients who have had two successive undetectable Thyrogen-stimulated Tg tests is likely to be limited and have little impact on the cost-effectiveness or financial impact estimates of Thyrogen presented in the current submission. However, the sponsor is willing to discuss ways in which this concern may be ameliorated with the MSAC through appropriate targeting of therapy.	NA

Issue raised during development of the DAP	Sponsor's response	Location in submission
around the results of the economic analyses presented in the application should include the possibility that no incremental benefit is associated with increased use of stimulated Tg assessment compared with unstimulated Tg assessment in these patients (see p.9)		
Issue 5 (p.4): There may be a clinical place for the use of thyrotropin alfa-rch in a small group of patients who would not be assessed for recurrence of thyroid cancer by assessment of serum Tg due to the presence of Tg antibodies because such testing in these patients has reduced sensitivity to detection of recurrence (see p.11); the applicant may wish to consider providing evidence to support listing of thyrotropin alfa-rch in these patients (i.e. evidence comparing stimulated total body iodine scan versus unstimulated total body iodine scan in these patients)	While there is a clear clinical need for Thyrogen in this patient population, the Sponsor is not aware of a study of Thyrogen performed in this specific patient population. However, presumably, the diagnostic evidence presented in the MSAC submission for Thyrogen-stimulated WBS versus THT-withdrawal stimulated WBS would also be applicable to this population.	NA
Issue 6 (p. 4): Ideally, the assessment of the clinical need, the clinical evidence, and economic evidence for thyrotropin alfa-rch should be conducted only for the incremental population that becomes eligible for reimbursed thyrotropin alfa-rch as a consequence of the proposed extension to the current listing given that thyrotropin alfa-rch is currently available for part of the total population covered by the proposed MBS item (see p.12). The PASC does, however, acknowledge that it might be difficult to present analyses only for the incremental population if studies	There are no sub-group analyses available from the pivotal clinical trials on which to base a cost-effectiveness analysis of the incremental population eligible for reimbursed Thyrogen. Genzyme thanks the PASC for acknowledging the difficulties in presenting information and analyses in this sub-group and requests MSAC considers the entire patient population that would be covered under the amended MBS listing for Thyrogen. The submission shows that Thyrogen is a cost-effective intervention in the entire population, regardless of whether or not it is more cost-effective in a sub group of patients. Furthermore, from the clinician survey conducted for this submission, it is clear that only a very small proportion (7.4%; 35/475) of patients currently receive Thyrogen under the current reimbursement arrangements. Therefore, incorporation of this population in the economic analysis (were it possible) would make little difference to the cost-effectiveness of Thyrogen in this setting.	NA

Issue raised during development of the DAP	Sponsor's response	Location in submission
have not reported outcomes for the two subgroups separately. Although MSAC would prefer to have evidence presented for the two subgroups separately, in the situation where evidence for the subgroups is not available, MSAC would consider evidence for the entire group.		
Issue 7 (p.4): Resource use associated with management of adverse events associated with thyrotropin alfa-rch should also be included in the economic analysis (see p.19)	Thyrogen is typically well-tolerated with short-lived and generally mild adverse effects. In the previous MSAC evaluation of Thyrogen, it was concluded that 'In general, the adverse events associated with the use of Thyrogen appear to be mild in nature.' The most common of these adverse effects include: nausea (approximately 10% incidence), headache (approximately 7% incidence) and asthaenia (approximately 3% incidence). In comparison, the costs of managing these minor ailments are likely to pale in comparison to the costs associated with the management of profound hypothyroidism secondary to THT-withdrawal. This is supported by the findings of Dueren *et al*, 2010 which found that medical practitioner visits was significantly reduced in the Thyrogen treated patients than those undergoing THT-withdrawal (and the need for additional medication was higher under THT-withdrawal (20.8% patients requiring additional pharmaceuticals) than when Thyrogen was used (11.2% patients requiring additional pharmaceuticals). Furthermore, withdrawal-induced hypothyroidism is overwhelmingly symptomatic, with many individuals experiencing several problems simultaneously. In a survey of 130 subjects, 92% experienced at least one symptom, 63% experienced two to five symptoms, and 25% experienced six or more of nine listed symptoms (Luster *et al*, 2005). Approximately two thirds of patients reported that hypothyroidism restricted or precluded activities of daily living and *almost half sought medical attention* for hypothyroid complaints (Luster *et al* 2005). These symptoms, including fatigue, difficulty concentrating, cold intolerance, weight gain, sleep disturbance, dry skin, constipation, hoarseness, and puffy face and hands have a considerable impact on functioning and quality of life. In addition to this hypothyroidism interferes with renal clearance and drug metabolism which increases the risk of cardiac complications and medication adverse events. Therefore, it was not considered necessary or informative to include management costs for Thyrogen associated adverse events.	NA
Issue 8 (p.4): The inclusion of "lifetime thyroid cancer" costs in the economic analysis is likely to result in double counting of several resources; costs should be related more explicitly to use of	While this is true, it is likely that the vast majority of these costs will be borne towards the end of the patient's life. A series of sensitivity and threshold analyses was conducted to explore the impact reducing these costs would have on the cost-effectiveness of Thyrogen. To attempt to account for this the lifetime cost of Thyroid cancer is reduced by 20% in the base case analysis. Furthermore, as shown in **Figure 16**, altering the lifetime costs of Thyroid cancer treatment has little impact on the cost-effectiveness of Thyrogen. This is not surprising given that these costs are	Section 11.6.15.6, p. 115

Issue raised during development of the DAP	Sponsor's response	Location in submission
specific resources (see p.19)	accrued late in the time horizon of the economic model and are, therefore, heavily discounted. In fact, even when these costs were entirely removed from the economic analysis (which is clearly inaccurate) the ICER for Thyrogen only increased from $39,129.66 per QALY to $39,317.10 per QALY (**Table 40**).	
Issue 9 (p 4.): The assumption of "additional costs" incorporating specialist visits and co-ordination of assessment for recurrence of thyroid cancer should be related more explicitly to use of specific resources (see p.19)	The MBS item number 12201 captures a number of costs, including the cost of: 1) Thyrogen – powder for injection 0.9 mg × 2 vials; 2) Thyrogen administration; 3) specialist attendances associated with the preparation and follow up of patients undergoing this diagnostic process; 4) arranging the dxWBS; and, 5) arranging the Tg test. This 'composite cost' for the MBS item for Thyrogen, which includes the cost of Thyrogen as well as 'additional costs' associated with monitoring and management, was presumably developed by the Department of Health in consultation with the MSAC and the relevant craft group. Unfortunately, the Sponsor was not privy to the deliberations and calculations that underpinned the final derivation of these costs and, as such, are unable to accurately disaggregate these costs further. Therefore, the Sponsor requests that the MSAC provide the assessing evaluation group with these disaggregated costs details directly. Regardless, it is clear that many of these costs (i.e. 3, 4 and 5) will be borne by the MBS regardless of whether the patient is undergoing Thyrogen-stimulated testing or THT-withdrawal-stimulated testing. Furthermore, where Thyrogen is injected by the administering practitioner benefits are not payable for an attendance on the day the second dose is administered. In these circumstances no additional costs are borne by the MBS for Thyrogen administration. Where Thyrogen is administered by a general practitioner only a small fee is allowed (i.e. a Level A consultation). Also it is important to note that patients undergoing THT-withdrawal stimulated testing require additional clinician visits (compared to Thyrogen) to monitor TSH levels (sometimes on multiple occasions) to determine the optimal timing of WBS and Tg test. Therefore, the Sponsor believes that the assumption that these 'additional' costs are the same for Thyrogen and THT-withdrawal is appropriate and may actually be conservative, favoring THT-withdrawal.	Section 11.4, p. 79
Issue 10 (p.5): The base case modelled economic evaluations presented in the application should be respecified to include more reasonable rates of: (i) non-compliance with stimulated Tg assessment (see p.17) ;and (ii) recurrence of thyroid cancer (see p.25)	<u>Non-compliance with stimulated Tg</u> In line with the MSAC 2002 evaluation, 20% of patients in the THT-withdrawal-stimulated arm of the economic model are assumed to be non-compliant and leave intensive follow-up prior to their second THT-withdrawal-stimulated diagnostic test (i.e. at 28 months) so as to avoid the debilitating effects of profound hypothyroidism. There is a dearth of information in the literature regarding non-compliance to follow-up testing. Therefore, as part of the expert opinion survey conducted for the current MSAC submission (Appendix 1), the following question was asked: *Q6. "In your experience what percentage of your patients with well differentiated Thyroid cancer do not comply with THT-withdrawal stimulated diagnostic testing due to the negative effects of hypothyroidism?"* A total of 11 clinicians answered this question in the survey. A mean of 14.4% (95% CI: 13.3–15.4%) of the patients managed by these clinicians were non-compliant to THT-withdrawal stimulated diagnostic testing due to the negative effects of hypothyroidism. In line with this finding the proportion of patients that are non-compliant with THT-	Section 11.6.7, p.87; Appendix 1 AND Section 11.6.15.6, p. 115

Issue raised during development of the DAP	Sponsor's response	Location in submission
	withdrawal testing has been reduced from 20% to 14.4% in the base case of the economic model. Recurrence of Thyroid cancer AND remnant thyroid tissue This estimate is supported by the publication by Haugen *et al*, 1999 which found that 49% of patients had a positive WBS at their first post-ablation diagnostic test. The MSAC 2002 evaluation estimated that 20% of patients were disease positive when they reached their second post-ablation follow-up scan. It is important to note that this estimate captures not only those patients in which disease has re-occurred but also those patients that that have remnant thyroid tissue (i.e. incomplete ablation), as one cannot determine unequivocally whether these patients do or do not have residual or recurrent cancer. Furthermore, both of these patient groups are treated in the same manner in clinical practice (i.e. with repeat radioiodine ablation). However, as requested in the DAP, the proportion of patients that are disease/remnant positive has been reduced. Further, it is reasonable to expect that after a patient tests positive and has another round of ablation the probability of a patient testing disease/remnant positive tests will decrease markedly. Therefore, the model has been respecified so that at the first analysis the probability of testing disease positive is halved (i.e. 25%), and from then on the probability of disease positivity decreases again to half that initially estimated as the disease positivity rate for the 28 month test in the original MSAC evaluation (i.e. 20%/2 =10%) and then to 5% at subsequent 28 month scans. This impact of altering this probability is also explored in a threshold/sensitivity analysis in which the probability of disease/remnant positivity is varied over a broad range (5%–70%) at the first 10-month diagnostic scan (**Figure 16**). This analysis shows that altering these parameters in the economic model has minimal impact on the cost-effectiveness of Thyrogen.	
Issue 11 (p.5): The assumption that unstimulated Tg assessment has no sensitivity in detecting recurrent thyroid cancer also is considered inappropriate; the inclusion of costs but no benefits from such testing in the economic evaluation was considered inappropriate (see p.25).	The economic model has been respecified to explicitly capture the sensitivity and specificity of unstimulated Tg testing in patients that have tested negative to two rounds of stimulated testing, or in patients that are non-compliant to THT-withdrawal stimulated testing *per se*. Data from the publication by Schlumberger *et al*, 2007 were used to derive the sensitivity and specificity of unstimulated Tg testing and the probability of disease recurrence in patients that are at low-risk of disease recurrence (i.e. patients with no evidence of persistent disease after initial treatment).	Section 11.6.7 p. 87
Issue 12 (p.10): The clinical experts advised that neck ultrasound (reimbursed under MBS items 55032 and 55033) is increasingly also being used in assessing patients for recurrence of thyroid cancer.	To the Sponsor's knowledge the diagnostic performance of ultrasound for the detection of Thyroid cancer recurrence has never been assessed by the MSAC and data is limited on this diagnostic modality in this setting. Therefore, while this testing modality may be used in some practices, it is unclear, whether this reflects good clinical practice. The use of ultrasound does not require stimulation and is therefore unaffected by stimulation, whether by Thyrogen use of THT withdrawal.	Section 11.6.15.6, p. 115

Issue raised during development of the DAP	Sponsor's response	Location in submission
	However, to attempt to inform the MSAC of the possible implications of ultrasound use in this setting, the effect of neck ultrasound on the cost-effectiveness of Thyrogen is explored in sensitivity analyses (Table 40). When the cost of ultrasound was added to diagnostic tests that do not include WBS, and it was assumed that ultrasound combined with Tg tests provided increased sensitivity but decreased specificity, the ICER increased from $39,126.66 per QALY to $44,103.84 per QALY. When the cost of ultrasound was added to diagnostic tests that do not include WBS and it was assumed that ultrasound combined with Tg tests provided perfect sensitivity and specificity, the ICER decreased from $39,126.66 per QALY to $25,862.69 per QALY.	

Abbreviations: ATA, American Thyroid Association; CRAFT, DAP, decision analytic protocol; dxWBS, diagnostic whole body scan; GNZ, Genzyme; ICER, incremental cost effectiveness ratio; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; PASC, Protocol Advisory Sub-committee; PBAC, Pharmaceutical Benefits Advisory Committee; rhTSH, recombinant thyroid stimulating hormone; Tg, Thyroglobulin; THT, thyroid hormone withdrawal; WBS, whole body scan.

Executive summary

Submission background and rationale

Thyroid cancer, although relatively rare, is the most common endocrine neoplasm. Over the last five decades, a trend of increasing incidence of thyroid cancer has been reported both internationally and in Australia (AIHW, 2010). There are three main forms of thyroid cancer: well differentiated, medullary, and anaplastic (or poorly differentiated) (Hu *et al*, 2008). The treatment for the majority of patients with well-differentiated cancer is a total or near-total thyroidectomy followed by an ablative dose of radioiodine (^{131}I). Patients are then treated with synthetic thyroid hormones for maintenance of basic bodily function and to suppress serum levels of thyroid stimulating hormone (TSH) and hence minimise TSH-induced tumour growth.

Following treatment, patients are periodically screened for persistent or recurrent disease using serum Thyroglobulin (Tg) measurements, usually with diagnostic radioiodine whole body scans (dxWBS) or with neck ultrasound. TSH-stimulation is an important pre-requisite for serum Tg measurement and radioiodine diagnostic whole body scan (dxWBS). Thyroid hormone stimulation in post-thyroidectomy patients has traditionally required individuals to discontinue their thyroid hormone suppression therapy (THT) in order to stimulate the production of endogenous TSH, which in turn promotes the uptake of radioiodine and release of Tg. The major disadvantage of THT-withdrawal stimulation, however, is that it causes patients to suffer the debilitating effects of profound hypothyroidism. Using the recombinant form of TSH, Thyrogen®, as an exogenous method of stimulation for such tests, avoids the detrimental health and quality of life effects of hypothyroidism by allowing the patient to be maintained on THT during testing.

At present, the diagnostic use of Thyrogen is covered by MBS item number 12201. However, this application seeks to amend the current MBS listing so that Thyrogen is made available to all patients currently undergoing THT-withdrawal for diagnosis of remnant thyroid tissue or recurrence of thyroid cancer, not just those patients that are medically contraindicated to THT-withdrawal as described in the current MBS listing. This will allow patients to avoid the significant morbidity and lost quality of life associated with hypothyroidism and will promote compliance with diagnostic follow-up. In addition, the proposed change to the MBS listing will mean that patients no longer require one THT-withdrawal stimulated follow-up serum Tg test or dxWBS prior to Thyrogen-stimulated Tg and/or dxWBS being used.

Proposed change to the MBS listing for Thyrogen

The proposed amended wording of the MBS listing for Thyrogen will bring it in line with the current TGA approved indication where Thyrogen may be used in conjunction with Tg testing with or without dxWBS (item numbers 66650 and 61426, respectively). Furthermore, these changes would bring the MSAC reimbursement criteria in line with current clinical practice guidelines world-wide that consider Thyrogen and THT-withdrawal stimulation to be diagnostically equivalent. In addition such changes would address a pressing clinical need for the avoidance of unnecessary hypothyroidism that is emphasised by national thyroid cancer experts and related medical associations. As a result, Thyrogen would be available to all post-thyroidectomy thyroid cancer patients undergoing stimulated follow-up, rather than limited to use in those susceptible to psychiatric disturbance whilst undergoing THT-withdrawal induced hypothyroidism or those in whom THT-withdrawal is medically contraindicated. The proposed change removes the need for a patient to undergo an initial THT-withdrawal stimulated test prior to subsequent Thyrogen testing, which is not considered necessary in current practice, as these tests are considered equivalent in terms of their diagnostic performance (British Thyroid Association and Royal College of Physicians, 2007; Cooper *et al*, 2009; Pacini *et al*, 2006a; Pitoia *et al*, 2009; Pacini *et al*, 2010). The suggested wording of the amended MBS reimbursement listing for Thyrogen is:

Administration arranged by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) for use with serum thyroglobulin (Tg), with or without radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

Clinical evidence

As noted above, available evidence is considered by peak clinical organisations to support equivalent diagnostic performance for stimulation with either Thyrogen or THT withdrawal. This evidence must be evaluated in the light of an imperfect reference standard. A perfect reference standard test is one which correctly identifies the patient's true disease status in all cases. In many clinical circumstances there is no perfect reference standard that can unequivocally determine a patient's disease state. This is the case for patients undergoing monitoring for well differentiated thyroid cancer. The previous MSAC evaluation report used THT-withdrawal stimulated testing (i.e. the comparator) as a proxy for a perfect reference standard, despite the fact it is not 100% accurate at determining the true disease state of the patient. Therefore, by definition, in these analyses, THT-withdrawal stimulated testing will appear to have 100% diagnostic accuracy. Furthermore, any other testing method that is compared to this test will appear to have less than perfect diagnostic accuracy. Consequently, the diagnostic accuracy results from the MSAC Evaluation Report, which

indicated that Thyrogen-stimulated testing had a slightly lower sensitivity and specificity than THT-withdrawal-stimulated testing, represent a worst case scenario for Thyrogen. Equally, the opposite could apply and Thyrogen could have superior diagnostic performance.

A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation preparatory methods is that they have similar diagnostic accuracy. This is reflected by the high level of concordance seen between THT-withdrawal and Thyrogen-stimulation reported in the literature (Haugen *et al* 1999: 87% for serum Tg alone and 89.4% for dxWBS alone). In the event that these tests do not agree, the patient's true disease state will be best reflected by Thyrogen-stimulated testing in some cases and by THT-withdrawal stimulation in others. In fact, this is the conclusion drawn in a systematic review of Thyrogen (Eustatia-Rutten *et al* 2004) published since the 2002 MSAC review. The conclusion that Thyrogen and THT-withdrawal stimulation preparatory methods have equivalent diagnostic accuracy is further supported by the leading clinical practice guidelines for the management of thyroid cancer published around the world (Pacini *et al*, 2006a, Cooper *et al* 2006/2009, Pacini *et al* 2010). These expert groups recommended Thyrogen as a viable alternative to THT-withdrawal and these recommendations are based on a comprehensive literature search and careful analysis of all available data, as well as expert clinical opinion. In addition, a wealth of published data supports the contention that Thyrogen is as accurate as THT-withdrawal in diagnostic follow-up (Giusti *et al* 2003, David *et al* 2005, Kohlfuerst *et al* 2005, Crocetti *et al* 2008, Wong *et al* 2009).

The value of Thyrogen lies principally in the important patient benefits of avoiding the signs, symptoms and significant morbidity of hypothyroidism and improving overall patient quality of life. Historically, THT-withdrawal has been the principal method of achieving the TSH stimulation required for follow-up monitoring in differentiated thyroid cancer. However, the acute adverse effects associated with withdrawal-induced hypothyroidism have a significant impact on patients and their compliance with follow-up. Preference-based health-related quality of life (utility weights) for this submission were obtained directly from head-to-head data in the patient population of interest show that patients rendered hypothyroid by the withdrawal of THT had a mean utility of 0.637, however when patients were maintained on THT prior to Thyrogen administration and WBS, mean utility was maintained at 0.803, a difference of 0.166 ($p < 0.0001$). This difference was identical to that observed between the Thyrogen and THT-withdrawal arms in the pivotal trial for ablation (Pacini *et al* 2006b) and accepted by the PBAC. The magnitude of disutility observed in both trials is not surprising given the clinical aim of THT- withdrawal is to increase serum TSH levels as rapidly as possible to the same target (>30 mU/L) that renders patients profoundly hypothyroid.

Economic evidence

The economic analysis presented investigates the cost-utility of Thyrogen stimulation compared to THT-withdrawal stimulated preparation for diagnostic testing with WBS and/or serum Tg testing. The primary outcome of this analysis was the cost per QALY gained in all patients with well-differentiated non-metastatic thyroid cancer undergoing diagnostic testing using these two preparatory methods for initial and subsequent follow-up diagnostic tests. The economic evaluation is presented in three steps to enhance the transparency of the analyses presented. These steps are as follows:

Step 1 (preliminary economic analysis) only captures the costs and effects accrued during the diagnostic testing period for both the Thyrogen and THT-withdrawal-stimulated arm over a 13 week period. This period is where the bulk of the incremental costs and benefits of the different methods of patient preparation are incurred.

Step 2 (20 year analysis) also captures the costs and effects accrued during the diagnostic testing period, however, Step 2 also captures any therapeutic radioiodine ablation episodes, the waiting periods between tests and ablation periods, the impact of poor compliance with follow up in the THT-withdrawal-stimulated arm and the impact of late stage cancer and premature cancer mortality. This analysis also explicitly captures the diagnostic performance of unstimulated Tg testing in patients after two negative Thyroid cancer tests or in those patients that are non-compliant with withdrawal-based diagnostic testing.

Step 3 (lifetime analysis – base case) is identical to Step 2 except that the time horizon of the economic model is extended to the patient's lifetime. This analysis captures the full impact of premature mortality in this patient cohort.

The base case economic analysis shows that the incremental cost-effectiveness ratio (ICER) for Thyrogen versus THT-withdrawal stimulation in all patients undergoing initial and subsequent diagnostic tests was ***$39,129.66 per QALY***. Furthermore, the cost-effectiveness of Thyrogen remains stable when the input parameters to the economic model are modified over a range of plausible scenarios.

In conclusion, Thyrogen represents good value for money for the Australian health care system and allows this small group of cancer sufferers to comply with appropriate monitoring for disease recurrence without having to suffer the debilitating effects of profound hypothyroidism. Thyrogen is a viable alternative to THW that provides very strong clinical value to the patient and the clinician in the diagnostic follow-up setting.

Utilisation

There will be no change to the number of 'services' of the comparator (THT-withdrawal stimulated testing) *per se*, however, Thyrogen will replace a proportion of THT-withdrawal stimulations as the means for TSH elevation for Tg testing and dxWBS. No change would be expected in the number of diagnostic services (e.g. serum Tg or dxWBS) undertaken as a result of the proposed changes to the MBS listing for Thyrogen, as only the method of preparation would differ. Under the current MBS listing, Thyrogen is only utilised by a small proportion of the prevalent pool of patients requiring monitoring with dxWBS and serum Tg measurement for differentiated thyroid cancer, because of the restrictive MBS eligibility criteria (Clincian survey: 35/475; 7.4%).

Based on analysis in Section 7 (i.e. the market-share approach), there is expected to be a net increase in Thyrogen diagnostic services reimbursed through the MBS of 565 in Year 1 (2011/12 financial year), up to 780 in Year 5. Given the current listed price of Thyrogen is $1901.42, this equates to a modest additional cost to the MBS of $1,073,705 in Year 1 and up to $1,482,915 in Year 5.

Conclusion

Since the completion of the MSAC Assessment Report for Thyrogen in 2002 (Application 1043), clinical guidance for patients with differentiated thyroid cancer has changed, such that the MSAC Assessment Report no longer reflects current clinical practice or the cost-effectiveness of Thyrogen in Australia. It is the view of the Sponsor and expert clinicians in the field (Section 14 refers) that the effectiveness, safety and cost-effectiveness information in this application supports the reimbursement of Thyrogen for all patients that are undergoing THT-withdrawal stimulation for diagnosis of thyroid cancer, without restricting availability for patients who will derive a substantial benefit. We therefore request that MSAC recommend that the proposed listing be implemented.

Submission background

In 2001, Thyrogen®, thyrotropin alfa-rch, was approved by the Therapeutic Goods Administration (TGA) for use in Australia as an adjunct diagnostic agent for radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer. In 2002, Genzyme Australasia Pty Ltd applied to the Medical Services Advisory Committee (MSAC) and received approval to have Thyrogen listed on the Medicare Benefits Schedule (MBS), albeit with a restricted listing. In 2004, the TGA approved indication for Thyrogen was expanded to include Thyrogen use as an adjunct diagnostic tool for serum Thyroglobulin (Tg) testing with or without radioiodine imaging. In 2006, Thyrogen received TGA approval to be used for stimulation in patients undergoing a remnant ablation therapeutic procedure.

In 2007, Thyrogen received a positive recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) and was listed on the Pharmaceutical Benefits Scheme (PBS) as a single treatment per lifetime for the ablation of thyroid remnant tissue in post thyroidectomy adults with no known metastasis. In 2008, the age restriction and the limitation of one treatment per lifetime were removed, with the PBAC noting that: patients with thyroid cancer have a chronic, stable and long term condition and the dosage with thyrotropin is also stable with patients generally requiring one or two treatments per lifetime. In 2009, Thyrogen received an 'authority required (streamlined)' listing meaning prescribers no longer have to telephone for preapproval to prescribe. The history of Thyrogen registration and reimbursement in Australia is presented in **Table 2**.

Table 2 History of Thyrogen registration and reimbursement in Australia

Date	Description
2001–	TGA approved diagnostic label: *"Thyrogen is indicated for use with radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy."*
2002–	MSAC approval for MBS reimbursement of Thyrogen (MBS Item Number 12201 – Thyrogen (thyrotropin alfa – rch)). Administration, by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone), and arranging services to which both items 61426 and 66650 apply, for the detection of recurrent well-differentiated thyroid cancer in a patient who: (a) has had a total thyroidectomy and one ablative dose of radioactive iodine; and (b) is maintained on thyroid hormone therapy; and (c) is at risk of recurrence; and (d) on at least one previous whole body scan or serum thyroglobulin test when withdrawn from thyroid hormone therapy did not have evidence of well differentiated thyroid cancer; and (i) withdrawal from thyroid hormone therapy resulted in severe psychiatric disturbances when hypothyroid; or (ii) withdrawal is medically contraindicated because the patient has: - unstable coronary artery disease; or - hypopituitarism ; or - a high risk of relapse or exacerbation of a previous severe psychiatric illness payable once only in any twelve month period.
2004–	TGA approved change to diagnostic indication to include serum thyroglobulin (Tg) testing: *"Thyrogen is indicated for use with serum thyroglobulin (Tg) testing, with or without radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone therapy."*
2006–	TGA label extension allowing use of Thyrogen for stimulation in post-thyroidectomised patients undergoing a remnant ablation therapeutic procedure: *"Thyrogen is indicated for therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine"*
2007–	Price of Thyrogen decreases by 7%, from $1953 to $1825 per vial (price to pharmacist)
2007–	Thyrogen PBS 'Authority required' listed for: *"Ablation of thyroid remnant tissue, in combination with radioactive iodine, in a post thyroidectomy adult aged 18 years or older without known metastatic disease. This drug is only PBS-subscribed for one treatment in a patient's lifetime."*
2008-	Thyrogen approved for patients < 18 years of age. Limitation of one treatment per lifetime removed from the PBS restriction.
2009–	Thyrogen recommended as an 'authority required (streamlined)' item, meaning prescribers no longer have to telephone for preapproval to prescribe.
Current TGA indication	Thyrogen is indicated for: (i) Use as a preparatory agent 'with serum Tg testing, with or without radioactive iodine imaging and undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy'. (ii) Therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine

Abbreviations: MBS, Medicare benefits Schedule; MSAC, Medical Services Advisory Committee; PBS, Pharmaceutical Benefits Advisory Committee; Tg, Thyroglobulin; TGA, Therapeutic Goods Administration.

Purpose of this application

The treatment for the majority of patients with well-differentiated papillary or follicular thyroid cancer is a total or near-total thyroidectomy followed by an ablative dose of radioiodine (^{131}I). Patients are then treated with synthetic thyroid hormones, thyroid hormone therapy (THT), to maintain basic bodily function and suppress serum levels of thyroid stimulating hormone (TSH) and hence minimise TSH-induced tumour growth. Following treatment, patients are periodically screened for persistent or recurrent disease using serum Thyroglobulin (Tg) measurements, with or without diagnostic radioiodine whole body scans (dxWBS) and/or neck ultrasound. TSH-stimulation is an important pre-requisite for serum Tg measurement and radioiodine diagnostic whole body scan. While the use of serum Tg and WBS predominate in Australia, other diagnostic tests such as neck ultrasound may also be used to supplement these tests, however this is only in a minority of patients in a limited number of centres. Regardless, neck ultrasound is unaffected by the TSH-stimulation status of the patient; therefore, THT-withdrawal or Thyrogen use will not affect the results of these tests. Consequently, as in the previous MSAC Assessment Report, this submission will focus on the use of serum Tg and dxWBS for follow-up of patients with well differentiated thyroid cancer.

Thyroid hormone stimulation in post-thyroidectomy patients has traditionally required individuals to discontinue their thyroid hormone therapy in order to stimulate the production of endogenous TSH. The major disadvantage of THT-withdrawal stimulation, however, is that it causes patients to suffer the debilitating effects of profound hypothyroidism, which can be associated with significant morbidity.Using the recombinant form of TSH, Thyrogen, as the method of stimulation for such tests, avoids the detrimental health and quality of life effects of hypothyroidism.

It is the view of thyroid cancer experts in Australia (see **Section 14**) that *'the current reimbursement availability criteria for Thyrogen (thyrotropin-alfa, rhTSH) on the Medicare Benefits Scheme (MBS) are inappropriately restrictive.'* These clinicians state that *'due to the existing restrictive MBS criteria, the majority of thyroid cancer patients do not currently qualify for subsidised Thyrogen, and thus must endure a period of thyroid hormone withdrawal to enable appropriate follow-up of thyroid cancer. These patients would have improved short and long-term outcomes from having access to Thyrogen.'*

We therefore request that MSAC recommend the expanded listing of Thyrogen for these patients.

Requested change to the MBS listing for Thyrogen

At present, the diagnostic use of Thyrogen is covered by MBS item number 12201. However, this application seeks to amend the current MBS listing so that Thyrogen is made available to all patients currently undergoing THT-withdrawal for diagnosis of remnant thyroid tissue or recurrence of thyroid cancer, not just those patients that are medically contraindicated to THT-withdrawal as described in the current MBS listing.

In addition, the proposed change to the MBS listing will mean that patients no longer require one THT-withdrawal stimulated follow-up serum Tg test and dxWBS prior to Thyrogen-stimulated Tg and dxWBS being used.

Rationale for the evidence presented in the submission

Since the completion of the MSAC Assessment Report for Thyrogen in 2002 (Application 1043), clinical guidance for patients with differentiated thyroid cancer has changed, such that the MSAC Assessment Report no longer reflects current clinical practice or the cost-effectiveness of Thyrogen in Australia.

These changes are as follows:

1. A number of international thyroid cancer management guidelines have been published (Pacini *et al* 2006, Cooper *et al* 2006/2009, Pacini *et al* 2010). All these state that Thyrogen is as effective as THT-withdrawal for the diagnostic follow-up of well differentiated thyroid cancer and therefore that Thyrogen is a suitable alternative to THT-withdrawal. These recommendations are based on a comprehensive literature search and careful analysis of all available data, as well as expert clinical opinion.

2. A wealth of published data supports the equivalent accuracy of Thyrogen and THT-withdrawal in diagnostic follow-up. This is in contrast to the MSAC conclusion in 2002 that Thyrogen use results in a substantial drop in sensitivity. One of the reasons for this discrepancy is that the MSAC evaluation report used THT-withdrawal stimulated testing (i.e. the comparator) as a proxy for a perfect reference standard, despite the fact it is not 100% accurate at determining the true disease state of the patient. Therefore by definition, any other testing method that is compared to this will appear to have less than perfect diagnostic accuracy. A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation is that they have similar diagnostic accuracy. This is reflected by the high level of concordance between THT-withdrawal and Thyrogen-stimulation reported in the literature (Haugen *et al* 1999, Pacini *et*

al 2001 and Ladenson *et al* 1997). This interpretation was supported by a meta-analysis that concluded Thyrogen is as accurate as THT-withdrawal (Eustatia-Rutten *et al,* 2004).

3. The impact of hypothyroidism on a wide range of patients is now much better understood. Several studies show that this state affects multiple body systems and has the potential for significant morbidity. New data about the effects on daily life, family life and ability to work have been published. In addition, more compelling utility data are now available from the pivotal trial and other comparative studies.

4. In the 2002 analysis, the ICER was $AUS 51,344 and this was considered to be unfavourable. Since that time, the price of Thyrogen has decreased to $1755.06 ex-manufacturer; $1825.00 price to pharmacist; $1901.42 dispensed price per maximum quantity (a reduction of 7% from the initial submission). This is the price at which Thyrogen is now reimbursed through the PBS. The MSAC report states: "this [cost-effectiveness] result is highly sensitive to the proposed cost of Thyrogen per se." (p. 62).

5. The TGA listing for Thyrogen has been substantively altered, such that Thyrogen is now indicated for use in conjunction with "serum thyroglobulin (Tg) testing, with or without radioactive iodine imaging" where previously Thyrogen was only indicated for use in Tg testing in conjunction with radioactive iodine imaging. This reflects the changing practices of thyroid cancer management.

6. Thyrogen received a positive recommendation by the PBAC in 2007 and is now reimbursed by the PBS for avoidance of hypothyroidism prior to the ablation of thyroid remnant tissue in post thyroidectomy patients. This assessment is pertinent to the diagnostic setting as it provides an independent assessment of the magnitude of the utility and QALY benefits that are likely to be realised in patients that avoid hypothyroidism by using Thyrogen in the diagnostic setting. It should be noted that the disutility associated with the period of THT-withdrawal is exactly the same irrespective of whether the patient is being prepared for ablation or diagnostic monitoring.

7. A considerable number of the clinical experts and medical associations that manage thyroid cancer in Australia believe that the current MBS listing for Thyrogen is inappropriately restrictive (see **Section 14**). This list of experts includes three members of the Supporting Committee that were involved in the initial MSAC assessment of Thyrogen (i.e. Professor Bruce Robinson; Professor Leigh Delbridge; and Associate Professor Monica Rossleigh).

8. It has become clear that there is no possibility for leakage of Thyrogen outside the listed indication. There are currently very few post-thyroidectomy patients receiving Thyrogen

for diagnostic purposes, as shown by the low patient numbers under MBS item number 12201 (N=162 in the 2010/11 financial year).

It is the view of the Sponsor and expert clinicians in the field that this information supports the reimbursement of Thyrogen for all patients that are undergoing THT-withdrawal stimulation for diagnosis of thyroid cancer, without the current restrictive MBS eligibility criteria.

Section 1 Applicant details

1.1 Name of applicant

Genzyme Australasia

1.2 Company or organisation contact person

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1.7 Corporation/partnership details

Corporation name

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ABN 24 083 420 526

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Postal address

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Australia

Partnership details (if the entity is a partnership, please list the names of all partners)

NA

1.8 Preferred mode of contact

□ **Phone**

✓ **E-mail**

□ **Fax**

□ **Postal**

□ **Other**

The treatment for the majority of patients with well-differentiated papillary or follicular thyroid cancer is a total or near-total thyroidectomy followed by an ablative dose of radioiodine (^{131}I). Patients are then treated with synthetic thyroid hormones, predominantly thyroxine sodium (T4), to replace endogenous hormones and suppress TSH secretion. The synthetic hormone T4 suppresses serum levels of TSH and hence minimises TSH-induced tumour growth (Schlumberger *et al*, 2004).

Following treatment, patients are screened for persistent or recurrent disease using serum thyroglobulin (Tg) measurements, with or without diagnostic radioiodine whole body scans (dxWBS). The two principal monitoring methods are complementary, and both types of tests are much more accurate when performed with TSH stimulation. In the case of dxWBS, the TSH level must be adequately elevated to stimulate the selective uptake of ^{131}I by thyroid remnants, local or metastatic disease. Indeed dxWBS is not possible without a significant rise in the serum TSH. TSH stimulation is also critical for serum Tg measurement because elevated circulated TSH concentrations increase any Tg production and secretion by occult differentiated thyroid cancer cells and hence significantly improve the sensitivity of Tg testing in detecting these cells (Cooper *et al*, 2009).

TSH stimulation in post-thyroidectomy patients has traditionally required individuals to discontinue their thyroid hormone suppression therapy in order to stimulate the production of endogenous TSH levels. In general, patients are withdrawn from thyroid hormone therapy (THT) for a period of four to six weeks, at which time TSH levels become sufficiently elevated for patients to undergo diagnostic testing. After diagnostic testing patients resume THT and gradually recover from the hypothyroid state. The major disadvantage of THT-withdrawal, however, is that it causes patients to suffer the effects of profound hypothyroidism. Using the recombinant form of TSH, Thyrogen, as the method of stimulation for such tests can avoid these debilitating effects by maintaining the patient in a euthyroid state.

While it has not been captured in the current submission, another very important practical benefit of Thyrogen that should not be underestimated is the ease of scheduling of patients for their diagnostic follow-up tests. The timing of these tests is dependent upon patients reaching threshold hypothyroid (TSH) status, for which time taken can vary considerably between patients undergoing

withdrawal. This means that scanning appointments often need to be cancelled or reschduled at short notice.

2.1 Service type

Effective follow-up requires periodic stimulation by TSH to be maximally effective. This has traditionally been achieved by stopping THT. Elevation of TSH is necessary to facilitate uptake of radioiodine into thyroid tissue (or undifferentiated thyroid cancer) and for the optimal release of Tg from persistent or recurrent disease tissue. Withdrawal from THT usually lasts for 4–6 weeks. This is followed by a period of sub-optimal utility as patients return to normal thyroid hormone levels following testing. The major disadvantage of THT-withdrawal stimulation is that it causes patients to suffer the debilitating effects of profound hypothyroidism. Using the recombinant form of TSH, Thyrogen, TSH can be stimulated exogenously, thus avoiding the detrimental health and quality of life effects of hypothyroidism and avoiding potential morbidity.

☐ **A procedure**

✓ **A diagnostic test (Section 12 has been completed)**

☐ **Other medical service**

Although not strictly a 'diagnostic test', the drug proposed for an amended MBS restriction (Thyrogen) is an agent used to prepare a patient for diagnostic tests being used for periodic monitoring of the cancer patient. Therefore, it is most suitably assessed within this category. Accordingly, Section 10 has been left blank and the pivotal evidence supporting the expanded listing of Thyrogen on the MBS can be found in **Section 12**.

2.2 Name of service

Thyrogen® (thyrotropin alfa-rch)

Presentation and administration

Thyrogen (thyrotropin alfa-rch) powder for injection contains a highly purified recombinant form of human TSH, a glycoprotein which is produced by recombinant DNA technology. Thyrogen is supplied as a sterile, non-pyrogenic, white to off-white, lyophilised product, intended for intramuscular administration after reconstitution with sterile water for injection. The recommended dose regimen for Thyrogen is 0.9 mg, administered by intramuscular injection twice (once every 24 hours for two doses), such that the second dose is given 24 hours prior to radioiodine administration. Seventy-two hours post second Thyrogen dose a blood sample is obtained for measurement of Tg and if necessary a diagnostic radioiodine 131 whole body scan is performed.

2.3 Is the proposed service already covered under an existing MBS item?

✓ **yes**

□ **no**

2.3.1 If yes

What is the item number(s)?

MBS Item Number 12201.

How does the proposed service differ from the service(s) covered under this item number(s)?

This application is for an amendment to the current MBS restricted listing for Thyrogen (Item Number 12201). There have been substantial changes in guidelines (and subsequently clinical management) since the original MBS listing for Thyrogen in 2002 such that the current listing is not sufficient for use in the management of thyroid cancer patients post-thyroidectomy.

It is proposed that Thyrogen becomes available to all patients with well-differentiated thyroid cancer that are currently undergoing THT-withdrawal as the method of preparation for diagnosis of remnant thyroid tissue or recurrence of thyroid cancer, not just those patients that are medically contraindicated to THT-withdrawal as described in the current MBS listing. The proposed change removes the need for a patient to undergo an initial THT-withdrawal stimulated test prior to subsequent Thyrogen-stimulated testing, which is no longer considered necessary in clinical practice because the two methods of patient preparation are considered equivalent.

REGULATORY REQUIREMENTS

2.4 Does the proposed service involve the use of a medical device or diagnostic test or pharmaceutical product (eg a radioactive tracer)?

✓ **yes**

□ **no**

Thyrogen itself is a pharmaceutical product. In clinical practice, Thyrogen is administered prior to serum Tg measurement with or without dxWBS.

2.4.1 If yes, please provide the name of the manufacturer and sponsor of the device/diagnostic test/pharmaceutical product.

Genzyme Australasia

2.5 Is the device or diagnostic test or pharmaceutical product used in the proposed procedure/test/service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?

☐ **yes**

✓ **no**

2.5.1 If yes, provide supporting documentation to this effect.

2.5.2 If no, has it been listed/registered on the Australian Register of Therapeutic Goods with the TGA?

✓ **yes, see 2.5.3**

☐ **no, see 2.5.4**

2.5.3 If listed/registered, please provide the following details.

TGA listing/registration number

Thyrogen (thyrotropin alfa-rch) 0.9 mg powder for injection (Number: AUST R 79777)

The indication (if registered)

Thyrogen is indicated for:

- Use as a preparatory agent '*with serum Tg testing, with or without radioactive iodine imaging and undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy*'.

- *Therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine* [not relevant to this submission as it is already covered by PBS item number 2700D]

A copy of any relevant report (eg TGA evaluation report) or TGA correspondence relating to the approval

The product information for Thyrogen is provided in the electronic files accompanying the submission.

2.5.4 If not listed/registered, is listing/registration pending?

N/A

Section 3 Commercial-in-confidence material

The Department of Health and Ageing undertakes that it will treat this application and its contents as commercial-in-confidence if you so request. The application and/or its contents will only be released to those people who will consider it for the purpose of advising the Minister. Such people will be bound by deeds of confidentiality, which must be signed before receipt of any commercial-in-confidence material.

If your application needs to be treated as commercial-in-confidence, you should complete the information below to specify which data must be treated as commercial-in-confidence, sign on the following page, and return these pages to the MSAC Secretariat, either with your application, or as a separate document if you are lodging your application electronically. Commercial-in-confidence information will not be included in the final printed report.

Documents in the possession of the Department are subject to the requirements of the Freedom of Information Act 1982. This means that the Department may be required to grant access to documents in its possession. Even if a document is stamped commercial-in-confidence, this does not mean that access under this Act can be denied. However, the Department is required to consult with the author of the document when that document appears to contain commercial-in-confidence material, and take the author's views into account when deciding to grant/not grant access to documents.

Name of procedure/test/service

Thyrogen thyrotropin alfa-rch

Name of applicant

Genzyme Australasia.

Is any part of the application commercial-in-confidence?

✓yes (Section 14)

☐ no

I have read the above and I acknowledge and accept that this application and/or its contents will be made available to those people who will consider it for the purpose of advising the Minister for Health and Ageing.

Signature

4.1 What are the proposed indications for the new procedure/ test/ service?

Current MBS listing

The current MBS listing for Thyrogen, thyrotropin alfa-rch, (Item Number 12201) is as follows:

Administration, by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone), and arranging services to which both items 61426 and 66650 apply, for the detection of recurrent well-differentiated thyroid cancer in a patient who:

(a) has had a total thyroidectomy and one ablative dose of radioactive iodine; and
(b) is maintained on thyroid hormone therapy; and
(c) is at risk of recurrence; and
(d) on at least one previous whole body scan or serum thyroglobulin test when withdrawn from thyroid hormone therapy did not have evidence of well differentiated thyroid cancer; and
(i) withdrawal from thyroid hormone therapy resulted in severe psychiatric disturbances when hypothyroid; or
(ii) withdrawal is medically contraindicated because the patient has:
- unstable coronary artery disease; or
- hypopituitarism ; or
- a high risk of relapse or exacerbation of a previous severe psychiatric illness

payable once only in any twelve month period.

(see below for explanatory notes)

Thyrotropin alfa-rch is a diagnostic agent that allows patients to remain on thyroid hormone therapy while being assessed for recurrent cancer. This item was introduced following an assessment by the Medical Services Advisory Committee (MSAC) of the available evidence relating to the safety, effectiveness and cost-effectiveness of thyrotropin alfa-rch. MSAC found that the use

of thyrotropin alfa-rch is associated with a lower diagnostic accuracy than when the patient has withdrawn from thyroid hormone therapy. Accordingly, benefits are payable under the item only for patients in whom thyroid hormone therapy withdrawal is medically contraindicated and where concurrent whole body study using radioactive iodine and serum thyroglobulin are undertaken. Services provided to patients who do not demonstrate the indications set out in item 12201 do not attract benefits under the item.

"Severe psychiatric illness" is defined as patients with a severe pre-existing psychiatric illness who are currently under specialist psychiatric care.

The item includes the cost of supplying thyrotropin alfa-rch and the equivalent of a subsequent specialist attendance. "Administration" means an attendance by the specialist or consultant physician (the administering practitioner) that includes:

- an assessment that the patient meets the criteria prescribed by the item; the supply of thyrotropin alfa-rch;

- ensuring that thyrotropin alfa-rch is injected (either by the administering practitioner or by another practitioner) in two doses at 24 hour intervals, with the second dose being administered 72 hours prior to whole body study with radioactive iodine and serum thyroglobulin test; and

- arranging the whole body radioactive iodine study and the serum thyroglobulin test.

Where thyrotropin alfa-rch is injected by the administering practitioner, benefits are not payable for an attendance on the day the second dose is administered. Where thyrotropin alfa-rch is injected by: a general practitioner - benefits are payable under a Level A consultation (item 3); other practitioners - benefits are payable under item 52.

Proposed MBS listing

The proposed amended wording of the MBS listing for Thyrogen will bring it in line with the current TGA approved indication where Thyrogen may be used in conjunction with Tg testing with or without dxWBS (item numbers 66650 and 61426, respectively). Furthermore, these changes would bring the MSAC reimbursement criteria in line with current clinical practice guidelines that consider Thyrogen and THT-withdrawal stimulation to be diagnostically equivalent. As a result, Thyrogen would be available to all post-thyroidectomy thyroid cancer patients undergoing stimulated follow-up, rather than limited to use in those susceptible to psychiatric disturbance or those in whom THT-withdrawal is medically contraindicated.

The proposed change removes the need for a patient to undergo an initial THT-withdrawal stimulated test prior to subsequent Thyrogen testing, which is not considered necessary in current

practice, as these tests are considered equivalent in terms of their diagnostic performance (British Thyroid Association and Royal College of Physicians, 2007; Cooper *et al*, 2009; Pacini *et al*, 2006a; Pitoia *et al*, 2009; Pacini *et al*, 2010).

The suggested wording of the amended MBS reimbursement listing for Thyrogen is:

Administration arranged by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) for use with serum thyroglobulin (Tg), with or without radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

4.2 State the therapeutic claim that you are making for this service (eg clinical benefit; relative safety).

Clinical benefit

Thyrogen stimulated and THT-withdrawal stimulated diagnostic follow-up testing for patients with well-differentiated thyroid cancer are now considered equivalent in terms of diagnostic accuracy. The value of Thyrogen lies principally in the important patient benefit of avoiding the symptoms of hypothyroidism and therefore improving overall quality of life. Hypothyroidism secondary to THT-withdrawal causes important morbidity, safety risks, and productivity impairment, benefits previously accepted by the PBAC (Borget *et al*, 2007; Duntas and Biondi, 2007; Luster *et al*, 2005; Schroeder *et al*, 2006). The MSAC concluded that '*..periods of morbidity associated with hypothyroidism and hospitalisations associated with radioiodine ablation/treatment of recurrent or residual disease are features of the disease*'. More detail on the health and quality of life benefits of Thyrogen are provided in **Section 12** of this application.

At present, patients undergo a 13-week period of sub-optimal utility which involves preparing for diagnostic testing (4 weeks of significant symptomatic hypothyroidism), completing the diagnostic testing (1 week of significant symptomatic hypothyroidism) and an 8 week period in which patients gradually return to a normal utility level (PBAC Submission 2006). This is an important disincentive for a significant number of thyroid cancer patients to undergo recommended protocols of follow-up for detection of cancer remnants or recurrence (Cohen *et al*, 2004; Duntas and Biondi, 2007). In contrast, Thyrogen:

- allows patients to avoid the impaired quality of life and morbidity associated with induced hypothyroidism;

- promotes patient compliance with diagnostic monitoring protocols following thyroidectomy and remnant ablation, which may lead to earlier diagnosis of cancer recurrence and better clinical outcomes for patients; and

- allows simple scheduling of patients for their diagnostic follow-up tests, as tests are not dependent upon patients reaching threshold hypothyroid status (which often leads to inefficient health resource use, including the cancellation/rescheduling of hospital bookings).

Safety

Thyrogen is typically well-tolerated with short-lived and generally mild nausea, headache and asthaenia being the most common side effects. In general, the adverse events associated with the use of Thyrogen are mild in nature compared to the significant morbidity and quality of life effects experienced by patients undergoing a period of profound hypothyroidism due to THT-withdrawal.

Further information on the relative efficacy and safety of Thyrogen is provided in **Section 12**.

Section 5 Clinical need, public health significance and patient selection

Thyroid cancer, although relatively rare, is the most common endocrine neoplasm. Thyroid cancer affects women more commonly than men and the majority of cases occur in the most productive period of a patient's lifetime, between the ages of 25 and 65 (Hu *et al*, 2008). There are three main forms of thyroid cancer: well differentiated, medullary, and anaplastic (or poorly differentiated) (Hu *et al*, 2008). The differentiated form accounts for approximately 80-90% of all thyroid cancers, and the most common types are papillary and follicular (Sherman *et al*, 2003). These types of differentiated thyroid cancer are generally regarded as slow-growing with the potential for prolonged remission, with relatively good long-term survival rates for most patients who receive early treatment and who comply with appropriate ongoing monitoring (Sciuto *et al*, 2009; Luster *et al*, 2008).

Over the last five decades, a trend of increasing incidence of thyroid cancer has been reported both internationally and in Australia (AIHW, 2010). In Australia, in 2006, primary thyroid cancer was diagnosed in 1657 people (AIHW, 2010). The limited duration (23-year) prevalence in Australia, as at the end of 2004, was 14,574. Approximately 5900 of those people were living with thyroid cancer within five years prior to December 2004. Whilst the incidence of thyroid cancer in Australia has been increasing, mortality rates have been decreasing. There were 105 deaths due to thyroid cancer in Australia in 2007.

At present, the diagnostic use of Thyrogen is covered by MBS item number 12201. However, this application seeks to amend the current MBS listing so that Thyrogen is made available to all patients currently undergoing THT-withdrawal, for diagnosis of remnant thyroid tissue or recurrence of thyroid cancer, not just those patients that are medically contraindicated to THT-withdrawal as described in the current MBS listing. The proposed change to the MBS listing will mean that patients no longer require one THT-withdrawal stimulated follow-up serum Tg test and dxWBS prior to Thyrogen-stimulated Tg and/or dxWBS being used.

5.1 Provide a summary of information about the condition for which the proposed procedure/test/service is to be used

SUMMARY OF INFORMATION RELATING TO THE CONDITION

Background

Thyroid cancer, although relatively rare, is the most common endocrine neoplasm. Thyroid cancer affects women more commonly than men and the majority of cases occur between ages 25 and 65; that is, in generally otherwise healthy, active individuals (Hu *et al*, 2008). There are three main forms of thyroid cancer: well differentiated, medullary, and anaplastic (or poorly differentiated) (Hu *et al*, 2008). The differentiated form accounts for approximately 80-90% of all thyroid cancers, and the most common types are papillary and follicular (Sherman *et al*, 2003). These types of differentiated thyroid cancer generally are regarded as indolent (slow-growing) with the potential for prolonged remission, with relatively good long-term survival rates for most patients with definitive primary (initial) treatment who comply with ongoing monitoring (Sciuto *et al*, 2009; Luster *et al*, 2008).

Well differentiated thyroid cancer is charcterised by the tumour cells that retain many characteristics of normal thyroid cells, including the ability to take up and retain iodine and the ability to manufacture and secrete Tg. Over time some differentiated thyroid cancer cells may lose these functions and the tumours may then become more difficult to treat. The ability of differentiated thyroid cancer cells to take up and retain iodine means that they can be imaged and/or destroyed by radioactive iodine. The unique ability of thyroid cells to secrete Tg makes serum Tg an ideal marker for the presence of thyroid cells. Consequently, serum Tg measurements are an important diagnostic test for differentiated thyroid cancer persistence or recurrence in patients whose thyroid gland has been removed (Hu *et al*, 2008).

Well differentiated thyroid cancer is usually slow-growing, and as a result, small numbers of cancer cells that persist in the body after primary treatment may take years to grow into detectable or clinically relevant tumours. Depending on the completeness of initial therapy, approximately 30% of patients suffer recurrences over several decades, with about one third of the recurrences occurring later than the first decade after primary treatment (Ladenson *et al*, 1997; Mazzaferri and Kloos, 2002; Ladenson *et al*, 1997). As a result, long-term patient monitoring is critical to detect persistent and recurrent disease at the earliest possible stage, when it can be more easily and effectively treated. Lack of compliance to monitoring means that recurrent disease will not be detected resulting in increased mortality (Mazzaferri and Jhiang 1994). Those patients who are not compliant with follow-up are likely to have delayed treatment with radioiodine ablation. Sciuto and colleagues (2009) have found that patients who have delayed treatment with radioiodine ablation

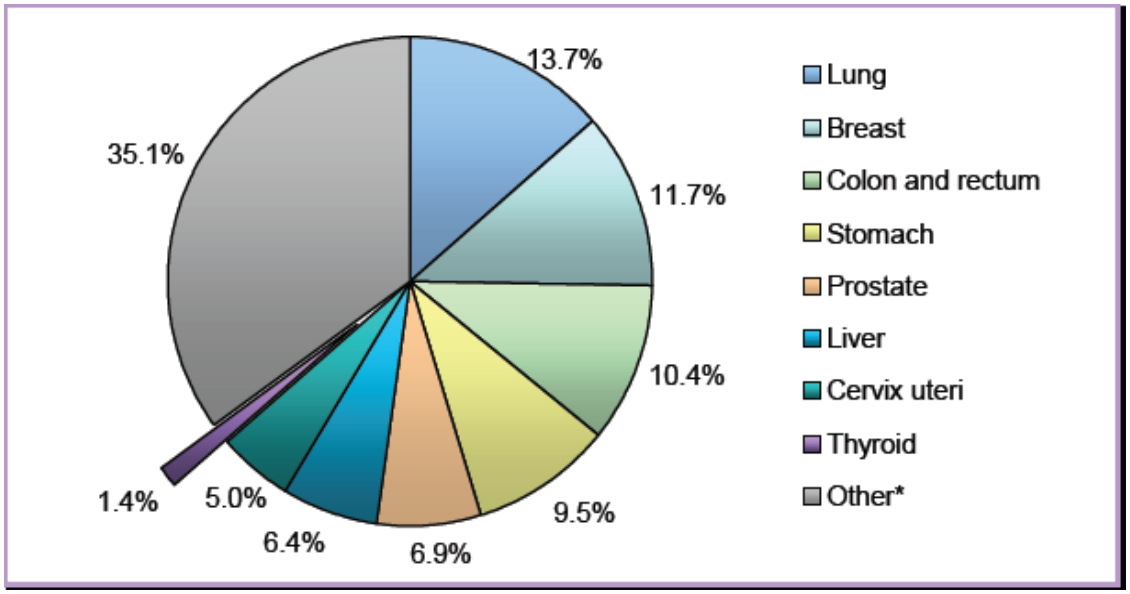
have a poor 10-year prognosis for survival (65%, which is considerably lower than for patients who have had their disease treated early).

The relative indolence of thyroid cancer should not diminish the magnitude of the disease, especially in light of its relatively high recurrence rates and the frequent difficulty or inability to cure its metastatic form. About one third to a half of distant metastases do not concentrate radioiodine. This means that advanced thyroid cancer is difficult to treat (Hu *et al*, 2008).

Clinical need and burden of disease

Worldwide, thyroid cancer accounts for less than 1.5% of cancer diagnoses (**Figure 1**). In 2002, approximately 140,000 cases of thyroid cancer were diagnosed, with over 35,000 deaths in the same year (Globocan, 2008). Due to its generally good prognosis, the 5-year prevalence of thyroid cancer is relatively high compared with incidence, and was reported as 530,000 in 2002 (Globocan, 2008).

Figure 1 Frequency of cancer diagnosis by site, 2002



Source: (Globocan, 2008)
Graphic shows all cancer sites that represent ≥5% of cancer diagnoses plus thyroid. Data from Globocan, 2002 * Includes the following cancers: testis, Hodgkin's lymphoma, nasopharynx, multiple myeloma, other pharynx, larynx, melanoma of skin, nervous system, corpus uteri, ovary, kidney, pancreas, oral cavity, leukemia, non-Hodgkin's lymphoma, bladder and esophagus.

Prevalence

Over the last five decades, a trend of increasing incidence of thyroid cancer has been reported both internationally and in Australia (AIHW, 2010). The limited duration (23-year) prevalence in Australia, as at the end of 2004, was 14,574. This included 3326 males and 11,248 females. In NSW, there were 5587 people (1176 male, 4411 female) living with thyroid cancer at the end of 2004 who were diagnosed between 1980 and 2004. The number of cases of thyroid cancer was slightly higher

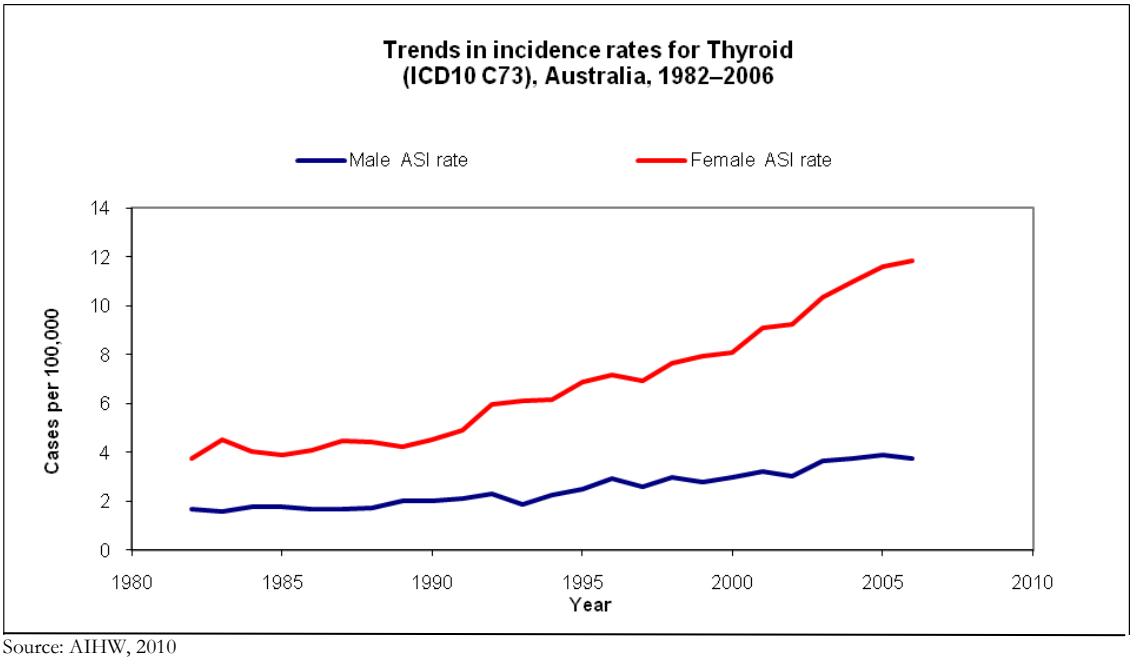
with 5862 (1264 male, 4598 female) cases, reflecting that some people had more than one case of cancer over the 25-year period of follow up (CINSW, 2006).

In Australia, 5899 people (1397 males and 4502 females) of the total 23-year prevalence had been diagnosed with thyroid cancer within five years prior to December 2004. In NSW, 2160 people (449 males and 1711 females), or 38.7% (38.2% male 38.8% female) of the total 25-year prevalence, had been diagnosed with thyroid cancer within five years prior to December 2004. Five-year age-standardised prevalence rates in NSW were 32 per 100,000 population overall: 13 per 100,000 population in males and 50 per 100,000 in females. For every person diagnosed with thyroid cancer in 2005, there were another three males and four females who had been diagnosed in the previous five years (CINSW, 2006). In NSW, at diagnosis, the majority of patients had localised disease (69%), then regional disease (20%), and distant metastases (3%). A total of 8% had unknown degree of spread at diagnosis (Tracey *et al* 2008).

Incidence

The incidence of thyroid cancer has increased in the past 30 years (**Figure 2**) (Davies *et al*, 2006; Tracey, 2008). In Australia, in 2006, primary thyroid cancer was diagnosed in 1657 people, with 112 deaths that same year (AIHW, 2010). Projections from the AIHW suggest that, for women, the number of new cases of cancers of the thyroid and other endocrine glands will increase to 1451 in 2011. For men, the number of new cases is projected to increase to 498. This equates to 1949 new cases of thyroid cancer and other endocrine tumours in 2011 (AIHW, 2010). Approximately 80-90% of these thyroid cancer cases will be differentiated thyroid cancer, with the remaining 10-20% non-differentiated thyroid cancer.

Figure 2 **Trends in incidence rates for Thyroid (ICD 10 C73), Australia, 1982–2006**

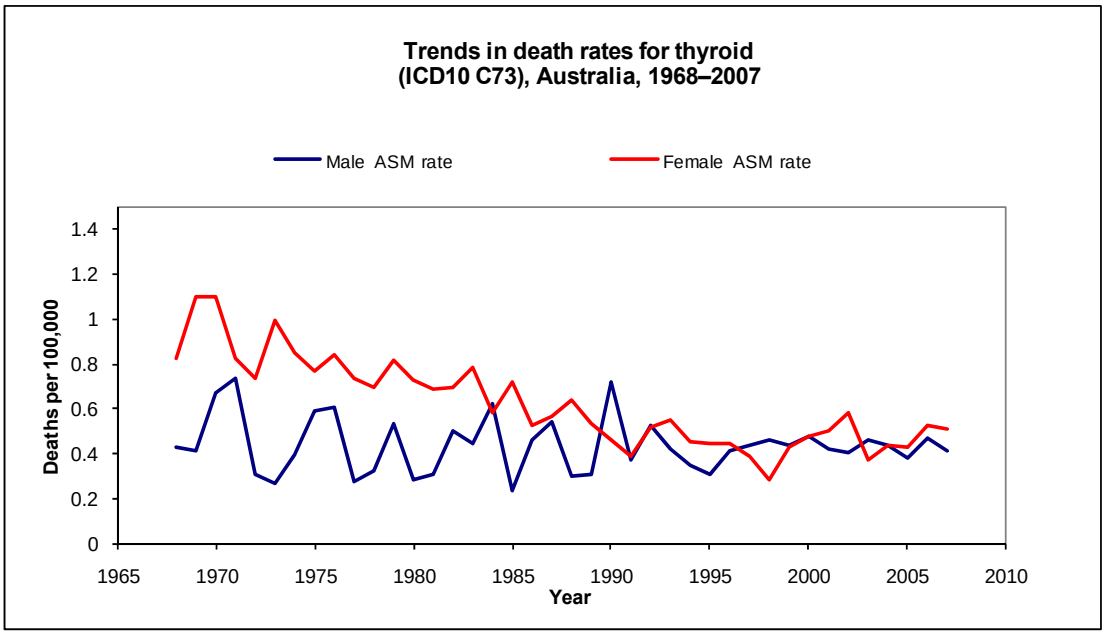


Source: AIHW, 2010
Abbreviations: ASI, age standardised incidence

Mortality

Whilst the incidence of thyroid cancer in Australia has been increasing over the last 30 years, mortality rates have been decreasing (AIHW, 2010). The trend in mortality attributable to thyroid cancer from 1968 to 2007 is shown in **Figure 3**. Although mortality due to thyroid cancer has been declining there were still 105 deaths due to thyroid cancer in Australia in 2007. Approximately 5.4% of deaths occur in people aged 0 to 49 years, 16.2% in those 50 to 64 years, 51.4% in those 65 to 79 years and 27.0% in those aged over 80 years (CINSW, 2006).

Figure 3 Trends in mortality due to thyroid cancer, Australia, 1968–2007



Source: AIHW, 2010
Abbreviations: ASM, age standardised mortality

Current treatment regimens

The management of differentiated thyroid cancer typically includes the following:

- Thyroidectomy (surgical removal of thyroid gland and cancer)
- Thyroid hormone replacement
- Remnant ablation to target any remaining cancer cells and healthy thyroid tissue
- Follow-up monitoring to detect recurrence (Cooper *et al*, 2009)
- Prompt treatment of persistent and recurrent disease

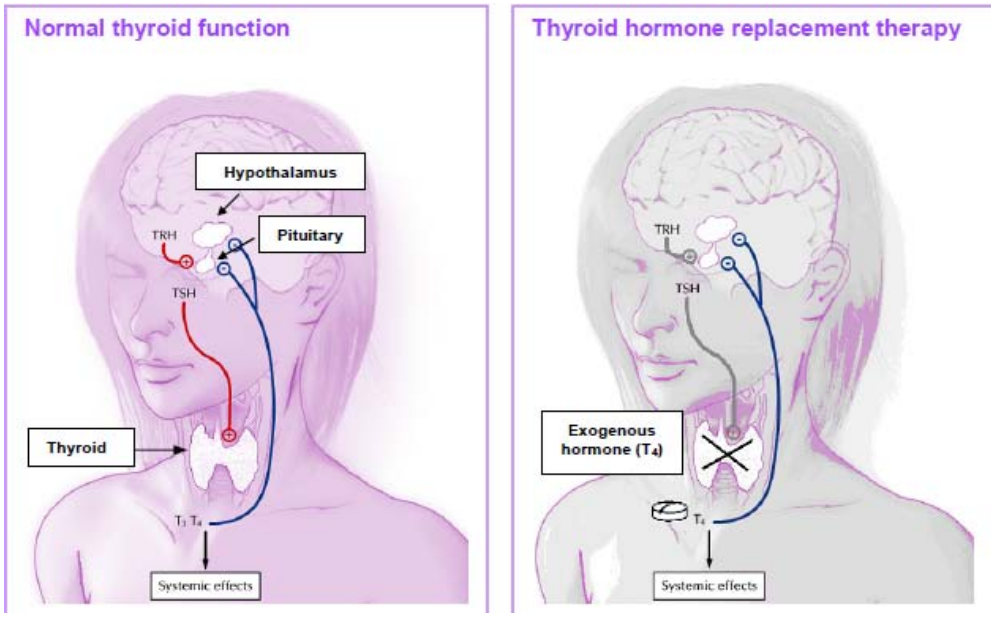
Surgery and thyroid hormone replacement

Following diagnosis, the majority of patients with well-differentiated thyroid cancer undergo near-total or total thyroidectomy. The completeness of surgical resection is important in determining a successful outcome. Lymph node dissection may also be performed at the same time as thyroidectomy as regional lymph node involvement is not uncommon, despite normal appearance on inspection (Cooper *et al*, 2009).

Removal of thyroid gland tissue during total or near-total thyroidectomy causes patients to become hypothyroid and exogenous thyroid hormone replacement is given to patients for the rest of their lives to retain an essentially normal metabolism (Pacini *et al*, 2006a). High levels of exogenous

thyroid hormone reduce TSH secretion to below normal levels to prevent TSH-stimulated growth of tumours (**Figure 4**) (Ladenson *et al*, 1997).

Figure 4 Thyroid hormone replacement therapy in post-thyroidectomy patients



Source: Genzyme Corporation (2010)
Abbreviations: TRH, thyrotropin releasing hormone; TSH, thyroid-stimulating hormone; T3, tri-iodothyronine, T4, thyroid hormone

Remnant ablation

Following surgery, thyroid remnant ablation, using a large dose of ^{131}I, is carried out. Depending on the individual case, a dose of between 30 and 200 mCi is administered (typically ~100 mCi; 3.7 GBq) (Cooper *et al*, 2009). The principle purposes of remnant ablation are to:

- Destroy residual tumour cells in order to reduce the risk of disease recurrence and possibly mortality.
- Destroy any remaining healthy thyroid tissue to significantly improve the sensitivity of subsequent monitoring for recurrence. Any detection of Tg, the marker for thyroid cells, would be indicative of recurrent disease, persistent disease, or metastasis, as opposed to residual healthy tissue. Also dxWBS is more sensitive when there is no remnant tissue present.
- Allow for a post-ablation scans to be performed. This may reveal previously unsuspected loco-regional and distant disesae.

Follow-up monitoring

Due to the long-term risk of thyroid cancer recurrence, regular monitoring is recommended following surgery and ablation. Patients are monitored using ongoing serum Tg measurements with or without dxWBS. The results of monitoring inform whether additional treatment is required. In

both Tg testing and dxWBS, the detection of residual thyroid cells is suggestive of recurrent disease because all thyroid tissue should have been removed/destroyed following surgery and remnant ablation procedures (Cooper *et al*, 2009).

Following thyroidectomy and remnant ablation, Tg represents a highly specific and sensitive marker for the presence of residual or recurrent disease, and serum Tg measurements above a cut-off threshold are indicative of tumour presence. Due to variation between laboratories, this threshold differs between institutions; however, often a stimulated serum Tg of greater than 2 ng/mL is used as a threshold for presence of tumour cells (Cooper *et al*, 2009; Pacini *et al*, 2006a). Some laboratories in Australia consider a stimulated Tg of less than 1 ng/mL to be indicative of a patient free of disease, however, they would generally re-test or implement a wait-and-see approach if Tg was between 1 and 2 ng/mL. It is generally accepted that a patient with a Tg on THT of <1 ng/mL is free of disease.

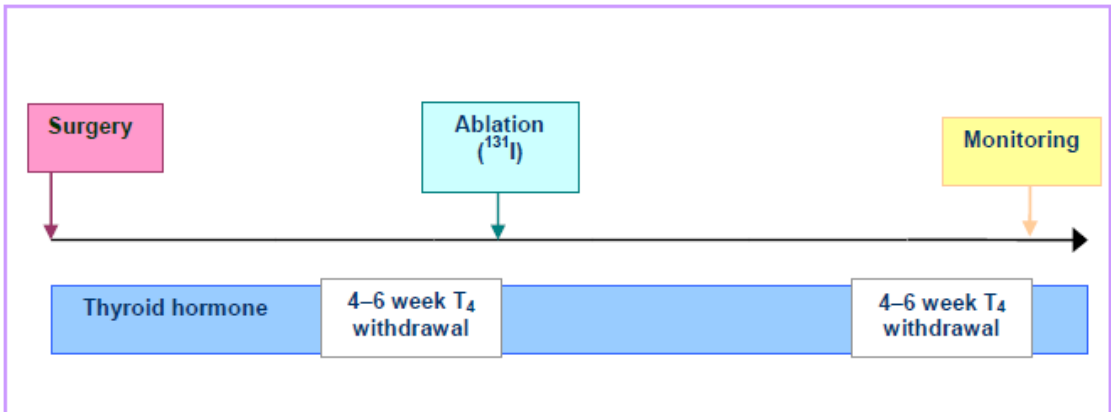
Diagnostic radioiodine whole body scan is a nuclear imaging technique performed after the administration of 4 mCi (0.15 GBq) ^{131}I dose – this is a much lower dose than that used for remnant ablation. Any thyroid cells that are present in the body will take up the bulk of the radioiodine, and any gamma rays emitted by the radioactive portion of that radioiodine are then detected by a gamma camera. Therefore, dxWBS can identify the distribution of cancer around the patient's body. This is particularly useful in determining the presence and anatomical positioning of metastatic disease.

The requirement for TSH stimulation

Effective remnant ablation and diagnostic monitoring are dependent upon the unique characteristics of healthy and/or malignant thyroid cells – remnant ablation and dxWBS require the uptake of radioiodine, whilst serum Tg measurement requires the secretion of Tg. Sufficient serum levels of TSH are required to optimise radioiodine absorption and Tg secretion. As a result, withholding or withdrawing THT has traditionally been required prior to ablation or monitoring in order to elevate endogenous TSH production.

Although the length of THT-withdrawal varies, it usually lasts for 4–6 weeks prior to ablation or monitoring until TSH levels are sufficiently elevated to above 30 mU/L (**Figure 5**) (Cooper *et al*, 2009). Following resumption of thyroid hormone, a further period is required for thyroid hormone levels to return to basal levels. This withdrawal renders the patient profoundly hypothyroid. The period of profound hypothyroidism is associated with high levels of psychological and physical morbidity which seriously impacts patients' ability to lead normal lives (Duntas and Biondi, 2007). Although unstimulated ultrasensitive Tg testing can be used to avoid profound hypothyroidism, its diagnostic accuracy remains unconvincing and subsequently THT withdrawal remains the standard diagnostic work-up for the majority of patients.

Figure 5 Thyroid hormone withdrawal during the course of differentiated thyroid cancer management



Source: Adapted from Cooper *et al*, 2009
Abbreviation: ^{131}I, radioiodine; T4, Thyroxine.

5.2 Please provide a copy of any data available to support the information described in 5.1 above.

A complete list of references is included at the end of this application.

5.3 In which patients with the condition will the proposed service be used? What are the contraindications in this patient group?

Due to the nature of differentiated thyroid cancer, all patients require regular follow-up and monitoring after undergoing thyroidectomy and radioiodine ablation. Detailed estimates of the potential utilisation of Thyrogen in Australia are provided in **Section 7**.

The use of Thyrogen will be limited to patients for the following indications:

- In the diagnostic setting as a preparatory agent *'with serum Tg testing, with or without radioactive iodine imaging, undertaken for the detection of thyroid remnant remains and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy'*

- In the ablation setting for *therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine* [not relevant to this submission as it is already covered by PBS item number 2700D]

There are no known contra-indications to the use of Thyrogen.

Precautions associated with Thyrogen use are outlined in the TGA-approved Product Information (provided with this submission).

5.4 Are there any particular considerations in relation to access to the proposed service which MSAC should consider when reviewing the application?

The MBS item number 12201 captures a number of costs, including the cost of: 1) Thyrogen – powder for injection 0.9 mg × 2 vials; 2) Thyrogen administration; 3) specialist attendances associated with the preparation and follow up of patients undergoing this diagnostic process; 4) arranging the dxWBS; and, 5) arranging the Tg test. It is important to note that many of these costs will be borne by the MBS regardless of whether or not the patient is undergoing Thyrogen-stimulated testing or THT-withdrawal-stimulated testing. Furthermore, as Thyrogen allows for more predictable timing of stimulation than THT-withdrawal it is likely that the patient will require fewer specialist attendances to ascertain patient stimulation levels to determine the optimal timing for diagnostic testing.

Section 6 Where the service will be performed, and who will perform it

6.1 How and where will the new service be used?

There will be no changes to how and where Thyrogen is currently used. The recommended dose regimen for Thyrogen is 0.9 mg, administered by intramuscular injection twice (once every 24 hours for two doses), such that the second dose is given 24 hours prior to radioiodine administration. Seventy-two hours post second Thyrogen dose a blood sample is obtained for measurement of serum Tg and if necessary a diagnostic scan is performed.

Thyrogen will continue to be administered by either a specialist or consultant physician in the practice of his or her speciality, or by a general practitioner. Where Thyrogen is injected by a general practitioner, benefits are payable under a Level A consultation (MBS Item 3); for other practitioners benefits are payable under Item 52. Where Thyrogen is injected by the administering practitioner; benefits are not payable for an attendance on the day the second dose is administered.

In terms of frequency of use, patients will continue to be followed up approximately 10 months after treatment, with a stimulated Tg with or without WBS diagnostic test. Patients with a negative test result wait until the next test which occurs 12-24 months after the initial diagnostic scan.

6.2 Specify which group of professionals will provide the service.

Thyrogen can be provided by a specialist, a consultant physician or a general practitioner, prior to diagnostic testing.

6.3 Specify what different or additional equipment and ancillary staff are required to perform the service compared to current services.

There will be no additional equipment or staff requirements if the expanded MBS listing for Thyrogen is approved.

Section 7 Estimated utilisation

Under the current MBS listing, Thyrogen is only utilised by a small proportion of the prevalent pool of patients requiring monitoring with dxWBS and serum Tg measurement for differentiated thyroid cancer, because of the restrictive MBS eligibility criteria (7.4% of patients according to the Thyrogen expert opinion survey). To estimate growth in the use of Thyrogen diagnostic services over time, the Thyroid cancer incidence rate (6.7%) was used. To calculate the net increase in utilisation of Thyrogen under the proposed expanded MBS listing, a market-share type approach was adopted using utilisation estimates from the Thyrogen expert opinion survey (**Appendix 1**).

It is assumed that 33% of all new Thyroid cancer patients who undergo diagnostic follow-up would be treated with Thyrogen-stimulated diagnostic testing (as per the Thyrogen expert opinion survey) and there is a 6.7% growth rate in Thyrogen use per year (as per the incidence rate of Thyroid cancer). Based on this, there is expected to be a net increase in Thyrogen diagnostic services reimbursed through the MBS of 565 in Year 1 (2011/12 financial year), up to 780 in Year 5. Given the current listed price of Thyrogen is $1901.42, this equates to a modest additional cost to the MBS of $1,073,705 in Year 1 and up to $1,484,915 in Year 5.

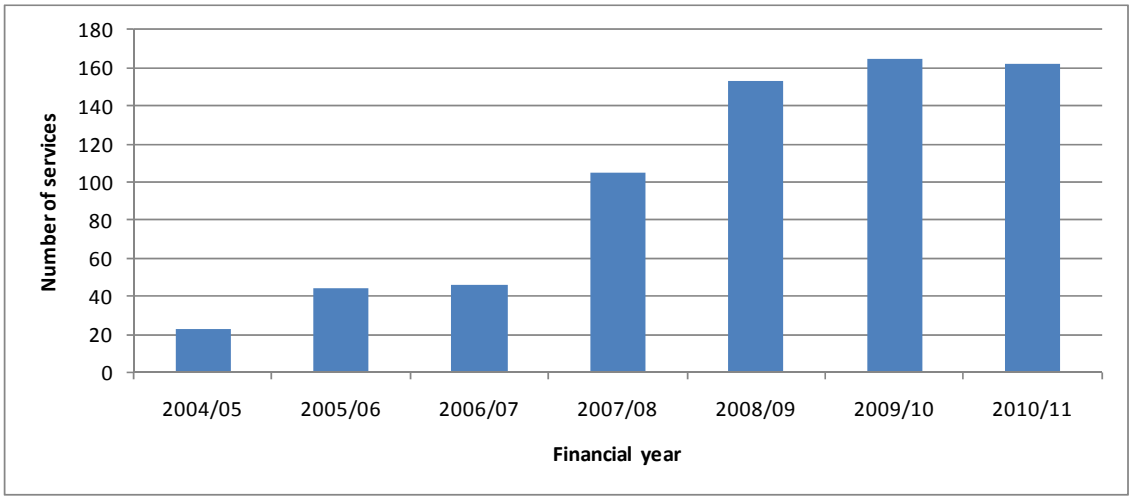
There will be no change to the number of 'services' of the comparator (THT-withdrawal stimulated testing) *per se*, however, Thyrogen will replace a proportion of THT-withdrawal stimulations as the means for TSH elevation for Tg testing and dxWBS. No change would be expected in the number of diagnostic services (e.g. serum Tg or dxWBS) undertaken as a result of the proposed changes to the MBS listing for Thyrogen, as only the method of preparation would differ.

7.1 Estimate the likely annual number of patients who will use the proposed service & financial impact to the MBS

Projected use and financial impact of Thyrogen for diagnostic purposes

The approach taken to estimate the use and financial impact of an expanded MBS listing for Thyrogen was a market-share type approach. The projected utilisation of Thyrogen was based on uptake rates determined via the Thyrogen expert opinion survey. The latest data on the number of Thyrogen services used for diagnostic purposes indicated that 162 services were dispensed in the 2010/2011 financial year (**Figure 6**).

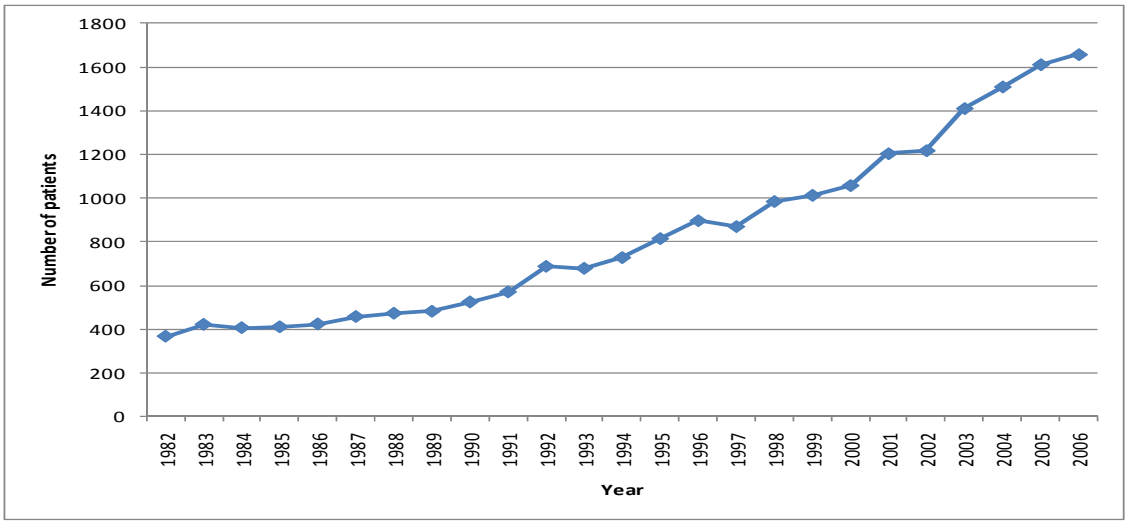
Figure 6 **Number of patients receiving Thyrogen for diagnostic purposes in Australia**



Source: Medicare Australia Statistics: MBS item number 12201

Based on the results of the clinician survey, Thyrogen was currently being used for diagnostic purposes in 35/475 (7.4%) of all managed patients. Survey respondents were asked how their use of Thyrogen would change under an expanded MBS listing and indicated that 157/475 (33.0%) patients would be treated with Thyrogen-stimulated diagnostic testing under the new listing. This represents a 4.5 fold increase in Thyrogen use in Year 1 and captures expected Thyrogen uptake. If this is applied to the current number of services then there would be a total of 727 Thyrogen diagnostic services in Year 1. To estimate growth in the use of Thyrogen diagnostic services over time, the Thyroid cancer incidence rate (6.7%) was used (**Figure 7**).

Figure 7 Incidence of thyroid cancer in Australia (1982-2006)



Source: Australian Institute of Health and Welfare (2010)

If it is assumed that 33% of all new Thyroid cancer patients who undergo diagnostic follow-up would be treated with Thyrogen-stimulated diagnostic testing (as per the Thyrogen expert opinion survey) and that then there would be a 6.7% growth rate in Thyrogen use per year (following Year 1), then there would 775 services in Year 2, and up to 942 services in Year 5 (**Table 3**).

Table 3 Total number of Thyrogen diagnostic services under the current and proposed listing

Year	2010/11	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of Thyrogen diagnostic services (services under the current Thyrogen listing + services under the newly proposed Thyrogen listing)	162	727	775	827	883	942

To calculate the net increase in utilisation of Thyrogen under the proposed expanded MBS listing, the expected number of Thyrogen diagnostic services under the current MBS listing needed to be accounted for. The number of services prescribed for Thyrogen diagnostic use under the current MBS listing was 162 in 2010/11 and is assumed to remain constant over time. This reflects the trend observed in current MBS utilisation data, which shows that the number of Thyrogen diagnostic services has plateaued over the last three years (**Figure 6**). Assuming no further increase in uptake of Thyrogen diagnostic services is a conservative approach because of the growth in the thyroid cancer population and it is likely to result in higher net estimates for service use overall.

The net financial impact of the expanded MBS listing for Thyrogen is shown in **Table 4**. It is estimated there will be a net increase in Thyrogen diagnostic services of 565 in Year 1 and up to 780 in Year 5. Based on the current listed price of Thyrogen ($1901.42), this equates to a modest additional cost to the MBS of $1,073,705 in Year 1 and up to $1,482,915 in Year 5.

Table 4 Projected use of Thyrogen for diagnostic purposes

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of Thyrogen diagnostic services (services under the current Thyrogen listing + services under the newly proposed Thyrogen listing)	727	775	827	883	942
Current and projected Thyrogen diagnostic services (under current Thyrogen listing)	162	162	162	162	162
Net number of new Thyrogen diagnostic services	565	613	665	721	780
Dispensed price maximum quantity of Thyrogen	$1901.42	$1901.42	$1901.42	$1901.42	$1901.42
Net financial impact to MBS ($)	$1,073,705	$1,166,281	$1,265,060	$1,370,457	$1,482,915

Abbreviations: MBS, Medicare Benefits Schedule

7.2 Estimate the change, if any, in the use of other services, especially the comparator identified in Section 8

TSH stimulation in post-thyroidectomy patients has traditionally required individuals to discontinue their THT in order to stimulate the production of endogenous TSH. Thyrogen provides an exogenous source of TSH such that THT-withdrawal to elevate TSH levels is no longer necessary. The comparator for Thyrogen is THT-withdrawal. Therefore, there will be no change to the number of 'services' of the comparator *per se*, however, Thyrogen will replace a proportion of THT-withdrawal stimulations as the means for TSH elevation for Tg testing and dxWBS. No change would be expected in the number of diagnostic services (e.g. serum Tg or dxWBS) undertaken as a result of the proposed changes to the MBS listing for Thyrogen, as only the method of preparation would differ. Thyrogen allows simple scheduling of patients for their diagnostic follow-up tests, as tests are not dependent upon patients reaching threshold hypothyroid status. The avoidance of the signs and symptoms of profound hypothyroidism would also result in a reduced number of clinician visits for treatment of these symptoms. A 2005 study by Luster and colleagues found that 38% of patients on THT withdrawal required single or multiple consultations with a primary care physician specifically for the treatment of hypothyroid symptoms and 31% required one or more specialist visits for the treatment of hypothyroid symptoms.

Section 8 Choice of comparator

The comparator is considered to be the testing procedure most likely to be replaced in practice by the Thyrogen testing procedure. In the majority of cases this is preparation of the patient for serum Tg and DxWBS testing with THT-withdrawal stimulation. Therefore, Thyrogen-stimulated Tg and dxWBS will replace THT-withdrawal-stimulated Tg and dxWBS. For the minority of patients in whom serum Tg is used as a stand-alone diagnostic test, then Thyrogen-stimulated Tg alone will replace THT-withdrawal-stimulated Tg alone. Therefore, the nature of the test will stay the same but the method of patient preparation will differ.

At present, patients undergo a 13-week period of sub-optimal utility which involves preparing for diagnostic testing (4 weeks of significant symptomatic hypothyroidism), completing the diagnostic testing (1 week of significant symptomatic hypothyroidism) and an 8 week period in which patients gradually return to a euthyroid utility level. THT-withdrawal stimulation causes a period of profound hypothyroidism, which causes significant and debilitating psychological and physical side effects. Using the recombinant form of TSH, Thyrogen, as the method of stimulation for such tests avoids the detrimental health and quality of life effects of hypothyroidism.

There will be no change to the clinical management algorithm for follow-up of patients with differentiated thyroid cancer as a result of the proposed changes to the MBS listing for Thyrogen. Wherever there is TSH stimulation, this stimulation can be induced endogenously with THT-withdrawal, or exogenously with Thyrogen.

8.1 What is the most commonly used diagnostic or therapeutic intervention for this condition at present? What is the appropriate comparator(s) for the proposed service?

The comparator is considered to be the testing procedure most likely to be replaced in practice by the Thyrogen testing procedure. In the majority of cases this is preparation of the patient for testing with THT-withdrawal stimulation. Current clinical practice guidelines recommend patients are screened for persistent or recurrent disease using serial serum Tg measurements, with or without dxWBS. Therefore, the following situation is most likely to occur in clinical practice:

- **Thyrogen-stimulated** Tg and dxWBS

  will replace

- **THT-withdrawal-stimulated** Tg and dxWBS

For the minority of patients in whom serum Tg is used as a stand-alone diagnostic test, then:

- **Thyrogen-stimulated** Tg alone

  will replace

- **THT-withdrawal-stimulated** Tg alone

Therefore, the nature of the tests will stay the same but the method of patient preparation will differ. No ultra-sensitive unstimulated Tg tests will be replaced by Thyrogen, confirmed by the Expert Opinion Survey (Appendix 1).

8.2 Will the proposed procedure/test/service be used in addition to, or instead of, the comparator(s) identified in 8.1 above?

Thyrogen will be used instead of THT-withdrawal.

8.3 How does the proposed procedure/test/service differ from the comparator(s)?

TSH-stimulation in post-thyroidectomy patients has traditionally required individuals to discontinue their THT in order to stimulate the production of endogenous TSH. At present, patients undergo a 13-week period of sub-optimal utility which involves preparing for diagnostic testing (4 weeks of significant symptomatic hypothyroidism), completing the diagnostic testing (1 week of significant symptomatic hypothyroidism) and an 8 week period in which patients gradually return to a

euthyroid utility level (i.e. identical to the estimates accepted by the PBAC, in the 2006 PBAC submission for Thyrogen). In a minority of cases, individuals receive T3 during the hypothyroid period for "bridging" purposes. This is undertaken to reduce the symptoms of hypothyroidism despite evidence to suggest that it is ineffective (Leboeuf *et al*, 2007; Lee *et al* 2010; Dueren *et al* 2010). The major disadvantage of THT-withdrawal stimulation is that it causes patients to suffer the debilitating effects of profound hypothyroidism. Using the recombinant form of TSH, Thyrogen, as the method of stimulation for such tests avoids the detrimental health and quality of life effects of profound hypothyroidism.

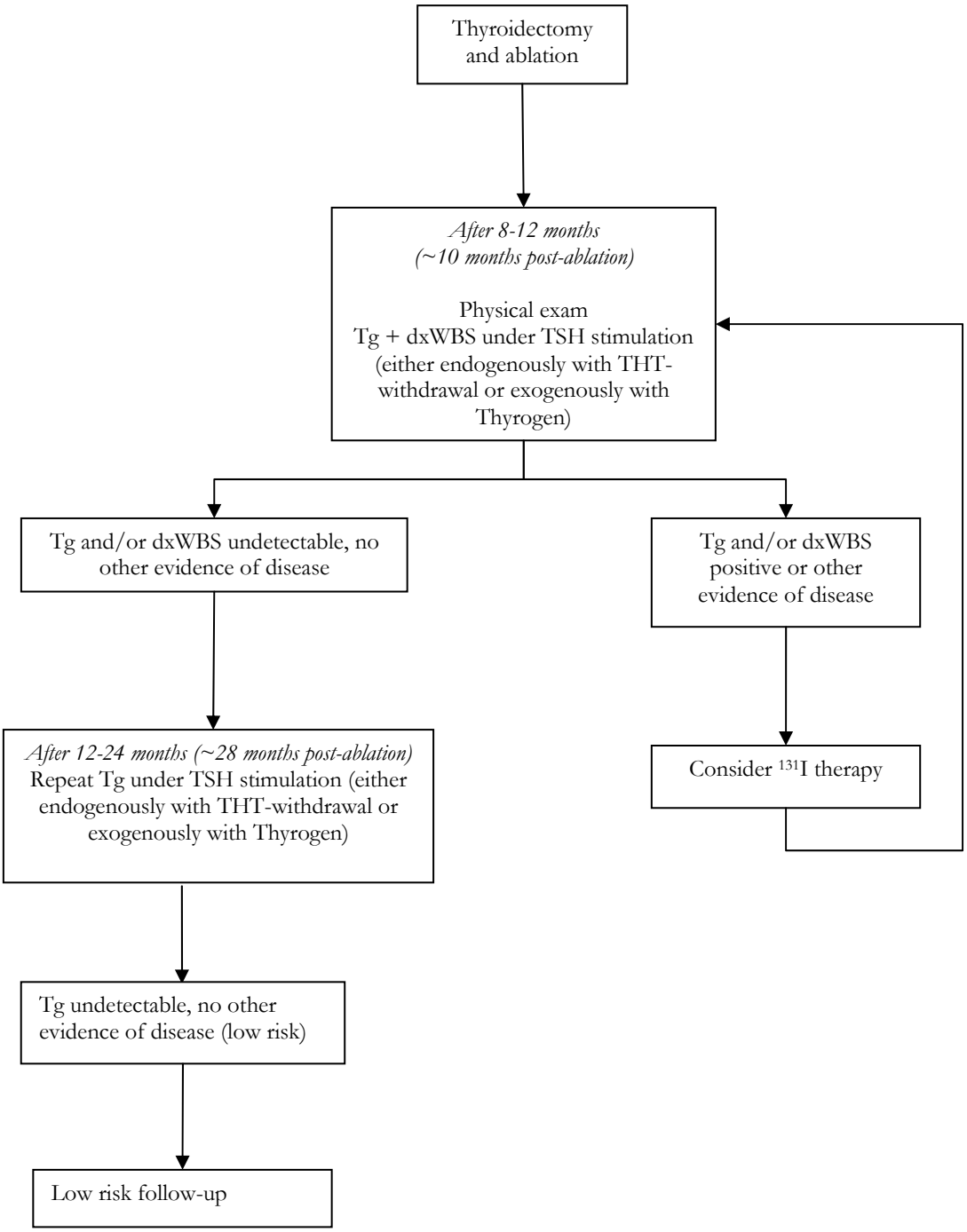
Thyrogen is administered to patients by a physician via intramuscular injection twice (once every 24 hours), such that the second dose is given 24 hours prior to radioiodine administration. Seventy-two hours post second Thyrogen dose a blood sample is obtained for measurement of Tg and if necessary a diagnostic scan is performed.

8.4 Provide a clinical flowchart to illustrate any differences in the clinical pathway linking the procedure/test/service with patient outcomes with that of the comparator service(s).

There will be no change to the clinical management algorithm for follow-up of patients with differentiated thyroid cancer as a result of the proposed changes to the MBS listing for Thyrogen. Wherever there is TSH stimulation, this stimulation can be induced endogenously with THT-withdrawal, or exogenously with Thyrogen.

A depiction of the clinical management algorithm for the follow-up of patients with differentiated thyroid cancer after thyroidectomy and ablation in Australia is presented in **Figure 8**.

Figure 8 Generalised clinical management algorithm for the follow-up of patients with differentiated thyroid cancer after thyroidectomy and ablation



Source: Adapted from Sundram *et al* (2006)
Abbreviations: dxWBS, diagnostic whole body scan; Tg, Thyroglobulin; THT, thyroid hormone withdrawal; TSH, Thyroid stimulating hormone

9.1 Provide a copy of the literature search which has been undertaken to identify evidence in support of the safety and effectiveness of the proposed service.

A literature search was conducted to identify studies that described the efficacy and safety of Thyrogen for diagnostic use in the follow-up of patients with differentiated thyroid cancer. The literature search was not limited by date. Citations were cross-checked with the previous MSAC assessment report (1043) to ensure all relevant studies published prior to 2003 had been included. The search strategy is described below.

Primary databases

Searches of the Embase.com (Medline and Embase) and Cochrane library databases were conducted on1 September and 23 August 2010, respectively. These searches were updated on 29 August 2011 to ensure any relevant papers published since the original Thyrogen submission had been identified. The search terms used are presented in **Table 5**. In the original literature search, there were 818 citations identified from Embase.com and 10 from the Cochrane library database. The reference lists of key papers were also hand searched resulting in the retrieval of three additional citations. The literature search update yielded 107 citations, 99 from Embase.com and eight from the Cochrane library database. Therefore, a total of 938 citations were identified as providing potentially relevant information for the submission.

Table 5 Embase.com and Cochrane library search results for Thyrogen

Database	Keywords/search terms	Results	
		Original search (2010)	Updated search (2011)
Embase.com (Medline and Embase)	'recombinant thyrotropin'/exp OR 'thyrogen'/exp OR 'thyrotropin alpha' OR 'thyrotropin alfa-rch' OR 'recombinant thyroid stimulating hormone' OR 'recombinant human tsh'	818	99
Cochrane library (clinical trials, technology assessments, economic evaluations	"recombinant thyrotropin":ti,ab,kw or "thyrogen":ti,ab,kw or "thyrotropin alpha" :ti,ab,kw or "thyrotropin alfa-rch":ti,ab,kw or "recombinant thyroid stimulating hormone":ti,ab,kw or "recombinant human tsh":ti,ab,kw	10	8
Hand search of key papers reference lists and cross-checking with previous submission	Diagnostic use of thyrogen	3	0
	Subtotal	**831**	**107**
	Total	**938**	

Secondary databases

In addition to the searches of the primary medical literature databases above, a search was undertaken of health technology assessment (HTA) websites using a combination of terms relating to Thyrogen. A list of secondary databases and websites searched and the number of citations retrieved from each is shown in **Table 6**.

Table 6 Health technology assessment websites searched

Country	Organisation(s); webpage(s)	Results	
		Original search (2010)	Updated search (2011)
Australia	Centre for Health Economics, Monash University http://www.buseco.monash.edu.au/centres/che/	0	0
	Medical Services Advisory Committee http://www.msac.gov.au/	5	0
Canada	Canadian Agency for Drugs and Technology in Health http://www.cadth.ca/index.php/en/home	1	0
Europe	European Agency for the Evaluation of Medicinal Products http://www.emea.eu.int/	2	0
United Kingdom	National Institute for Health and Clinical Excellence (NICE) http://www.nice.org.uk/	12	0
	Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/	2	0
United States	Agency for Healthcare Research and Quality http://www.ahrq.gov	6	0
	US Food and Drug Administration (FDA) [Search: Drugs and Medical Devices Only] http://www.fda.gov/	9	0
	Subtotal	**37**	**0**
	Total	**37**	

Selection criteria

Inclusion and exclusion criteria were developed *a priori* to determine eligibility of relevant studies assessing the diagnostic accuracy of Thyrogen in patients with differentiated thyroid cancer (**Table 7**). The objective was to identify prospective, comparative studies of Thyrogen versus THT-withdrawal, presenting measures of diagnostic accuracy including concordance, sensitivity, specificity, positive predictive value and negative predictive value.

Table 7 Inclusion and exclusion criteria for health

Characteristics	Inclusion	Exclusion
Participants	A study of patients with well differentiated thyroid cancer	Studies of other disease indications
Intervention	A study of Thyrogen used as a diagnostic agent in the follow-up of patients	• Not a study of Thyrogen • Studies of the therapeutic or ablative use of Thyrogen
Comparator	Thyroid hormone therapy withdrawal	None defined
Outcomes	Concordance and/or diagnostic accuracy measures (e.g. sensitivity, specificity, positive predictive value, negative predictive value)	None defined

Results from literature search

All citations identified in **Table 5** and **Table 6** were reviewed for inclusion. Initially, this was performed using the publication title and, where available, the abstract. **Table 8** summarises the reasons publications were excluded from consideration (including Embase.com, Cochrane Library and HTA websites).

A total of 975 publications were identified from the literature search, 935 from the search of Embase.com/Cochrane library, 37 from HTA databases and 3 from a hand search of reference lists. Following a review of the title and abstract (where available), 928 were excluded and the remaining 47 sourced for full text review. After reviewing the full text, a further 23 articles were excluded.

Of the remaining 24 articles, there were 6 comparative studies and 17 non-comparative studies and one systematic review describing the diagnostic use of Thyrogen in patients with well-differentiated thyroid cancer. A summary of all 24 studies is provided in **Table 9**. A list of excluded citations and their reason for exclusion is provided in **Appendix 2**.

Table 8 Summary of exclusion of citations from literature search

	Embase & Medline	Cochrane Library	HTA Websites	Hand search
	917	18	37	3
Number of consolidated citations	975			
Number of citations excluded after title/abstract review				
Duplicate citations	14			
Non-systematic review, editorial, letter, news article, survey or opinion piece and non-human or in vitro studies	475			
Not a study of Thyrogen	134			
Not a diagnostic accuracy study with relevant outcomes (including studies of the therapeutic or ablative use of Thyrogen)	305			
Total number of excluded citations after title/abstract review	928			
Number of citations excluded after full text review				
Non-systematic review, editorial, letter, news article, survey or opinion piece and non-human or in vitro studies	10			
Not a study of Thyrogen	0			
Not a diagnostic accuracy study with relevant outcomes (including studies of the therapeutic or ablative use of Thyrogen)	9			
Not available in English	4			
Total number of included studies	**24**			

Abbreviations: HTA, health technology assessment

Table 9 Studies identified in literature search

Reference	Included in previous MSAC submission (1043)	Included for discussion	Study type
Systematic reviews			
Eustatia-Rutten C, Smit J, Romijn J, van der Kleij-Corssmit E, Pereira A, Stokkel M, Kievit J (2004) Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma, a structured meta-analysis. Clin Endocrinol (Oxf) 61:61-74.		✓	Systematic review
Comparative studies			
Haugen BR, Pacini F, Reiners C, *et al* (1999) A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. Journal of Clinical Endocrinology and Metabolism 84:3877-3885.	✓	✓	Prospective, evaluator-blinded, with sequential diagnostic measurements
Ladenson PW, Braverman LE, Mazzaferri EL, *et al* (1997) Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. New England Journal of Medicine 337:888-896.	✓	✓	Prospective, evaluator-blinded, with sequential diagnostic measurements

Reference	Included in previous MSAC submission (1043)	Included for discussion	Study type
Mazzaferri EL and Kloos RT. (2002) Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? Journal of Clinical Endocrinology and Metabolism 87:1490-1498.	✓	✓	Retrospective, with a combination of variable reference standards
Pacini F, Molinaro E, Lippi F, *et al* (2001) Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. Journal of Clinical Endocrinology and Metabolism 86:5686-5690.	✓	✓	Prospective, with sequential diagnostic measurements
Robbins RJ, Chon JT, Fleisher M, *et al* (2002) Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? Journal of Clinical Endocrinology and Metabolism 87:3242-3247.	✓	✓	Retrospective, parallel cohort
Meier CA, Braverman LE, Ebner SA, *et al* (1994) Diagnostic use of recombinant human thyrotropin in patients with thyroid carcinoma (phase I/II study). Journal of Clinical Endocrinology and Metabolism 78:188-196.	✓	✓	Prospective, dose ranging, evaluator blinded, with sequential diagnostic measurements
Non-comparative studies			
Crocetti U, Durante C, Attard M, *et al* (2008) Predictive value of recombinant human TSH stimulation and neck ultrasonography in differentiated thyroid cancer patients. Thyroid 18:1049-1053.		✓	Case series in consecutive patients
David A, Blotta A, Bondanelli M, *et al* (2001) Serum thyroglobulin concentrations and ^{131}I whole-body scan results in patients with differentiated thyroid carcinoma after administration of recombinant human thyroid-stimulating hormone. Journal of Nuclear Medicine 42:1470-1475.	✓	✓	Case series
David A, Blotta A, Rossi R, *et al* (2005) Clinical value of different responses of serum thyroglobulin to recombinant human thyrotropin in the follow-up of patients with differentiated thyroid carcinoma. Thyroid 15:267-273.		✓	Case series
Diaz-Soto G, Puig-Domingo M, Martinez-Pino I, Martinez De Osaba MJ, Mora M, Rivera-Fillat F, Halperin I (2011) Do thyroid cancer patients with basal undetectable Tg measured by current immunoassays require rhTSH testing? Exp Clin Endocrinol Diabetes 119(6):348-52.		✓	Case series in consecutive patients
Durski JM, Weigel RJ, and McDougall IR. (2000) Recombinant human thyrotropin (rhTSH) in the management of differentiated thyroid cancer. Nuclear Medicine Communication 21:521-528.	✓	✓	Case series

Reference	Included in previous MSAC submission (1043)	Included for discussion	Study type
Fumarola A, Dalessandri M, Dicorato P, Grani G, Maiuolo A, Ruggieri M, Calvanese A (2010) Diagnostic accuracy of rhTSH test with neck ultrasonography in differentiated thyroid cancer follow-up. Exp Clin Endocrinol Diabetes 118(8):554-6.		✓	Case series in consecutive patients
Giovanni V, Arianna LG, Antonio C, *et al* (2002) The use of recombinant human TSH in the follow-up of differentiated thyroid cancer: Experience from a large patient cohort in a single centre. Clinical Endocrinology 56:247-252.	✓	✓	Case series
Giusti M, Zoccola R, Guazzini B, *et al* (2003) Recombinant human TSH changes the multidisciplinary approach to patients with differentiated thyroid carcinoma. Two-year experience. Minerva Endocrinologica 28:191-203.		✓	Case series in consecutive patients
Kohlfuerst S, Igerc I, and Lind P. (2005) Recombinant human thyrotropin is helpful in the follow-up and ^{131}I therapy of patients with thyroid cancer: A report of the results and benefits using recombinant human thyrotropin in clinical routine. Thyroid 15:371-376.		✓	Retrospective case series
Lippi F, Capezzone M, Angelini F, *et al* (2001) Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human THS. European Journal of Endocrinology 144:5-11.	✓	✓	Case series
Mariani G, Ferdeghini M, Augeri C, *et al* (2000) Clinical experience with recombinant human thyrotropin (rhTSH) in the management of patients with differentiated thyroid cancer. Cancer Biotherapy and Radiopharmaceuticals 15:211-217.	✓	✓	Case series
Pacini F, Molinaro E, Castagna MG, *et al* (2003) Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. Journal of Clinical Endocrinology and Metabolism 88:3668-3673.		✓	Retrospective case series in consecutive patients
Petrich T, Borner AR, Weckesser E, *et al* (2001) Follow-up of thyroid cancer patients using rhTSH - Preliminary results. NuklearMedizin 40:7-14.	✓	✓	Single-arm clinical trial in consecutive patients with historical controls
Robbins RJ, Chon JT, Fleisher M, *et al* (2002) Is the serum thyroglobulin response to recombinant human thyrotropin sufficient, by itself, to monitor for residual thyroid carcinoma? Journal of Clinical Endocrinology and Metabolism 87:3242-3247.		✓	Retrospective case series

Reference	Included in previous MSAC submission (1043)	Included for discussion	Study type
Torlontano M, Crocetti U, D'Aloiso L, *et al* (2003) Serum thyroglobulin and ^{131}I whole body scan after recombinant human TSH stimulation in the follow-up of low-risk patients with differentiated thyroid cancer. European Journal of Endocrinology 148:19-24.		✓	Case series in consecutive patients
Wartofsky L. (2002) Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. Thyroid 12:583-590.		✓	Case series in consecutive patients
Wong R, Topliss DJ, Bach LA, *et al* (2009) Recombinant human thyroid-stimulating hormone (Thyrogen) in thyroid cancer follow up: Experience at a single institution. Internal Medicine Journal 39:156-163.		✓	Retrospective chart review

Abbreviations: TSH, thyroid stimulating hormone

In addition, a grey literature search was undertaken to identify relevant international clinical practice guidelines and consensus documents for the management of patients with differentiated thyroid cancer. A list of included clinical practice guidelines is provided in **Table 10**. There were ten guidelines or consensus statements retrieved for review. Some were not available in English and required translation of the section pertaining to the diagnostic use of Thyrogen. Those that have been included for discussion in the results section are indicated by a tick (✓).

Table 10 International clinical practice guidelines

Country/region	Reference	Included in previous MSAC submission (1043)	Included in results
Asia Pacific	Sundram F, Robinson BG, Kung A *et al* (2006) Well-Differentiated Epithelial Thyroid Cancer Management in the Asia Pacific Region: A Report and Clinical Practice Guideline. Thyroid 16 (5):461-469.		✓
Europe (ESMO)	Pacini F, Castagna MG, Brilli L *et al* (2010) Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 21 (S5): 214-219.		✓
USA (ATA)	Cooper DS, Doherty GM, Haugen BR, *et al* (2009) Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 19 (11):1167-1214.		✓
Latin America (Thyroid Society)	Pitoia F, Ward L, Wohllk N *et al* (2009) Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer Arq Bras Endocrinol Metab. 2009;53(7):884-97		✓
Europe (European Association of Nuclear Medicine)	Luster M, Clarke SE, Dietlein M *et al* (2008) Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nuc Med Guidelines 35:1941-1959.		✓
UK (British Thyroid Association)	British Thyroid Association. Royal College of Physicians (2007) Guidelines for the management of thyroid cancer (2nd edition).		✓
Europe (European Thyroid Association)	Pacini F, Schlumberger M, Dralle H *et al* (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. European Journal of Endocrinology 154:787-803.		✓
France (Society for Endocrinology)	Society for Endocrinology (2007) Recommendations for the management of differentiated thyroid carcinoma of vesicular origin. Annals of Endocrinology 68; Supp2.		✓
Portugal (Society of endocrinology, diabetes and metabolism)	Rodrigues FJC, Limbert ES, Marques AP, *et al* (2005) Protocol for the treatment and follow-up of differentiated follicular thyroid carcinomas.		✓

Abbreviations: ESMO, European Society for Medical Oncology; EANM, European Association of Nuclear Medicine; USA, United States of America; ATA, American Thyroid Association

The literature search described above suggests there has been additional evidence published on the effectiveness of Thyrogen since the initial MSAC submission in 2002. Numerous clinical practice guidelines, prospective and retrospective case series have been identified which are discussed in detail in **Section 12**.

9.2 If there are other sources of evidence which support the proposed use of the service, please list them and provide copies.

A considerable number of the clinical experts and medical associations that manage thyroid cancer in Australia believe that the current MBS listing for Thyrogen is inappropriately restrictive and stress the clinical need for an amendment. This list of experts includes three members of the Supporting Committee that were involved in the initial MSAC assessment of Thyrogen (i.e. Professor Bruce Robinson; Professor Leigh Delbridge; and Associate Professor Monica Rossleigh).

An expert report which supports broadening the MBS indication for Thyrogen in Australia has been provided in **Section 14**.

Section 10 Summary of the evidence

10.1 From the literature search described in Section 9.1, provide a list of the studies which support the use of the service for the proposed indication(s). (You will usually need to attach this information.)

NA

10.2 Provide a summary of the evidence for the effectiveness and safety of the service based on the studies in 10.1.

NA

Section 11 Economic information

The economic analysis presented herein investigates the cost-utility of Thyrogen® stimulation compared to THT-withdrawal stimulated preparation for diagnostic testing with WBS and/or serum Tg testing.

The primary outcome of this analysis was the cost per QALY gained in all patients with well-differentiated non-metastatic thyroid cancer undergoing diagnostic testing using these two preparatory methods in initial and subsequent follow-up diagnostic tests.

The economic evaluation is presented in three steps to enhance the transparency of the analyses presented. These steps are as follows:

Step 1 (preliminary economic analysis) only captures the costs and effects accrued during the diagnostic testing period for both the Thyrogen and THT-withdrawal-stimulated arm over a 13 week period. This period is where the bulk of the incremental costs and benefits of the different methods of patient preparation are incurred.

Step 2 (20 year analysis) also captures the costs and effects accrued during the diagnostic testing period, however, Step 2 also captures any therapeutic radioiodine ablation episodes, the waiting periods between tests and ablation periods, the impact of poor compliance with follow up in the THT-withdrawal-stimulated arm and the impact of late stage cancer and premature cancer mortality.

Step 3 (lifetime analysis – base case) is identical to Step 2 except that the time horizon of the economic model is extended to the patient's lifetime. This analysis captures the full impact of premature mortality in this patient cohort.

The base case economic analysis shows that the incremental cost-effectiveness ratio (ICER) for Thyrogen-stimulated versus THT-withdrawal stimulation in all patients undergoing all diagnostic tests was ***$39,130 per QALY***.

This represents good value for money for the Australian Health Care System and allows cancer sufferers to comply with appropriate monitoring for disease recurrence without having to suffer the unnecessary debilitating effects of profound hypothyroidism.

The cost-effectiveness of Thyrogen remains stable when the input parameters to the economic model are modified over a range of plausible scenarios. Altering the probability of Thyroid cancer

mortality and the disutility associated with late stage cancer has little effect on the ICER as these outcomes occur late in the time horizon of the economic model and are heavily discounted. Similarly, the lifetime costs of Thyroid cancer treatment (which are applied in the economic model near the end of a patient's life) have little impact on the cost-utility of Thyrogen-stimulated versus THT-withdrawal stimulated diagnostic testing as these costs are also accrued late in the time horizon of the economic model and are heavily discounted.

The economic model appears modestly sensitive to the price of Thyrogen, the probability that patients are compliant with treatment in the THT-withdrawal stimulated arm of the economic model and the comparative sensitivity and specificity of rhTSH based diagnostic testing compared with THT-withdrawal stimulated testing. As the sensitivity and specificity of unstimulated Tg testing increases, the cost-effectiveness of rhTSH improves, primarily due to reduced follow up treatment costs.

11.1 Provide a list of all economic studies of the service identified in your literature search.

Literature searches were conducted to identify economic analyses that described the cost-effectiveness of Thyrogen for diagnostic use in patients with differentiated thyroid cancer. Searches of Embase.com (Medline and Embase) and the Cochrane Library were conducted on 25 November 2010. The search strategies used to identify pertinent publications are presented in **Table 5**.

There were 75 citations identified from Embase.com. A total of three publications were identified in the search of the Cochrane database.

Table 11 Literature search strategy to identify economic analyses of Thyrogen

No.	Query	Results	Date
EMBASE.com literature search			
#1	'recombinant thyrotropin'/exp OR 'thyrogen'/exp OR 'thyrotropin alpha' OR 'thyrotropin alfa-rch' OR 'recombinant thyroid stimulating hormone' OR 'recombinant human tsh'	837	24 Nov 2010
#2	'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'health economics'/exp OR 'health economics' OR 'cost minimization analysis'/exp OR 'cost minimization analysis' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'qaly'/exp OR 'qaly' OR 'life year saved'	488730	24 Nov 2010
#3	#1 AND #2	75	24 Nov 2010
Cochrane literature search			
#1	"'recombinant thyrotropin' OR 'thyrogen' OR 'thyrotropin alpha' OR 'thyrotropin alfa-rch' OR 'recombinant thyroid stimulating hormone' OR 'recombinant human tsh' AND 'Cost'	3	24 Nov 2010
	Duplicates	*3*	
	Total	***75***	

After the removal of a three duplicates a total of 75 citations were included for review. The inclusion criteria presented in **Table 12** were then applied.

Table 12 Inclusion and exclusion criteria and results

Inclusion / exclusion criteria	Excluded citations
The citation presents a description of a cost-effectiveness analysis comparing the use of Thyrogen stimulation with THT-withdrawal stimulation in the diagnostic setting (excludes general review articles, protocols, opinion pieces, general clinical guidelines, methodological studies, non-English articles).	56
The citation presents a cost-effectiveness analysis in the appropriate patient population (i.e, a representative sample of adult patients with differentiated thyroid cancer undergoing diagnostic testing – excludes therapeutic studies, paediatric studies, Graves' hyperthyroidism, Goiter, metastatic disease).	17
Included citations	**2**

After the application of these exclusion criteria a total of two pertinent publications were identified for inclusion (**Table 13**). Both of these publications discuss the same analysis conducted by MSAC in 2002 and later published in the ANZ Journal of Surgery by Blamey *et al,* in 2005. Therefore, from herein, these publications are referred to as MSAC 2002.

Table 13 Included citations

#	Citation
1	Blamey S, Barraclough B, Delbridge L, Mernagh P, Standfield L, and Weston A. (2005) Using recombinant human thyroid-stimulating hormone for the diagnosis of recurrent thyroid cancer. ANZ Journal of Surgery 75:10-20.
2	Medical Services Advisory Committee (2002) Recombinant human thyroid-stimulating hormone (rhTSH). Diagnostic agent for use in well-differentiated thyroid cancer

11.2 Make an assessment of the quality of the studies and their relevance to the Australian setting.

There are a number of areas in which the cost-effectiveness analysis conducted by MSAC in 2002 no longer reflects the clinical setting in which Thyrogen will be used in Australia in 2010. These changes include the following:

1. There have been new guidelines published supporting the diagnostic use of Thyrogen since the publication of the initial MSAC Assessment Report 2002. The MSAC Assessment report concluded that preparation with Thyrogen has a high level of concordance with THT-withdrawal-stimulated serum Tg and dxWBS. Importantly, the Assessment Report makes it abundantly clear that interpreting the diagnostic effectiveness of Thyrogen relative to the comparator is difficult when the comparator serves as the reference standard and is recognised as imperfect. This means that if a perfect reference standard were available, such that the patients true disease state was known with certainty, Thyrogen stimulated

testing may well prove to have an equivalent, or even improved, diagnostic accuracy to THT-withdrawal-stimulated testing. In these cases the extent of concordance is more relevant. In fact, this is reflected in the recent update of the American Thyroid Association Guidelines (Level A recommendation) (Cooper *et al*, 2009), the European Thyroid Association (Pacini *et al*, 2006) and the European Association of Nuclear Medicine (Luster *et al*, 2008) which conclude that Thyrogen stimulated and THT-withdrawal-stimulated testing are equivalent in terms of diagnostic performance. This guidance has altered current practice such that an initial diagnostic test using THT-withdrawal stimulation rather than Thyrogen stimulation (i.e. as specified in the current MBS indication) is no longer considered necessary in Australia.

2. The price of Thyrogen has decreased to $1755.06 ex-manufacturer; $1825.00 price to pharmacist; $1901.42 dispensed price per maximum quantity (a reduction of 7% from the initial submission). This is the price at which Thyrogen is now reimbursed through the PBS. Therefore the MSAC 2002 analysis no longer accurately reflects the true price and cost-effectiveness of Thyrogen in Australia in 2011.

3. Thyrogen received a positive recommendation by the PBAC in 2007 and is now reimbursed by the PBS for avoidance of hypothyroidism prior to the ablation of thyroid remnant tissue in post thyroidectomy adults. This assessment is pertinent to the diagnostic setting as it provides an independent assessment of the magnitude of the QALY benefits that are likely to be realised in patients that avoid hypothyroidism by using Thyrogen in the diagnostic setting. The disutility associated with the period of THT-withdrawal stimulation is the same irrespective of whether the patient is being prepared for ablation or diagnostic monitoring.

4. The MSAC 2002 economic analysis included ablation in the diagnostic model, however, at the time of the analysis Thyrogen stimulation was not approved for use in the ablation setting and, therefore, patients in the MSAC 2002 economic model received ablation after a period of thyroid hormone therapy withdrawal (i.e. THT-withdrawal stimulation). This is no longer an accurate reflection of clinical practice in Australia today as the majority of these patients will now undergo ablation after preparation with Thyrogen stimulation.

5. The secondary economic model presented in the MSAC 2002 report assumed that patients received three Thyrogen stimulated or THT-withdrawal-stimulated tests at 6, 12 and 36 months post-surgery and ablation. Current expert advice suggests that patients only receive two Thyrogen stimulated or THT-withdrawal-stimulated tests post surgery, one at around 8-12 months (~10 months after treatment) and then 12-24 months later (or a total of ~28 months after initial surgery and ablative treatment).

6. The TGA listing for Thyrogen has been substantively altered, such that Thyrogen is now indicated for use in conjunction with "serum thyroglobulin (Tg) testing, with or without radioactive iodine imaging" where previously Thyrogen was only indicated for use in Tg testing in conjunction with radioactive iodine imaging.

7. The primary analysis in the MSAC 2002 report was for patients who had one prior negative test using THT-withdrawal-stimulation. The present application is for the use of Thyrogen inclusive of this first diagnostic test.

Therefore, a new economic analysis was developed that appropriately incorporates these changes in diagnostic performance, unit costs and clinical practice.

11.3 List the components of the service and their respective costs as well as the source(s) of information used to derive the costs.

Thyrogen is currently reimbursed through MBS under item number 12201 (**Table 14**). MBS item number 12201 captures a number of costs, including the cost of: 1) Thyrogen – powder for injection 0.9 mg × 2 vials; 2) Thyrogen administration; 3) specialist attendances associated with the preparation, scheduling and follow up of patients undergoing dxWBS and Tg testing; 4) arranging the dxWBS; and, 5) arranging the Tg test.

It is important to note that many of these costs (components 3–5) will be borne by the MBS regardless of whether or not the patient is undergoing Thyrogen-stimulated testing or THT-withdrawal-stimulated testing. Furthermore, as Thyrogen allows for more predictable timing of stimulation than THT-withdrawal it is likely that the patient will require fewer specialist attendances to ascertain patient TSH-stimulation levels to determine the optimal timing for diagnostic testing.

11.4 State the proposed fee for the service and the reasons why this fee is deemed appropriate.

Table 14 lists the current dispensed price per maximum quantity for thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) powder for injection 0.9 mg × 2 vials. This price is inclusive of the seven percent decrease in the price of Thyrogen agreed for the ablative use of Thyrogen as reimbursed through the PBS. Therefore, the Sponsor is requesting that Thyrogen stimulation is reimbursed at the same price as it is currently reimbursed through the PBS and as shown in **Table 14**.

Table 14 also presents the additional costs captured in MBS Item number 12201. As the Sponsor was not privy to the calculations underpinning the final derivation of these costs, the magnitude of the additional costs have been ascertained by simply subtracting the price of Thyrogen (DPMQ) from the current total MBS Item fee. The reader is reminded that many of these additional costs will be borne by the MBS regardless of whether or not the patient is undergoing Thyrogen-stimulated testing or THT-withdrawal-stimulated testing.

Whole body scanning using radioiodine (MBS Item 61426) and thyroglobulin testing (MBS Item 66650) are currently reimbursed through the MBS. As these diagnostic tests are used in conjunction with Thyrogen stimulation the current fees for these items are also presented in **Table 14**.

Table 14 Fees for Thyrogen and related unit costs

Item	Unit cost	Source
Thyrogen stimulation		
Thyrotropin alfa-rch: (recombinant human thyroid-stimulating hormone) powder for injection 0.9 mg × 2 vials	$1901.42	PBS Item 2700 D (DPMQ)
Additional costs: Initial and subsequent specialist attendances at which Thyrogen is administered[a] and co-ordination of radioiodine WBS and Tg tests.	$400.83	Calculated (Total MBS Item fee - Thyrogen DPMQ; $2302.25-$1901.42=$400.83)
Proposed Total fee for Thyrogen and associated clinician costs	***$2302.25***	***Identical to current MBS Item 12201***
Diagnostic test fees		
Whole body study using radioiodine	$554.80	MBS 61426 (includes radio-pharmaceutical)
Thyroglobulin (Tg) test	$24.50	MBS 66650

[a]Where thyrotropin alfa-rch is injected by the administering practitioner, benefits are not payable for an attendance on the day the second dose is administered. Where thyrotropin alfa-rch is injected by: a general practitioner - benefits are payable under a Level A consultation (item 3); other practitioners - benefits are payable under Item 52.

11.5 State the fee for the comparator.

As discussed previously, the cost of the comparator treatment (THT-withdrawal stimulation) consists of many of the same resource use items as required in the Thyrogen-stimulation-based testing. However, these costs will be borne by the MBS and claimed through a range of MBS item numbers that are not specific to THT-withdrawal. These resource use items include: 1) specialist attendances associated with the preparation and follow up of patients undergoing this diagnostic process – including additional clinician attendances to ascertain patient stimulation levels to determine the optimal timing for diagnostic testing; 2) arranging the dxWBS; and, 3) arranging the Tg test. Given that these procedures are not captured in a specific THT-withdrawal-stimulated related MBS item number, it is assumed the costs associated with THT-withdrawal are the same as

the *additional costs* listed in **Table 14** (i.e. the difference in cost between the Thyrogen MBS fee (Item 12201) and the cost of Thyrogen itself). This assumption is tested in sensitivity analysis in **Section 11.6** of this submission.

Again, as WBS using radioiodine and thyroglobulin testing are used in conjunction with THT-withdrawal the current fees for these items are presented in **Table 15**.

Table 15 Fees for Comparator and related unit costs

Item	Unit cost	Source
THT-withdrawal-stimulation		
Initial and subsequent specialist attendances, monitoring of TSH levels to determine optimal timing of WBS and Tg test. Co-ordination of WBS and Tg tests.	$400.83	Calculated
Average number of TSH tests = 1.1	$27.72	PBAC submission 2006, MBS 66650
Total fee for the comparator	***$428.55***	***Calculated see Table 14***
Diagnostic test fees		
Whole body study using radioiodine	$554.80	MBS 61426 (includes radio-pharmaceutical)
Thyroglobulin (Tg) test	$24.50	MBS 66650
Thyroglobulin (Tg) antibody test	$34.80	MBS 71165

Abbreviations: THT, Thyroid hormone therapy; TSH, Thyroid Stimulating Hormone
[a]Where thyrotropin alfa-rch is injected by the administering practitioner, benefits are not payable for an attendance on the day the second dose is administered. Where thyrotropin alfa-rch is injected by: a general practitioner - benefits are payable under a Level A consultation (item 3); other practitioners - benefits are payable under Item 52

11.6 Provide a formal economic evaluation if required.

11.6.1 Introduction

An economic evaluation comparing the cost-utility of Thyrogen-stimulated compared to THT-withdrawal-stimulated diagnostic testing for well-differentiated thyroid cancer is provided within this Section of the submission. Where appropriate the economic analysis has been altered and updated to address the issues raised in the final decision analytic protocol (DAP).

11.6.2 Population reflected in the economic evaluation

The study population reflected in the publication by Haugen *et al*, 1999 and described more fully in the *post hoc* analyses conducted in the MSAC 2002 report matches the population included in the economic evaluation well. This is the population receiving their initial surgery and post-ablation scan. A comparison of the population captured in the clinical study and in the economic analysis is presented in **Table 16**.

Table 16 Comparison of populations captured in the clinical study and in the economic analysis

Trial ID	Does the trial include patients appropriate for the economic analysis?	Is the age of patients consistent with the Australian approved PI?	Is the dose of medication used in the patients consistent with the Australian approved PI?	Does the study include the correct comparator?	Does the study include the appropriate diagnostic tests?	Are the key efficacy outcomes measured appropriately?
Haugen *et al*, 1999 & *post hoc* analyses presented in MSAC 2002	Yes. The trial includes patients with non-metastatic well-differentiated thyroid cancer that are undergoing their initial post-treatment diagnostic scan	Yes. The trial included adult patients with a mean age of 44 years (arm 1). This is slightly younger than the mean age at diagnosis in Australia ~49.2 years; CINSW 2008	Yes/No. Only study arm 1 included the approved dosage and schedule of Thyrogen use. Therefore, only this arm of the trial is pertinent to the current submission.	Yes. The study uses thyroid hormone therapy withdrawal stimulation as the comparator	Yes. The study reports the use of radioiodine WBS and serum Tg tests.	Yes. The key outcomes reported in these publications included: sensitivity, specificity, and accuracy. However, as noted in the MSAC 2002 report these measures are determined through comparison with an imperfect reference standard that also acts as the comparator. This biases the results of these analyses against Thyrogen.

11.6.3 Generation of the base case economic analysis

The economic evaluation is presented in three steps to enhance the transparency of the analyses presented. Details of these steps are presented below.

Step 1: Preliminary economic analysis

This economic analysis only captures the costs and effects accrued during the diagnostic testing period for both the Thyrogen-stimulated and THT-withdrawal-stimulated arm (13 weeks; **Table 17**). This analysis does not capture any costs or effects associated with any potential differences in diagnostic performance of the Thyrogen-stimulated or THT-withdrawal-stimulated methods of preparing patients for diagnostic testing. Further, this analysis does not capture the differences in costs associated with poor compliance with follow-up testing in the THT-withdrawal-stimulated arm, nor the resultant effects poor compliance with follow-up has on a patient's ultimate prognosis.

Step 2: Twenty year analysis

Like **Step 1**, this economic analysis captures the costs and effects accrued during the diagnostic testing period. However, **Step 2** also captures the costs and effects of any therapeutic radioiodine ablation episodes that the patient may have (**Table 17**). In addition to this **Step 2** also captures the costs and effects accrued during the waiting periods between tests and ablation periods and in low risk patients that leave active follow up (i.e. patients with two consecutive negative tests). Furthermore, **Step 2** also capture the costs and effects accrued in patients that are not compliant with follow up due to the side effects associated with hypothyroidism in the THT-withdrawal-stimulated arm. Finally, this analysis captures the costs and effects of late stage cancer and premature cancer mortality. This analysis is limited to a time horizon of 20 years and, therefore, does not capture the full impact of premature cancer mortality on the patient cohort of interest.

Step 3: Lifetime analysis (base case)

Step 3 is identical to **Step 2** except that the time horizon of the economic model is extended to the patient's lifetime (**Table 17**). This analysis captures the full impact of premature mortality in this patient cohort.

Table 17 Steps included in the economic analysis

Step	Costs	Outcomes	Time-frame
Step 1: *Preliminary analysis*	***Diagnostic costs*** Thyrogen (Thyrogen-stimulated arm only) Clinician visits (diagnostic) Clinician visits for hypothyroid management (THT-withdrawal-stimulated arm only) T4 T3 (THT-withdrawal-stimulated arm only) Radioiodine whole body scan Serum Tg test Tg antibody test TSH test (THT-withdrawal-stimulated only)	QALYs accrued during: hypothyroid / euthyroid diagnostic testing period only	13 weeks

Step	Costs	Outcomes	Time-frame
Step 2: *Twenty year analysis*	***Diagnostic costs*** Thyrogen (Thyrogen-stimulated arm only) Clinician visits (diagnostic) Clinician visits for hypothyroid management (THT-withdrawal-stimulated arm only) T4 T3 (THT-withdrawal-stimulated arm only) Radioiodine whole body scan Serum Tg test Tg antibody test TSH test (THT-withdrawal-stimulated only) ***Therapeutic costs*** Thyrogen (Thyrogen-stimulated and THT-withdrawal-stimulated arms) Clinician visits (therapeutic) T4 Radioiodine ablation Time in radioprotective ward Post-ablation radioiodine whole body scan Post-ablation serum Tg tests Post-ablation Tg antibody test ***Between tests, after testing and non-compliant costs*** T4 ***Late stage cancer costs*** Life time costs of cancer treatment	QALYs accrued during: Hypothyroid / euthyroid diagnostic testing period During radioiodine ablation period Between diagnostic tests and radioiodine treatment After testing is complete up to a 20 year time horizon In non-compliant patients up to a 20 year time horizon In patients with late stage cancer to up to a 20 year time horizon	20 years

Step	Costs	Outcomes	Time-frame
Step 3: *Lifetime analysis (base case)*	***Diagnostic costs*** Thyrogen (Thyrogen-stimulated arm only) Clinician visits (diagnostic) Clinician visits for hypothyroid management (THT-withdrawal-stimulated arm only) T4 T3 (THT-withdrawal-stimulated arm only) Radioiodine whole body scan Serum Tg test Tg antibody test TSH test (THT-withdrawal-stimulated only) ***Therapeutic costs*** Thyrogen (Thyrogen-stimulated and THT-withdrawal-stimulated arms) Clinician visits (therapeutic) T4 Radioiodine ablation Time in radioprotective ward Post-ablation radioiodine whole body scan Post-ablation serum Tg tests Post-ablation Tg antibody test ***Between tests, after testing and non-compliant costs*** T4 ***Late stage cancer costs*** Life time costs of cancer treatment	QALYs accrued during: Hypothyroid / euthyroid diagnostic testing period During radioiodine ablation period Between diagnostic tests and radioiodine treatment After testing is complete up to end of life In non-compliant patients up to end of life In patients with late stage cancer to end of life	Lifetime

11.6.4 Type of economic evaluation

As discussed in **Section 12** patients that undergo diagnostic testing with Thyrogen stimulation avoid the significant morbidity and consequent reduction in preference-based quality of life (utility) associated with THT-withdrawal stimulation which renders a patient hypothyroid. Furthermore, the evidence presented in this submission shows that the diagnostic performance of WBS and Tg testing is broadly equivalent regardless of which method is used to prepare the patient for these tests.

In summary, Thyrogen stimulation significantly reduces patient morbidity, thereby improving a patient's utility without reducing the diagnostic performance of the radioiodine WBS and Tg tests. Thyrogen stimulation also improves patient compliance with follow-up testing, thereby increasing detection of recurrent disease. Therefore, a cost-effectiveness analysis is appropriate for this submission. Specifically, the economic analysis presented herein takes the form of a cost-utility analysis.

11.6.5 Perspective of the economic evaluation

The economic model presented herein takes a whole of healthcare perspective and only captures direct health care costs. While the morbidity associated with hypothyroidism is known to be associated with substantial productivity losses, these have not been captured in the economic evaluations presented herein. This is a conservative assumption and favours the THT-withdrawal-stimulated arm of the economic model.

11.6.6 Software package and electronic version of the economic model

A total of four electronic files are included with this submission. **Step 1** (preliminary economic evaluation) of the economic evaluation was built in Microsoft® Office Excel® 2007. **Step 2** and **3** of the economic evaluation were constructed in TreeAge Pro 2009. Calculations used to support the analyses in **Step 2** and **3** are presented in an accompanying Microsoft® Office Excel® workbook.

Table 18 List of electronic files accompanying this submission

File description	File name	File format
Step 1: Preliminary economic evaluation comparing Thyrogen and THT-withdrawal diagnostic tests	Step 1 Preliminary economic analysis Thyrogen (Final).xls	Microsoft® Office Excel® 2007
Step 2: 20 year economic evaluation comparing Thyrogen and THT-withdrawal diagnostic tests	Step 2 20 year economic analysis Thyrogen (Final).pkg	TreeAge Pro 2009
Step 3: Base case. Life time evaluation comparing Thyrogen and THT-withdrawal diagnostic tests	Step 3 Life time economic analysis Thyrogen (Final).pkg	TreeAge Pro 2009

File description	File name	File format
Supportive calculations for the Thyrogen economic evaluation	Supportive calculations Thyrogen (Final).xls	Microsoft® Office Excel® 2007

11.6.7 Structure of the economic model

A generalised structure of the economic model used in the base case analysis (**Step 3**) is presented in **Figure 9** below. **Figure 10** shows a simplified version of the economic model as it has been designed in TreeAge 2009.

All patients enter the model at the time of their initial post surgery / ablation diagnostic test with WBS and Tg. This scan occurs between 8–12 months post-treatment. For the purposes of this analysis it is assumed that these tests occur 10 months after the initial treatment for well-differentiated thyroid cancer. At this initial 10-month diagnostic test patients may return one of four possible test results: true positive, true negative, false positive or false negative. In the base case analysis the current evidence and clinical practice guidelines show that these tests have equal sensitivity and specificity regardless of the method used to prepare patients for these tests (i.e. Thyrogen stimulation or THT-withdrawal stimulation). For the purposes of the base case analysis, Tg and WBS are assumed to have perfect sensitivity and specificity regardless of the preparatory method used for these tests such that none of the cohort record false positive or false negative results at this 10 month test.

Patients with a true positive or false positive test result receive Thyrogen-stimulated radioiodine ablation (i.e. under the current PBS indication for Thyrogen). After this treatment, these patients return to the beginning of the model and are followed up 10 months after treatment with a stimulated Tg and WBS diagnostic test.

Patients with a true negative or false negative test result wait until the next test which occurs 12-24 months after the initial 10 month diagnostic scan. For the purposes of this model this is assumed to occur at 18 months after the initial scan (or 28 months after the patient receives their initial surgical/ablative treatment).

In the base case the 28 month stimulated scan is assumed to be conducted with stimulated Tg alone. Again these patients can return one of four test results: true positive, true negative, false positive or false negative. In the base case analysis the current evidence and clinical practice guidelines show the Tg test has equal sensitivity and specificity regardless of the method used to prepare patients for these tests (i.e. Thyrogen stimulation or THT-withdrawal stimulation). For the purposes of the base case analysis, the Tg test is assumed to have equal sensitivity (i.e. at 81%; **Table 21**) and perfect specificity (100%; **Table 21**) regardless of the preparatory method used for

these tests. Therefore, in the base case no patients return a false positive result, however, some patients return a false negative result.

Again, patients that return a true positive or false positive test result receive stimulated radioiodine treatment. After this therapy, these patients return to the beginning of the model and are followed up 10 months after treatment with a stimulated Tg and WBS diagnostic test.

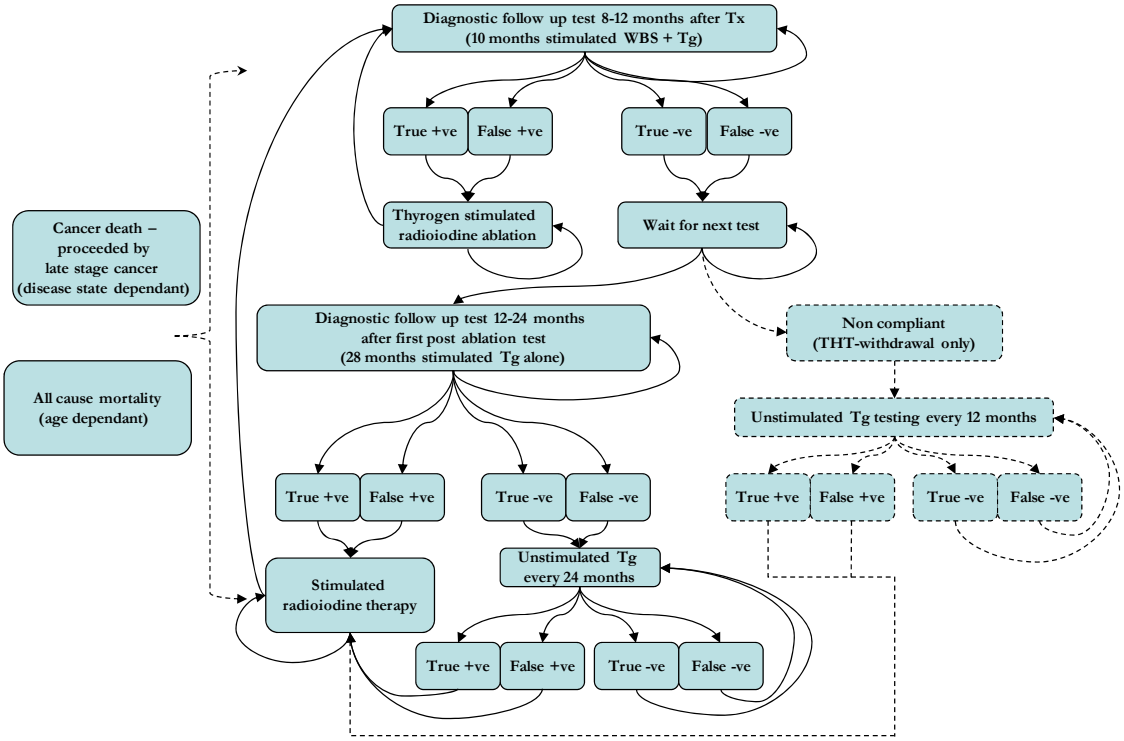
Patients that return a true negative or false negative result (i.e. their second negative test) are considered to be at low risk and move to less intensive follow up. This low intensity follow-up includes unstimulated Tg testing every 24 months. The economic model now explicitly models the diagnostic performance of these tests using sensitivity and specificity data reported by Schlumberger *et al*, 2007. As with previous tests patients may return a true positive or false positive test result at which point they are treated with thyrogen-stimulated radioiodine ablation (i.e. under the current PBS indication for Thyrogen). After this treatment, these patients return to the beginning of the model and are followed up 10 months after treatment with a stimulated Tg and WBS diagnostic test. Patients that return a true negative or false negative test result then wait until the next unstimulated Tg test is scheduled in 24 months.

A clinician treatment survey was conducted to determine the proportion of patients that are non-compliant to THT-withdrawal-stimulated testing. An average of 14.4% (95% CI: 13.3–15.4%) of the patients managed by these clinicians were non-compliant to THT-withdrawal stimulated diagnostic testing due to the negative effects of hypothyroidism. In line with this finding the proportion of patients that are non-compliant with THT-withdrawal testing at 28 months has been reduced from 20% to 14.4% in the base case of the economic model. Diagnostic follow-up in these patients consists of an unstimulated Tg test every 12-months. The economic model now explicitly models the diagnostic performance of these tests using sensitivity and specificity data reported by Schlumberger *et al*, 2007. Again, as with previous tests patients may return a true positive or false positive test result at which point they are treated with thyrogen-stimulated radioiodine ablation (i.e. under the current PBS indication for Thyrogen). After this treatment, these patients return to the beginning of the model and are followed up 10 months after treatment with a stimulated Tg and WBS diagnostic test. Patients that return a true negative or false negative test result then wait until the next unstimulated Tg test is scheduled in 12 months.

Throughout the economic model patients have a probability of dying from thyroid cancer. This probability is dependent on the patient's true disease state and their level of compliance with

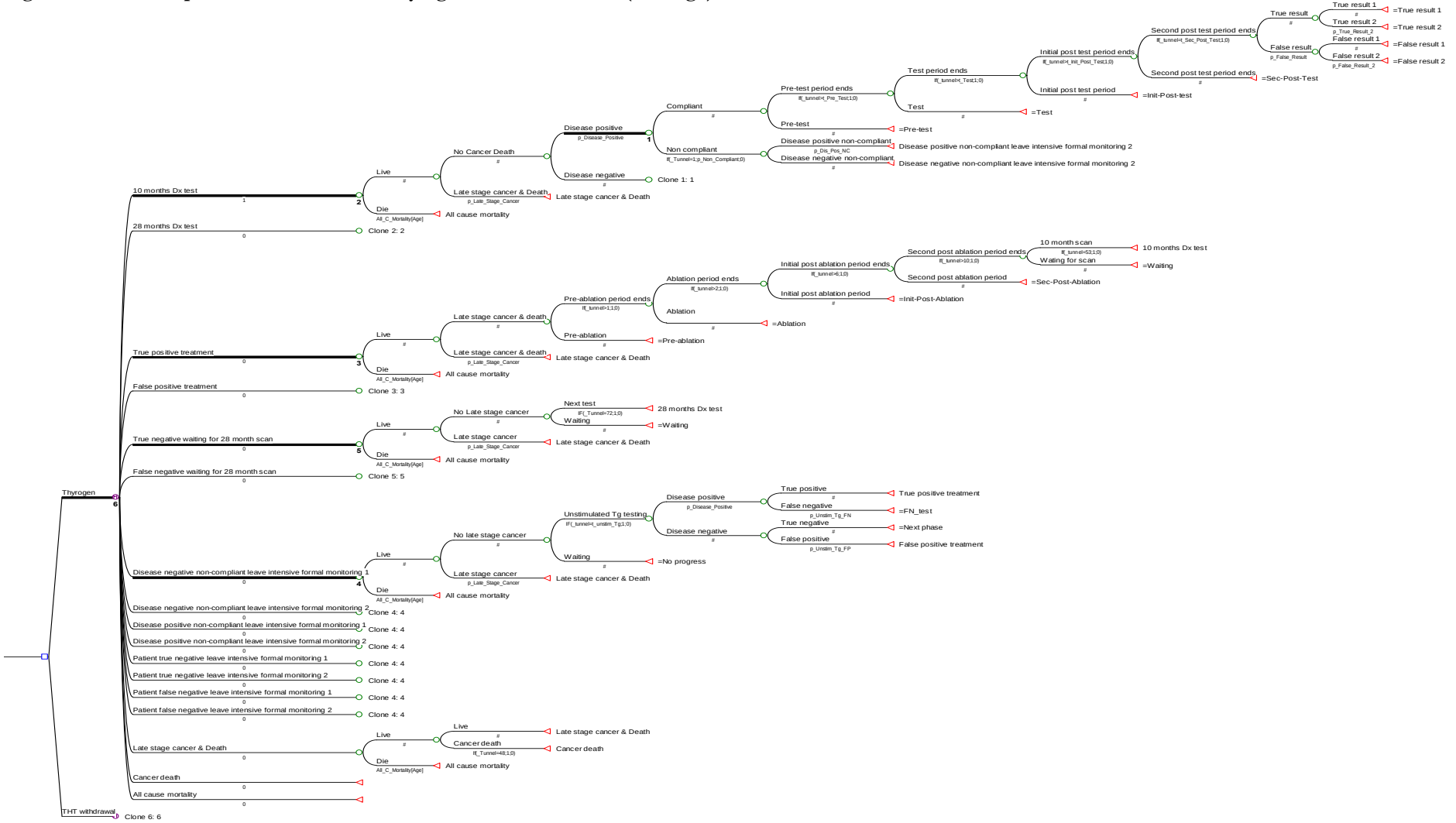
monitoring for recurrent disease (see **Figure 11**). All patients also have a probability of dying from other causes over the modelling period (i.e. all-cause mortality; ABS, 2010[1]).

Figure 9 Generalised structure of the Thyrogen economic model



[1] www.abs.gov.au

Figure 10 Simplified structure of the Thyrogen economic model (TreeAge)



11.6.8 Time horizon of the economic evaluation

Step 1 of the economic evaluation employs a time horizon of 13 weeks. This time horizon is based on the duration required for a patient to prepare for diagnostic testing, complete diagnostic testing and return to a normal utility level. The duration of this analysis is based on the Thyrogen submission for ablation submitted to the PBAC in 2006. Complete details of the phases this cohort of patients traverses during this 13 week period are presented in **Table 19**.

During this 13 week period patients in the comparator arm are withdrawn from THT in preparation for diagnostic testing (i.e. *pre-test period* = 4 weeks), then the patient receives the diagnostic test/s (*test-period* = 1 week) and then recovers from the hypothyroid state and gradually returns to the euthyroid state (*Initial post-test period* = 4 weeks and *Second post-test period* = 4 weeks).

In the Thyrogen stimulation arm of this analysis patients remain euthyroid (as they remain on thyroid hormone therapy). As patients do not have to wait until THT-withdrawal stimulation renders them hypothyroid, the *pre-test* period lasts a total of 1 week. As in the THT-withdrawal-stimulated arm patients then receive the diagnostic test/s (*test-period* = 1 week) and then recover gradually returning to a normal utility level (*Initial post-test period* = 4 weeks and *Second post-test period* = 4 weeks).

Table 19 Description of time-horizon by period, Step 1 economic evaluation

Description of period	Time (weeks)		Source
	THT withdrawal	rhTSH Test	
Pre-test period	4.0	1.0	PBAC Thyrogen submission 2006
Test period	1.0	1.0	
Initial post-test period	4.0	4.0	
Second post-test period	4.0	4.0	
General monitoring	0.0	3.0	
Total	**13.0**	**13.0**	

In **Step 2** of the economic evaluation the time-horizon is extended to twenty years. This allows the model to capture not only the diagnostic phase of testing (as presented in **Step 1**) but also downstream costs and effects associated with the follow up of patients being monitored for recurrent thyroid cancer. This version of the model allows exploration of the resource use and the health outcome implications of differing diagnostic test performance and compliance levels with follow up in sensitivity analyses (See **Section 11.6**). However, as this analysis is limited to a time horizon of 20 years it does not capture the full impact of premature cancer mortality on the patient cohort of interest.

Step 3 of the economic evaluation is identical to **Step 2** in that it allows the exploration of the implications of any potential differences in the diagnostic testing modalities, however, in this analysis the time horizon is extended to the patient's lifetime. Specifically, the model runs for 56 years allowing patients to live a maximum period of 100 years before the model terminates (as patients enter the model at a mean age of ~49.2 years (Tracey *et al*, 2008)). However, it should be noted that while it is possible for a patient to live to 100 years before model termination, the model is underpinned by all cause mortality data from Australian specific actuarial life tables (ABS, 2010) which ensure that the proportion of the cohort that survives to this age is small and accurately reflects survival in Australia. As this economic evaluation has a lifetime time-horizon it more fully captures the impact of premature cancer mortality in this patient cohort.

11.6.9 Outcomes used in the economic evaluation

As the primary benefit of Thyrogen stimulation is to allow patients to avoid the debilitating effects of hypothyroidism with THT-withdrawal and thereby improve the patient's quality of life and utility, it was important that all steps in the economic evaluation captured this outcome appropriately. Therefore, in **Steps 1–3** of the economic evaluation the economic models measure patient utility accrued over time, thereby generating quality-adjusted life year (QALY) estimates.

11.6.10 Modelling methods used to generate the results

In **Step 1** of the economic evaluation a simple economic 'model' has been developed. The model consists of weekly periods in which costs and QALYs are accrued. A full description of the duration of each of these periods is presented in a tabulated format in **Table 19**. The utility weights applied in each of these periods are presented in **Table 22** and the unit costs applied in the economic model are presented in **Table 20**. It is likely that the inclusion of the life time cost of thyroid cancer treatment will result in some double counting, however, like all cancers the vast majority of these costs are likely to be borne towards the end of the patient's life. To attempt to account for this the lifetime cost of thyroid cancer is reduced by 20% in the base case and a threshold analysis is conducted to explore the impact reducing these costs has on the cost-effectiveness of rhTSH (**Figure 15**).

These costs and QALY values are then simply summed over the 13 week time horizon for both the Thyrogen-stimulated and THT-withdrawal-stimulated arm of the economic model. These cumulative values reflect the cost and effectiveness of each intervention and are used to generate a summary incremental cost-effectiveness ratio (ICER). As the time-horizon of this model is less than 1 year, discounting was not applied. For simplicity, half cycle correction was not employed in this analysis.

Step 2 and **3** of the economic evaluation employ a Markov Cohort expected value analysis. The economic model has weekly cycles and runs for a total of 20 years in **Step 2** and the cohort's life time in **Step 3**. The economic model presented in **Step 2** and **3** employ a number of tunnel states (i.e. a series of temporary health states) which allow the time in particular health states to be specified and the Markovian assumption to be relaxed. Furthermore, time dependant probabilities are also employed in the economic model, which also serves to relax the Markovian assumption.

Both costs and effects are discounted at 5% per annum, in line with the PBAC and MSAC guidelines for economic analyses. The impact of discounting is explored in sensitivity analysis. Half-cycle correction is employed in **Steps 2** and **3** of the economic evaluation, as appropriate.

11.6.11 Unit costs applied in the economic model

As noted by PASC, it is likely that the inclusion of the life time cost of thyroid cancer treatment will result in some double counting, however, like all cancers the vast majority of these costs are likely to be borne towards the end of the patient's life. To attempt to account for this the lifetime cost of thyroid cancer is reduced by 20% in the base case and a threshold analysis is conducted to explore the impact reducing these costs has on the cost-effectiveness of rhTSH (Figure **15).**

Table 20**Table 20** lists the unit costs applied in the economic model along with their sources. These unit costs are presented by resource use type. The majority of unit costs presented were sourced from the PBS or the MBS in Australia. A day in a radioprotective ward (which is only applied to patients that undergo radioiodine ablation in the economic model) was sourced from the thyrogen therapeutic submission to the PBAC in November 2006 and based on data from the Transition Hospital Costing System from the Austin & Repatriation Medical Centre in Melbourne, Australia. The lifetime cost of thyroid cancer was sourced from the Australian Institute of Health and Welfare (AIHW) report on *Health system expenditures on cancer and other neoplasms in Australia*, published in 2005.

As noted by PASC, it is likely that the inclusion of the life time cost of thyroid cancer treatment will result in some double counting, however, like all cancers the vast majority of these costs are likely to be borne towards the end of the patient's life. To attempt to account for this the lifetime cost of thyroid cancer is reduced by 20% in the base case and a threshold analysis is conducted to explore the impact reducing these costs has on the cost-effectiveness of rhTSH (**Figure 15**).

Table 20 Unit costs applied in the economic model

Item description	Unit cost	Source
Medication costs		
MBS rhTSH alone	$1,901.42	Identical to PBS 2700D DPMQ
MBS rhTSH additional costs	$400.83	Calculated: MBS 12201fee - PBS DPMQ

Item description	Unit cost	Source
MBS rhTSH total	$2,302.25	MBS 12201 (incorporates specialist visits and co-ordination of WBS+Tg)
PBS rhTSH	$1,901.42	PBS 2700D
T4 (per pack)	$27.43	PBS 2173J (200 mg × 200 tablets)
T4 (per week – model cycle)	$0.96	Calculated (200 mg per day × 7 days)
T3 (per pack)	$83.53	PBS 2318B (20 ug × 100 tablets)
T3 (per week – model cycle)	$17.54	Calculated (60 ug per day × 7 days)
Consultation costs		
GP visit	$16.00	MBS 3 (Level A visit)
GP visit	$34.90	MBS 23 (Level B visit)
Specialist visit	$82.30	MBS 104 (initial)
Specialist visit	$76.40	MBS 108 (continuing)
Diagnostic tests		
^{131}I Whole body scan	$554.80	MBS 61426 (includes radiopharmaceutical)
Thyroglobulin (Tg) test	$24.50	MBS 66650
Thyroglobulin (Tg) antibody test	$34.80	MBS 71165
Thyroid stimulating hormone (TSH) level measurement	$25.20	MBS 66716
Therapeutic procedures		
^{131}I ablation	$480.95	MBS 16006
Hospitalisation costs		
Day in radioprotective ward (2006)	$1,125.00	PBAC submission November 2006 (Transition Hospital Costing System, Austin & Repatriation Medical Centre, Melbourne)
Day in radioprotective ward (inflated to 2010 prices)	$1,376.83	Inflated using Health CPI December 2001, June 2010 (Series ID: A2331111C)
Other costs		
Life time thyroid cancer cost	$8,792.00	AIHW 2005
Life time thyroid cancer cost (inflated to 2010 prices)	$14,122.25 × 0.8 = $11,297.80	Inflated using Health CPI December 2001, June 2010 (Series ID: A2331111C). Total cost reduced by 20% to account for double counting.

11.6.12 Probabilities applied in the economic model

Table 21 presents the probabilities applied in **Step 2** and **3** of the economic model along with their sources. As the preliminary economic model presented in **Step 1** of the economic evaluation is quite straightforward in nature and does not include the relative diagnostic performance of Thryogen stimulation and THT-withdrawal stimulation, or patient compliance, or mortality, the probability inputs presented in **Table 21** are not relevant to its construction.

Recent estimates from the Cancer Institute of NSW suggest that women constitute around 79% of the Thyroid cancer population diagnosed in the last five years. These data have been used to adjust the actuarial life table applied in the economic model to accurately reflect this gender imbalance in the cohort of interest. The MSAC 2002 evaluation of Thyrogen stimulation for diagnostic use estimated that 50% of patients tested positive for disease at their first post-ablation follow-up scan.

This estimate is supported by the publication by Haugen *et al*, 1999 which found that 49% of patients had a positive WBS at their first post-ablation diagnostic test. The MSAC 2002 evaluation estimated that 20% of patients were disease positive when they reached their second post-ablation follow-up scan. It is important to note that this estimate captures not only those patients in which disease has re-occurred but also those patients that that have remnant thyroid tissue (i.e. incomplete ablation), as one cannot determine unequivocally whether these patients do or do not have residual or recurrent cancer. Furthermore, both of these patient groups are treated in the same manner in clinical practice (i.e. with repeat radioiodine ablation). However, as requested in the DAP, the proportion of patients that are disease/remnant positive has been reduced. Further, it is reasonable to expect that after a patient tests positive and has another round of ablation the probability of a patient testing disease/remnant positive tests will decrease markedly. Therefore, the model has been respecified so that at the first analysis the probability of testing disease positive is halved (i.e. 25%), and from then on the probability of disease positivity decreases again to half that initially estimated as the disease positivity rate for the 28 month test in the original MSAC evaluation (i.e. 20%/2 =10%) and then to 5% at subsequent 28 month scans. As there is some uncertainty surrounding these estimates the impact of altering these values is explored in a threshold analysis in sensitivity analyses presented in **Section 11.6.15.6** (**Figure 16**) of this submission.

The diagnostic performance of Thyrogen stimulation versus THT-withdrawal stimulation is assumed to be identical in all Steps of the economic evaluation. This assumption is supported by the evidence presented in **Section 12** (showing a high level of concordance between Thyrogen stimulated and THT-withdrawal stimulated testing) and the current clinical practice guidelines for the diagnostic use of Thyrogen stimulation in patients with well differentiated Thyroid cancer (see **Table 12**). However, in sensitivity analysis (**Section 11.6**), these diagnostic performance measures are substituted with the conservative estimates of diagnostic performance based on the imperfect reference standard presented in the MSAC 2002 submission to determine the impact of assuming a lower sensitivity and specificity for Thyrogen stimulation versus THT-withdrawal stimulation.

The diagnostic performance of unstimulated Tg testing in patients that have had two sequential negative tests for thyroid cancer (i.e. at 10 months and 28 months) or who are non-compliant with THT-withdrawal monitoring in the comparator arm was derived from the publication by Schlumberger *et al*, 2007. This publication reports the sensitivity and specificity of standard and highly sensitive unstimulated Tg testing in patients at low risk of disease progression. These data were weighted by the proportion of standard (34%) and highly sensitive unstimulated Tg testing (66%) use reported in the clinician survey conducted for this application (**Appendix 1**). Full details of these calculations are provided in the accompanying spreadsheet <*Supportive calculations Thyrogen (Final).xls*>. The impact of altering these estimates is explored in sensitivity analyses.

The probability of disease progression in low risk patients (i.e. patients that have had two sequential negative tests for thyroid cancer (i.e. at 10 months and 28 months) was also derived from the publication by Schlumberger *et al*, 2007. This publication found that a total of 30/944 (3.2%) low risk patients had recurrent disease at a mean follow-up time of 28 months. This value was then adjusted to suit its application in the economic model (i.e. to a biennial or annual probability as appropriate). Again, full details of these calculations are provided in the accompanying spreadsheet <*Supportive calculations Thyrogen (Final).xls*>. The impact of altering these estimates is explored in sensitivity analyses. The probability of disease progression in non-compliant disease negative patients was assumed to be twice that of patients that have only undergone a single thyroid cancer test and have then become non-compliant to stimulated testing (see accompanying <*Supportive calculations Thyrogen (Final).xls*> spreadsheet for details of these calculations). This assumption is tested in sensitivity analysis.

As in the MSAC 2002 Assessment Report, it is assumed that all patients undergoing their first post-ablation diagnostic test will comply with follow up (i.e. 0% non-compliance). As per the clinician survey conducted for this submission, it is assumed that 14.4% of patients that are scheduled for diagnostic follow up with THT-withdrawal stimulation at 28-months will avoid this process so as not to suffer the significant morbidity associated with being rendered hypothyroid during this time. These patients leave formalised follow up in the economic model. As patients receiving Thyrogen stimulation do not suffer the morbidity associated with profound hypothyroidism, they remain compliant with the appropriate diagnostic follow up regimen. This assumption is in keeping with that presented in the MSAC 2002 Assessment Report.

Patients undergoing a period of profound hypothyroidism, such as those in the THT-withdrawal stimulation arm, are known to consume more health care resources. In 2005, Luster and colleagues found that 38% (38/101) of patients required single or multiple consultations with primary care physicians specifically for the treatment of hypothyroid symptoms. Furthermore, 31% (29/95) of patients required one or more specialist visits for the treatment of hypothyroid symptoms. In this analysis it is assumed that where patients reported multiple clinician visits these patient's required two visits. This is a conservative assumption. For example, a total of 38 patients required a physician visit, 20 of these patients required more than one visit, therefore, the average number of physician visits required per patient in the THT-withdrawal stimulation arm for hypothyroidism = ((((38-20)/101)×1.0) + ((20/101)×2.0)) = 0.57. Full details of these calculations are provided in the accompanying workbook <*Supportive calculations Thyrogen (Final).xls*>

During THT withdrawal a small proportion of patients receive liothyroxine sodium (T3) for a brief bridging period in place of thyroxine sodium (T4). In the PBAC 2006 Thyrogen submission it was estimated that five percent of patients receive a complete pack of this medication, the same estimate is applied here. It is important to note that the use of T3 has been shown not to reduce a

patient's hypothyroid symptoms (Leboeuf *et al,* 2007; Lee *et al* 2010; Dueren *et al* 2010). Therefore, in line with this evidence, no impact of T3 on patient utility is applied in the economic model. However, the cost of T3 treatment in this small group of patients is captured in the economic analyses. The cost of T3 is removed from the base case evaluation in the sensitivity analyses reported in **Section 11.6.15.6** of this submission. Removing these costs has no material impact on the cost-effectiveness results for Thyrogen.

Thyroid cancer survival data are presented in **Figure 11** (five year survival) and **Table 21** (weekly probability of mortality). Thyroid cancer mortality was estimated using data from three publications. Five year survival data for localised disease, regional spread, unknown spread and distant disease were obtained through the Australian publication entitled: *Cancer in New South Wales: Incidence and Mortality Report* published by the Cancer Institute NSW (CINSW) in 2006 (Tracey *et al,* 2008). To provide estimates of survival for various health states, the CINSW survival estimates were weighted by the proportion of patients with localised disease, regional spread and distant disease as appropriate. These stage distributions were obtained from stage at diagnosis data reported in the Australian publication entitled: *Thyroid Cancer in NSW (April 2008)* by the Cancer Institute NSW 2008. Survival estimates for disease positive patients that were non-compliant with follow up and treatment were taken from the publication by Sciuto *et al*, 2009. Full details of these calculations are provided in the workbook accompanying this submission < *Supportive calculations Thyrogen (Final).xls* >.

In brief, patients that enter the economic model were assumed to have localised disease, regional spread or unknown spread of thyroid cancer (5 year survival 96.6%; **Figure 11**). The survival of patients with distant disease was removed from this weighted estimate as these patients are not eligible for Thyrogen use. For patients that are compliant with monitoring but are disease negative, it was assumed that their five year survival would lie midway between that of a patient with localised disease and no cancer-related mortality (i.e. a five year survival of 99.1%; **Figure 11**). Disease positive patients that were compliant with monitoring and treatment were assumed to have the five year survival of any patient positive for thyroid cancer (i.e. a five year survival of 93.5% or the weighted average survival of patients with localised disease, regional spread, unknown spread, or distant disease) as they are detected at their next follow-up scan. Disease negative patients that were non-compliant with monitoring were assumed to have a slightly higher probability (i.e. five year survival of 98.1% - the survival of a patient with early stage disease) of cancer mortality than disease negative patients that have complied with stimulated testing, have had at least two consecutive negative tests and have left intensive monitoring as they are considered at low risk of disease recurrence. Disease positive patients that are non-compliant with follow up and treatment, or patients that have false positive test results and are not aware of their true positive disease status, have the poorest 5 year survival prognosis (80.7%). This probability was derived from the survival

of patients that have delayed radioiodine treatment as reported in the publication by Sciuto *et al*, 2009.

Figure 11 Five year survival applied to patient cohorts, by disease state and compliance with monitoring

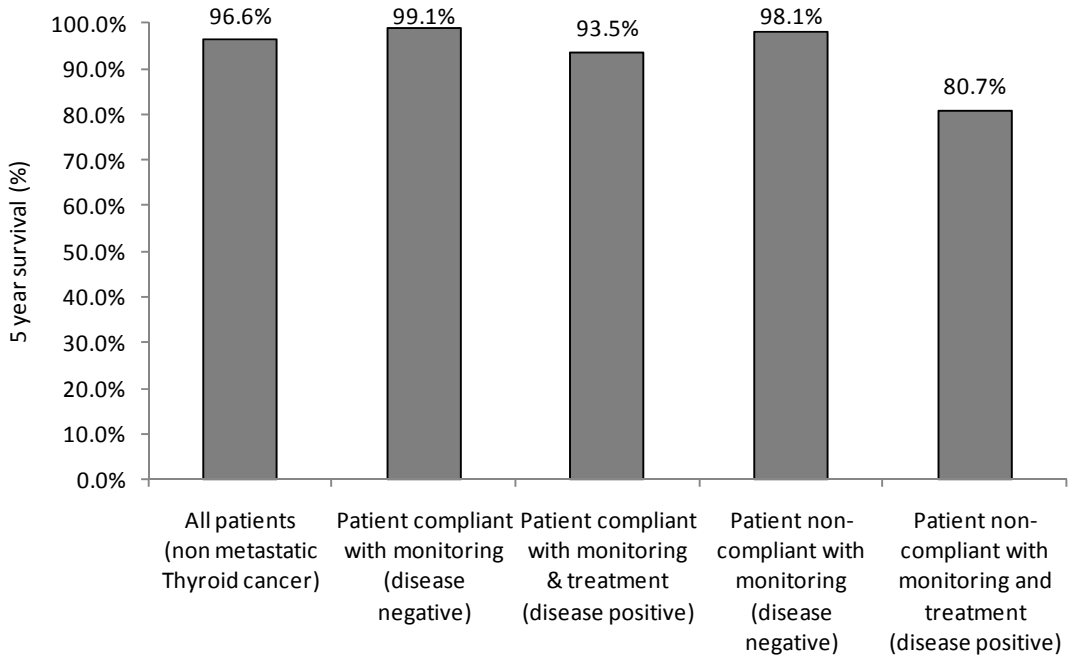


Table 21 Probabilities applied in step 2 and 3 of the economic model

Probability description	Probabilities applied in economic model		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
Gender				
Probability of female gender in model cohort	0.79	0.79	Applied to actuarial life tables to generate appropriate life expectancy for patient cohort	CINSW, 2006. 5 year prevalence gender split (p. 223)
Disease status				
Disease / remnant positive at *first* 10 month test	0.25	0.25	Tested in sensitivity / threshold analysis	Reduced, as requested in the DAP. (original estimate based on MSAC 2002 Haugen *et al*, 1999. p. 3880)
Disease / remnant positive at *subsequent* 10 month tests	0.10	0.10	Tested in sensitivity / threshold analysis	Reduced disease positivity as requested in DAP
Disease / remnant positive at 28 month test	0.05	0.05	Tested in sensitivity / threshold analysis	Reduced disease positivity as requested in DAP
Biennial probability of disease recurrence in low risk (i.e. with 2 × -ve stimulated tests) disease negative patients	0.0273	0.0273	Calculated from disease recurrence in low risk patients as reported in Schlumberger *et al*, 2007 [a]	Schlumberger *et al*, 2007
Annual probability of disease recurrence in disease negative non-compliant patients	0.02775	0.02775	Calculated from disease recurrence in low risk patients as reported in Schlumberger *et al*, 2007[a] × 2. Tested in sensitivity analysis.	Schlumberger *et al*, 2007
Diagnostic performance				
False negative test WBS + Tg at 10 month test	0.00	0.00	Assumes sensitivity of Thyrogen stimulation and THT-withdrawal stimulation are equal. Tested in sensitivity analyses	Section 12.
False positive test WBS + Tg at 10 month test	0.00	0.00	Assumes specificity of Thyrogen stimulation and THT-withdrawal stimulation are equal. Tested in sensitivity analyses	Section 12
False negative test Tg alone 28 month test	0.19	0.19	Assumes sensitivity of Thyrogen stimulation and THT-withdrawal stimulation are equal. Tested in sensitivity analyses	MSAC 2002.

Probability description	Probabilities applied in economic model		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
False positive test Tg alone at 28 month test	0.00	0.00	Both Thyrogen stimulation and THT withdrawal stimulation have 100% specificity in this setting	MSAC 2002.
False negative test unstimulated Tg alone (24 monthly) in patients that have two sequential negative tests (i.e. at 10 months and 28 months)	0.43	0.43	Calculated from Schlumberger *et al*, 2007 and weighted by standard Tg /ultrasensitive Tg proportions reported in clinician survey [a]	Schlumberger *et al*, 2007; Clinician survey (Appendix 1)
False positive test unstimulated Tg alone (24 monthly) in patients that have two sequential negative tests (i.e. at 10 months and 28 months)	0.21	0.21	Calculated from Schlumberger *et al*, 2007 and weighted by standard Tg /ultrasensitive Tg proportions reported in clinician survey [a]	Schlumberger *et al*, 2007; Clinician survey (Appendix 1)
False negative test unstimulated Tg alone in non-compliant patients (12 monthly test)	NA	0.43	Calculated from Schlumberger *et al*, 2007 and weighted by standard Tg /ultrasensitive Tg proportions reported in clinician survey [a]	Schlumberger *et al*, 2007; Clinician survey (Appendix 1)
False positive test unstimulated Tg alone in non-compliant patients (12 monthly test)	NA	0.21	Calculated from Schlumberger *et al*, 2007 and weighted by standard Tg /ultrasensitive Tg proportions reported in clinician survey [a]	Schlumberger *et al*, 2007; Clinician survey (Appendix 1)
Compliance				
Non-compliance at 10 month test	0.00	0.00		MSAC 2002
Non-compliance at 28 month test	0.00	0.144		Clinician survey conducted for this submission (Appendix 1)
Clinician visits for management of hypothyroid symptoms				
GP visits	0.00	0.57	Assumes patients with >1 visits to a GP have 2 visits.	Luster *et al*, 2005 p.1150
Specialist visits	0.00	0.42	Assumes patients with >1 visits to a Specialist have 2 visits	Luster *et al*, 2005 p.1150
Medication use				
Proportion of patients that use T3 in diagnostic phase of Tx	0.00	0.05		PBAC submission 2002. Table 46. Page 75
Cancer mortality (proceeded by late stage cancer)				

Probability description	Probabilities applied in economic model		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
All non-metastatic thyroid cancer patients progression to cancer death (proceeded by late stage cancer)	0.0001446	0.0001446	Weekly	CINSW, 2006 survival by stage and CINSW 2008 stage at diagnosis[a]
Compliant patient – Disease negative progression to cancer death (proceeded by late stage cancer)	0.0000398	0.0000398	Weekly	Assumption: Midpoint between localized disease mortality (CINSW, 2006) and no mortality[a]
Non-compliant patient – disease negative progression to cancer death (proceeded by late stage cancer)	0.0000799	0.0000799	Weekly	Assumption: survival of patient with localized disease (CINSW, 2006) and no mortality[a]
Compliant patient – aware of true disease positive health state progression to cancer death (proceeded by late stage cancer)	0.0002819	0.0002819	Weekly	CINSW, 2006 survival by stage and CINSW 2008 stage at diagnosis[a]
Non-compliant patient, or patient with a false negative test results. Disease positive progression to cancer death (proceeded by late stage cancer)	0.0008222	0.0008222	Weekly	Sciuto *et al*, 2009 (Survival in patients with delayed radioiodine therapy)[a]

[a] See accompanying workbook <Supportive calculations Thyrogen (Final).xls> for actual calculations

11.6.13 Preference-based quality of life (utility) measures applied in the economic model

Table 22 presents the preference-based quality of life measures applied in the economic model along with their sources. Only the *Diagnostic Phase* and the *Regular Monitoring* utilities are used in **Step 1** of the economic model. All the utility weights presented in **Table 22** are applied in the **Step 2** and **3** of the economic model.

Utility weights for the *Pre-test* and *Test* phase of the economic model were obtained from the Haugen *et al*, 1999 study by conversion of SF-36 quality of life data to SF-6D utility weights using the method of Brazier *et al*, 1998. These data were presented previously in the 2006 submission to the PBAC (data on file). It is important to note that these utility weights are derived from head-to-head evidence comparing Thyrogen-stimulated and THT-withdrawal stimulation directly in the patient population of interest. While the estimates were derived from a study in ablation, the disutility of hypothyroidism has been found to be identical in both ablation and diagnostic settings. The utility weights in the *Initial post-test* period were calculated assuming the same ratio as recorded in the *Pre-ablation* : *Initial Post-ablation* periods are replicated in the diagnostic setting. For example, in the THT-withdrawal-stimulated arm, patients in the *Initial Post-Ablation* health state recorded a utility weight of 0.548 and in the *Pre-ablation* health state they recorded a utility of 0.637. So, patients in the *Initial Post* ablation health state had a utility weight 1.1624 (0.637/0.548) times greater than patients in the *Pre-ablation* phase. This ratio was then applied to the utility weight recorded in patients in the *Pre-test* diagnostic phase generating a utility weight of 0.7405 (1.1624 × 0.637=0.7405) for the *Initial Post Test* health state. Like the ablation economic model presented in the Thyrogen submission to the PBAC 2006, the *Second Post-test* period simply reflects the return of a patient's utility back to normal levels after the testing period. This is simply calculated as the midpoint between the utility weight in the *Initial Post-test* period and the regular monitoring utility weight. For example, in the THT-withdrawal stimulation arm, the utility weight applied in the Second *Post-test* period is 0.795 ((0.740+0.850)/2=0.795). Full details of all these calculations are provided in the accompanying workbook: <*Supportive calculations Thyrogen (Final).xls*>

Utility weights for the ablation phase of the economic model were taken from the Thyrogen Ablation submission to the PBAC (2006). Again, it is important to note that these utility weights were derived from head-to-head evidence comparing the Thyrogen stimulation and THT-withdrawal stimulation directly in the patient population of interest and have been accepted by the PBAC as an accurate reflection of the disutility associated with hypothyroidism in these patients. Indeed, the validity of the extent of this disutility is reinforced by the exact replication of the

magnitude of the incremental disutility seen in the diagnostic and ablation settings (see **Figure 18** in **Section 12**).

As requested in the DAP, the impact of altering the duration of the hypothyroid period is explored in sensitivity analyses.

Patients that are undergoing active monitoring, have a false positive test, or are non-compliant with monitoring and treatment are assumed to have an annual utility weight of 0.850 until such time as they progress to late stage cancer (MSAC Assessment report 2002).

Patients who have had two negative tests at 10 and 28 months and are truly negative for disease have the utility of a otherwise healthy person (0.88; MSAC Assessment report 2002).

To account for the significant disutility associated with late stage thyroid cancer prior to death, patients with late stage disease accrue a disutility 0.330 (i.e. Symptomatic disease utility weight - healthy patient no longer undergoing active monitoring utility weight = 0.55-0.88= -0.33; Table 20. MSAC 2002). As the survival probabilities employed in the economic model actually reflect the time of a patient's death, not a transition to late stage disease, this disutility is retrospectively applied for a period of 48 weeks prior to the death of the patient (see Late Stage Cancer and Death **Step 2** and **3** of the economic model). The reader is reminded that this is ultimately heavily discounted so has limited effect on the cost-effectiveness of Thyrogen in this setting.

Table 22 Annual utility weights applied in the economic model

Utility description	Annual utility weights applied in economic model		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
Diagnostic phase				
Pre-test	0.803	0.637		PBAC 2006 submission (data on file)
Test	0.803	0.637		PBAC 2006 submission (data on file)
Initial post test	0.801	0.740		Calculated: Assuming ratio between *Pre-ablation* and the Initial-Post ablation utility weights are the same as those between the Pre-test and Initial Post test period.
Second post-test	0.825	0.795		Calculated: Midpoint between Test and Regular monitoring utility weight
Ablation phase (Step 2 & 3 only)				
Pre-ablation	0.714	0.714		PBAC 2006 submission; Pacini *et al* 2006 and Mernagh *et al* 2010
Ablation	0.614	0.614		
Initial post ablation	0.712	0.712		
Second post-ablation	0.776	0.776		

Utility description	Annual utility weights applied in economic model		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
Regular monitoring (Step 2 & 3 only)				
A patient undergoing regular monitoring	0.850	0.850		Table 20. MSAC 2002
Post-active monitoring (Step 2 & 3 only)				
A patient who has had two negative tests, is no longer being actively monitored and is disease negative	0.880	0.880		Table 20. MSAC 2002
A patient who has had two negative tests, is no longer being actively monitored and is disease positive (i.e. False negative)	0.850	0.850		Table 20. MSAC 2002
Non-compliant patients (Step 2 & 3 only)				
A non-compliant disease negative patient	0.850	0.850		Table 20. MSAC 2002
A non-compliant disease positive patient	0.850	0.850		Table 20. MSAC 2002
Cancer (Step 2 & 3 only)				
Disutility in patients with advanced cancer	-0.330	-0.330		Calculated. Difference between healthy utility weight and symptomatic disease utility weight. NB. this is a disutility and, therefore, is presented as a negative number). Table 20. MSAC 2002
Death (Step 2 & 3 only)				
A patient who is dead	0.000	0.000		Convention

11.6.14 Temporal variables applied in the economic model

The economic model incorporates a number of fixed time periods; these periods are described by the temporal values presented in **Table 23**, below. Again, only the Diagnostic Phase time periods apply to **Step 1** of the economic analysis.

To ensure that the economic model has the same time-horizon in the Thyrogen-stimulated and THT-withdrawal-stimulated arm (i.e. 13 weeks) in **Step 1** of the economic evaluation, patients in the Thyrogen-stimulated arm spend three weeks in the *monitoring* health state at the end of the testing period. This adjustment is not required in the more complex analyses presented in **Steps 2**

and **3** economic evaluation as the time-horizon of both arms of the economic model are set to equal durations.

All time periods used in the Diagnostic Phase of the economic model are assumed to be the same as the time periods in the Ablation Phase (i.e. as reported in the Thyrogen submission to PBAC 2006).

Waiting periods between tests are simply calculated to match the appropriate time periods. The model assumes a cycle period of one week and a 48 week year.

Finally, it is assumed that patients that die from cancer suffer from 48 weeks of significant disutility prior to death (i.e. late stage cancer).

Table 23 Temporal values applied in the economic model

Description of time period	Temporal values applied in economic model (number of cycles/weeks)		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
Diagnostic phase (Step 1 only)				
Pre-test	1.0	4.0		Identical to PBAC 2006 submission
Test	1.0	1.0		Identical to PBAC 2006 submission
Initial post test	4.0	4.0		Identical to PBAC 2006 submission
Second post-test	4.0	4.0		Identical to PBAC 2006 submission
Monitoring	3.0	0.0		Calculated
Diagnostic phase (Step 2 and 3 only)				
Pre-test	1.0	4.0		Identical to PBAC 2006 submission
Test	1.0	1.0		Identical to PBAC 2006 submission
Initial post test	4.0	4.0		Identical to PBAC 2006 submission
Second post-test	4.0	4.0		Identical to PBAC 2006 submission
Ablation phase				
Pre-ablation	1.0	4.0		PBAC 2006 submission
Ablation	1.0	1.0		PBAC 2006 submission
Initial post ablation	4.0	4.0		PBAC 2006 submission
Second post-ablation	4.0	4.0		PBAC 2006 submission
Waiting				
Waiting for 10 month test	40.0	40.0		10 months = 10 × 4 = 40 weeks
Waiting for 28 month test	72.0	72.0		18 months = 18 × 4 = 72.0 weeks

Description of time period	Temporal values applied in economic model (number of cycles/weeks)		Notes	Source
	Thyrogen-stimulated	THT-withdrawal-stimulated		
Waiting for unstimulated Tg test in patients that have two sequential negative tests (i.e. at 10 months and 28 months)	96.0	96.0		24 months = 24 × 4 weeks = 96 weeks
Waiting for unstimulated Tg test in patients that are non-compliant to THT-withdrawal	NA	48.0		12 months = 12 × 4 weeks = 48 weeks
Cancer				
Advanced cancer duration prior to death	48.0	48.0		Assumes 12 months = 12 × 4 = 48 weeks

11.6.15 Results of the economic analysis

11.6.15.1 Cost per patient

Table 24 presents the cost per patient of Thyrogen, concomitant medications, associated diagnostic tests and clinician visits over the diagnostic period for **Step 1**, **2** and **3** of the economic evaluation in patients receiving both a Tg measurement and a WBS.

Table 24 Cost per patient of Thyrogen and associated health care resource use during the diagnostic phase (WBS + Tg)

Item	Unit cost	Number of units	Total	Notes
Thyrogen				
MBS rhTSH alone	$1,901.42	1.00	$1,901.42	Identical to PBS 2700D DPMQ
		Subtotal	*$1,901.42*	
Concomitant medications				
T3	$83.53 (pack)	0.00	$0.00	PBS 2318B
T4	$0.96 (week)	13 weeks	$12.48	PBS 2173J Patients remain on T4
		Subtotal	*$12.48*	
Clinician visits				
MBS additional costs (captured in MBS fee)	$400.83	1.00	$400.83	Calculated: (MBS 12201 fee - PBS DPMQ)
Follow up specialist visit	$76.40	1.00	$76.40	MBS 108
Specialist visits for hypothyroid symptoms	$76.40	0.00	$0.00	MBS 108
General practitioner visits for hypothyroid symptoms	$34.90	0.00	$0.00	MBS 23
		Subtotal	*$477.23*	
Diagnostic scans				
WBS	$554.80	1.00	$554.80	MBS 61426 (includes radiopharmaceutical)
Tg	$24.50	1.00	$24.50	MBS 66650
Tg antibody	$34.80	1.00	$34.80	MBS 71165
TSH level measurement	$25.20	0.00	$0.00	MBS 66716
		Subtotal	*$614.10*	
		Total	**$3,005.23**	

Table 25 presents the cost per patient of THT-withdrawal, concomitant medications, associated diagnostic tests and clinician visits over the diagnostic period for **Step 1**, **2** and **3** of the economic evaluation in patients receiving both a Tg measurement and a WBS.

Table 25 Cost per patient of THT-withdrawal and associated health care resource use during the diagnostic phase (WBS + Tg)

Item	Unit cost	Number of units	Total	Notes
Thyrogen				
MBS rhTSH alone	$1,901.42	0.00	$0.00	Identical to PBS 2700D DPMQ
		Subtotal	*$0.00*	
Concomitant medications				
T3	$83.53 (pack)	0.05	$4.18	PBS 2318B

Item	Unit cost	Number of units	Total	Notes
T4	$0.96 (week)	8 weeks	$7.68	PBS 2173J
		Subtotal	*$11.86*	
Clinician visits				
MBS additional costs (captured in MBS fee)	$400.83	1.00	$400.83	Calculated: (MBS 12201 fee - PBS DPMQ)
Follow up specialist visit	$76.40	1.00	$76.40	MBS 108
Specialist visits for hypothyroid symptoms	$76.40	0.42	$32.17	MBS 108
General practitioner visits for hypothyroid symptoms	$34.90	0.57	$20.04	MBS 23
		Subtotal	*$529.44*	
Diagnostic scans				
WBS	$554.80	1.00	$554.80	MBS 61426 (includes radiopharmaceutical)
Tg	$24.50	1.00	$24.50	MBS 66650
Tg antibody	$34.80	1.00	$34.80	MBS 71165
TSH level measurement	$25.20	1.10	$27.72	MBS 66716
		Subtotal	*$641.82*	
		Total	**$1,183.12**	

11.6.15.2 Incremental health care costs

Table 26 presents the average cost of health care resources used in **Step 1** of the economic model, by resource type. In incremental terms, the most costly component generated in the economic model is the cost of Thyrogen itself.

Table 26 Incremental health care costs generated by the economic model (Step 1)

Item	Thyrogen-stimulated arm	THT withdrawal arm	Incremental
Step 1: Preliminary economic evaluation			
Thyrogen			
MBS rhTSH alone	$1,901.42	$0.00	$1,901.42
Other medications			
T3	$0.00	$4.18	-$4.18
T4	$12.48	$7.68	$4.80
Clinician visits			
MBS additional costs (captured in MBS fee)	$400.83	$400.83	$0.00
Follow up specialist visit	$76.40	$76.40	$0.00
Specialist visits for hypothyroid symptoms	$0.00	$32.17	-$32.17
General practitioner visits for hypothyroid symptoms	$0.00	$20.04	-$20.04
Diagnostic tests			
WBS	$554.80	$554.80	$0.00
Tg	$24.50	$24.50	$0.00
Tg antibody	$34.80	$34.80	$0.00
TSH level measurement	$0.00	$27.72	-$27.72
Total	***$3,005.23***	***$1,183.12***	***$1,822.11***

Table 27 presents the average cost of health care resources used in **Step 2** of the economic model, by resource type. In incremental terms, the most costly component generated in the economic model is the cost of Thyrogen itself. As the introduction of diagnostic Thyrogen reduces the number of patients that are non-compliant with suitably intense diagnostic follow up and reduces the debilitating effects of profound hypothyroidism, modest reductions in other health care costs are expected.

Table 27 Incremental health care costs generated by the economic model (Step 2)

Item	Thyrogen-stimulated arm	THT withdrawal arm	Incremental
Step 1: 20 year analysis			
Thyrogen (diagnostic phase)			
Thyrogen	$6,874.26	$0.00	$6,874.26
Thyrogen (treatment phase)			
Thyrogen	$2,296.54	$2,376.43	-$79.89
Clinician costs			
Specialist visits, pre and post test and ablation, and treatment of hypothyroid symptoms	$2,301.74	$2,422.91	-$121.17
Medication costs			
T3 & T4	$558.69	$555.57	$3.12
Diagnostic tests			
WBS	$1,824.99	$1,872.49	-$47.50
Other diagnostic tests (Tg, Tg antibody, TSH)	$379.52	$473.01	-$93.49
Ablation costs			
Cost hospitalisation (radioprotective ward and radioioidine ablation)	$3,906.76	$4,042.67	-$135.91
Cost cancer			
End of life costs of Thyroid cancer	$406.16	$435.06	-$28.89
Total	**$18,548.66**	**$12,178.13**	**$6,370.53**

NB. Rounding has been applied

Table 28 presents the average cost of health care resources used in **Step 3** of the economic model, by resource type. Again, in incremental terms, the most costly component generated in the economic model is the cost of Thyrogen itself. As the introduction of diagnostic Thyrogen reduces the number of patients that are non-compliant with suitably intense diagnostic follow up and reduces the debilitating effects of profound hypothyroidism, modest reductions in other health care costs are expected.

Table 28 Incremental health care costs generated by the economic model (Step 3)

Item	Thyrogen-stimulated arm	THT withdrawal arm	Incremental
Step 3: Lifetime analysis			
Thyrogen (diagnostic phase)			
Thyrogen	$8,059.73	$0.00	$8,059.73
Thyrogen (treatment phase)			
Thyrogen	$2,902.23	$3,021.94	-$119.71
Clinician costs			
Specialist visits, pre and post test and ablation, and treatment of hypothyroid symptoms	$2,751.30	$2,903.81	-$152.51
Medication costs			
T3 & T4	$715.45	$711.06	$4.39
Diagnostic tests			
WBS	$2,186.52	$2,248.44	-$61.93
Other diagnostic tests (Tg, Tg antibody, TSH)	$465.61	$577.01	-$111.40
Ablation costs			
Cost hospitalisation (radioprotective ward and radioioidine ablation)	$4,937.14	$5,140.79	-$203.65
Cost cancer			
End of life costs of Thyroid cancer	$523.25	$558.60	-$35.35
Total	**$22,541.23**	**$15,161.66**	**$7,379.57**

NB. Rounding has been applied

11.6.15.3 Incremental health care effects

Table 29 presents the annual utility weights applied in each of the health states of the preliminary economic model (**Step 1**). The table also presents the number of QALYs accrued in the Thyrogen-stimulated and THT-withdrawal-stimulated arm along with the number of incremental QALYs generated in the economic analysis over the 13-week time horizon.

Table 29 Annual utility weights, treatment effect by arm and incremental treatment effect generated by the preliminary economic model (Step 1)

Week	Thyrogen-stimulated arm			THT-withdrawal-stimulated arm			Incremental QALYs
	Health state	Annual utility weight	QALYs per week	Health state	Annual utility weight	QALYs per week	
Step 1: Preliminary economic analysis							
1	Pre-test	0.803	0.017	Pre-test	0.637	0.013	0.003
2	Test	0.803	0.017	Pre-test	0.637	0.013	0.003
3	Initial post-test	0.801	0.017	Pre-test	0.637	0.013	0.003
4	Initial post-test	0.801	0.017	Pre-test	0.637	0.013	0.003
5	Initial post-test	0.801	0.017	Test	0.637	0.013	0.003
6	Initial post-test	0.801	0.017	Initial post-test	0.740	0.015	0.001
7	Second post-test	0.825	0.017	Initial post-test	0.740	0.015	0.002
8	Second post-test	0.825	0.017	Initial post-test	0.740	0.015	0.002

Week	Thyrogen-stimulated arm			THT-withdrawal-stimulated arm			Incremental QALYs
	Health state	Annual utility weight	QALYs per week	Health state	Annual utility weight	QALYs per week	
9	Second post-test	0.825	0.017	Initial post-test	0.740	0.015	0.002
10	Second post-test	0.825	0.017	Second post-test	0.795	0.017	0.001
11	General monitoring	0.850	0.018	Second post-test	0.795	0.017	0.001
12	General monitoring	0.850	0.018	Second post-test	0.795	0.017	0.001
13	General monitoring	0.850	0.018	Second post-test	0.795	0.017	0.001
		Total QALYs	0.222		Total QALYs	0.194	
						Incremental QALYs	**0.028**

Figure 12 presents a pictographic representation of the QALYs accrued over time in the Thyrogen-stimulated and THT-withdrawal-stimulated arm in **Step 1** of the economic analysis. **Figure 12** also presents the incremental number of QALYs accrued per week in this preliminary analysis.

Figure 12 Treatment effect by arm and incremental treatment effect generated by the preliminary economic model (Step 1)

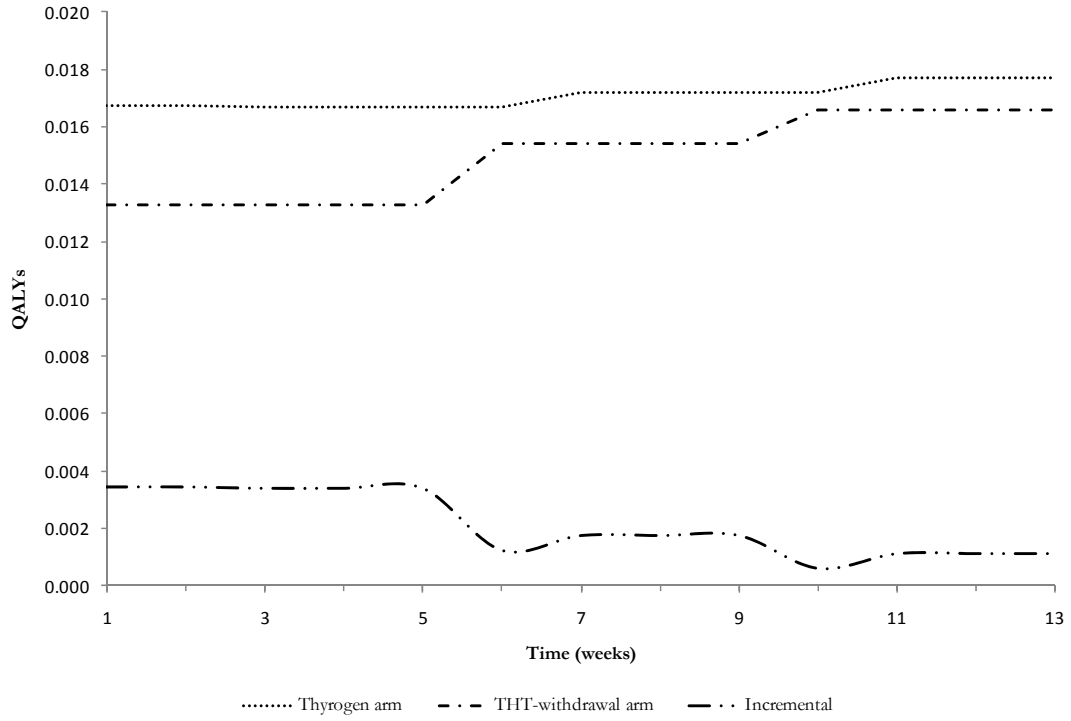


Table 30 presents the total treatment effect as measured in QALYs generated in **Step 2** of the economic model. This table also presents the total incremental treatment effect generated in this step of the analysis.

Like **Step 1**, this economic analysis captures the costs and effects accrued during the diagnostic testing period as this period takes into account the short term cost and benefits associated with the use of Thyrogen. However, **Step 2** also captures the costs and effects of any therapeutic radioiodine ablation episodes that the patient may have. In addition to this **Step 2** also captures the costs and effects accrued during the waiting periods between tests and ablation periods and in low risk patients that leave active follow up (i.e. patients with two consecutive negative tests). Furthermore, **Step 2** captures the costs and effects accrued in patients that are not compliant with follow up due to the side effects associated with hypothyroidism in the THT-withdrawal-stimulated arm. Finally, this analysis captures the costs and effects of late stage cancer and premature cancer mortality. As this analysis is limited to a time horizon of 20 it does not capture the full impact of premature cancer mortality on the patient cohort of interest.

Table 30 Total and incremental QALYs accrued (economic analysis: Step 2)

Health state	Thyrogen-stimulated arm	THT arm	Incremental
Step 2: 20 year analysis			
Total QALYs	***10.499***	***10.352***	***0.147***

Table 31 presents the total treatment effect as measured in QALYs generated in the base case economic analysis (**Step 3** life time analysis). This table also presents the total incremental treatment effect generated in this step of the analysis.

The base case analysis (**Step 3**) captures the same list of cost and benefits as **Step 2**, including the costs and effects accrued during the diagnostic testing period. However, the time horizon of the economic model in this step is extended to the patient's lifetime. Therefore, the base case analysis captures the impact of premature mortality in this patient cohort fully.

Table 31 Total and incremental QALYs accrued (economic analysis: Step 3 life time analysis – base case)

Health state	Thyrogen-stimulated arm	THT arm	Incremental
Step 3: Lifetime analysis			
Total	***13.450***	***13.262***	***0.189***

11.6.15.4 Markov traces

Figure 13 presents the Markov trace for the Thyrogen-stimulated arm of the economic model over 2688 cycles (i.e. a 56 year period). The cohort starts in the *10 months diagnostic test health* state and distributes throughout the economic model as specified by the probabilities presented in **Table 21**.

It is important to note that the model is designed as a cohort analysis which deals with a group of individuals with similar characteristics – rather than an individual patient. In a cohort analysis, the expected value is calculated by multiplying the percentage of the cohort in a health state by the incremental cost or utility assigned to that health states, and aggregating the products across health states and cycles to obtain the overall expected value. This means that the probability of being in the health state (as well as its interpretation) is associated with the aggregate study cohort – not specific and adherent to any individual patients.

The reader is referred to the full versions of the economic model accompanying this submission *<Step 3 Life time economic analysis Thyrogen (Final).pkg>* for full details of these calculations.

Figure 13 Markov trace for Thyrogen-stimulated arm of the economic model over 56 years

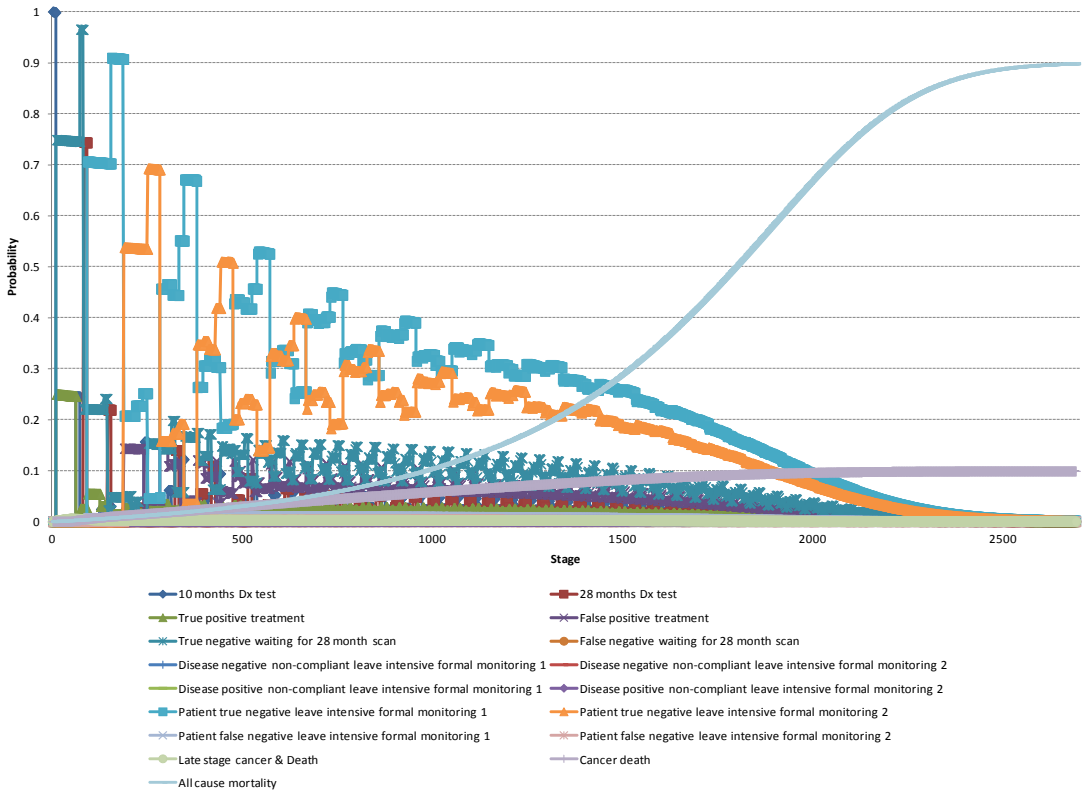
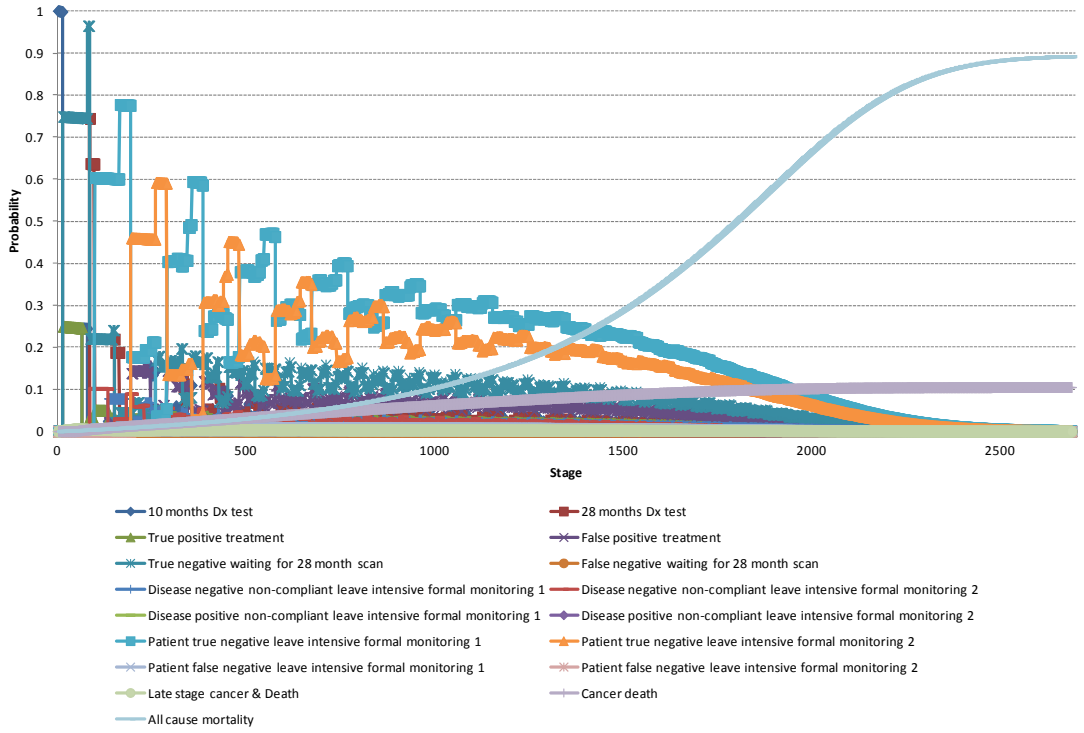


Figure 14 presents the Markov trace for the THT-withdrawal-stimulated arm of the economic model over 2688 cycles (i.e. a 56 year period). The cohort starts in the *10 month diagnostic test health* state and distributes throughout the economic model as specified by the probabilities presented in **Table 21**.

Figure 14 Markov trace for THT-withdrawal-stimulated arm of the economic model over 56 years



11.6.15.5 Incremental cost effectiveness ratio (ICER, cost per QALY)

Table 32 presents the incremental cost-effectiveness ratios (ICERs) measured as the cost per QALY for **Step 1–3** of the economic evaluation.

The base case economic analysis shows that the incremental cost-effectiveness ratio (ICER) for Thyrogen-stimulated versus THT-withdrawal stimulation in all patients undergoing all diagnostic tests was **$39,130 per QALY**. This represents good value for money for the Australian Health Care System and allows well-differentiated thyroid cancer sufferers to comply with appropriate monitoring for disease recurrence without having to suffer the debilitating effects of profound hypothyroidism.

Table 32 Incremental cost-effectiveness ratios Step 1–3

	Thyrogen-stimulated	THT-withdrawal-stimulated	Incremental
Step 1: (Preliminary economic analysis – 13 weeks)			
Cost ($)	$3,005.23	$1,183.12	$1,822.11
Effect (QALYs)	0.222	0.194	0.028
ICER (cost per QALY)			**$65,623.43**
Step 2: (20 year analysis)			
Cost ($)	$18,548.66	$12,178.13	$6,370.53
Effect (QALY)	10.499	10.352	0.147
ICER (cost per QALY)			**$43,390.88**
Step 3: (Lifetime analysis – Base case)			
Cost ($)	$22,541.23	$15,161.66	$7,379.57
Effect (QALY)	13.450	13.262	0.189
ICER (cost per QALY)			**$39,129.66**

11.6.15.6 Sensitivity analyses

A number of sensitivity/threshold analyses have been conducted to explore areas of uncertainty that have been raised in the DAP or identified while developing this economic evaluation. **Figure 15** shows that altering the 'life-time cost of cancer' over a broad range of values has almost no effect on the cost effectiveness of rhSTH (i.e. from $0.00–$50,000). Therefore, any double counting that may be present in this estimate is unlikely to have any material impact on the cost-effectiveness of Thyrogen in this analysis.

Figure 15 Sensitivity / threshold analysis life time cost of cancer versus cost-effectivness of rhTSH (cost per QALY)

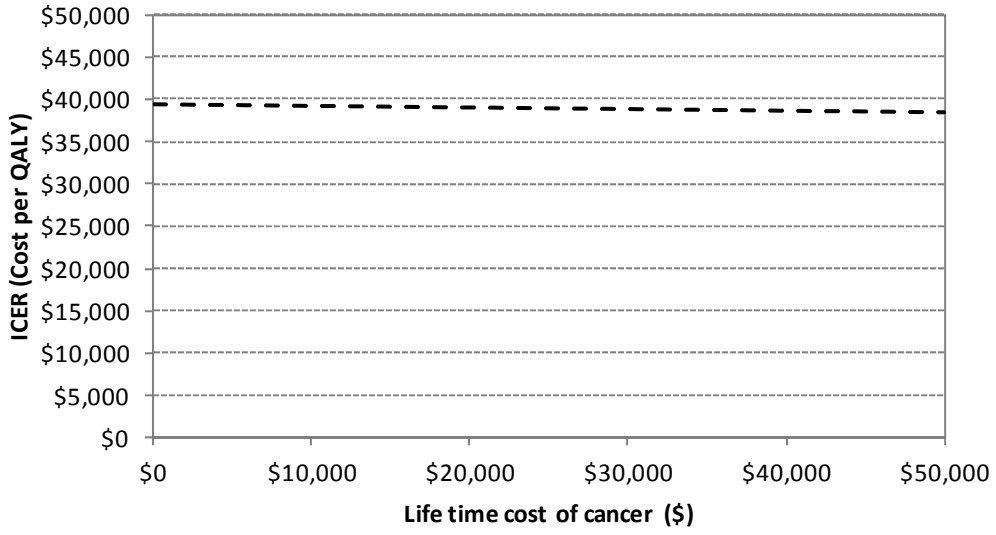
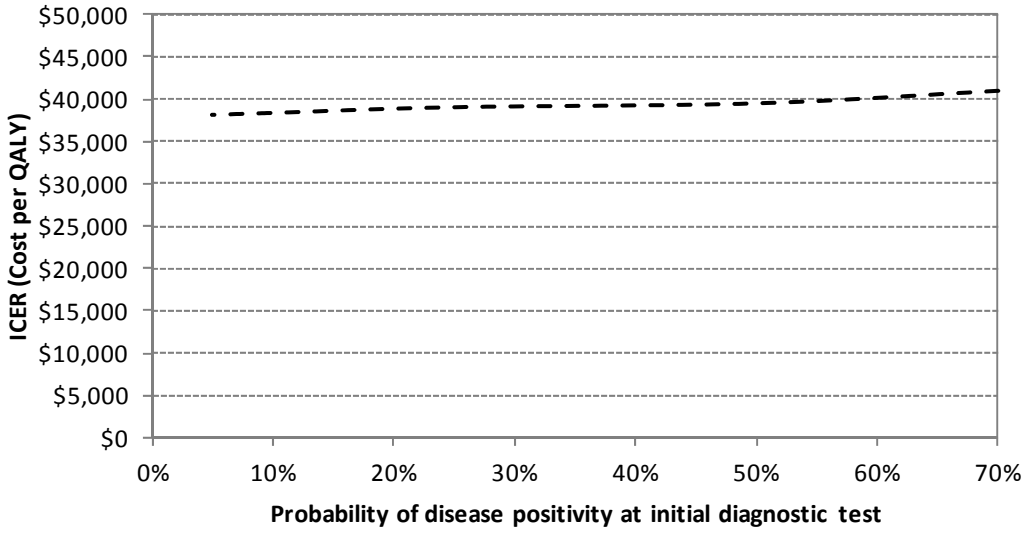


Figure 16 shows a sensitivity/threshold anaylsis exploring the impact of varying the probability of disease/remnant positivity over a broad range (5%–70%) at the first 10-month diagnostic scan. Again, as shown in the figure altering these parameters in the economic model has minimal impact on the cost-effectiveness of Thyrogen.

Figure 16 Sensitivity / threshold analysis probability of disease positivity at initial 10 month diagnostic test versus cost-effectivness of rhTSH (cost per QALY)



General sensitivity analyses are presented in **Table 33** below. The cost-effectiveness of Thyrogen remains stable when the input parameters to the economic model are modified over a range of plausible scenarios. Altering the probability of Thyroid cancer mortality and the disutility associated with late stage cancer has little effect on the ICER as these outcomes occur late in the time horizon of the economic model and are heavily discounted. Similarly, the lifetime costs of Thyroid cancer treatment (which are applied in the economic model near the end of a patient's life) have little impact on the cost-utility of Thyrogen-stimulated versus THT-withdrawal stimulated diagnostic testing as these costs are also accrued late in the time horizon of the economic model and are heavily discounted.

As requested in the DAP, when the duration of incremental benefit of rhTSH in the second-post test period is removed by setting the second post-test utility in THT arm to parity with Thyrogen arm the ICER increases to $41,330 per QALY.

The economic model appears modestly sensitive to the price of Thyrogen, the probability that patients are compliant with treatment in the THT-withdrawal stimulated arm of the economic model and the comparative sensitivity and specificity of rhTSH based diagnostic testing compared with THT-withdrawal stimulated testing. As the sensitivity and specificity of unstimulated Tg

testing increases the cost-effectiveness of rhTSH improves, primarily due to reduced follow up treatment costs.

Table 33 Sensitivity analyses

Scenario	Incremental cost	Incremental outcome	ICER (cost per QALY)
Base-case	***$7,379.57***	***0.189***	***$39,129.66***
Costs			
Thyrogen price decreased by 10%	$6,585.57	0.189	$34,919.52
Thyrogen price decreased by 20%	$5,791.57	0.189	$30,709.38
Thyrogen price increased by 10%	$8,173.57	0.189	$43,339.80
Thyrogen price increased by 20%	$8,967.57	0.189	$47,549.95
MBS additional costs reduced by 20% in THT-withdrawal arm	$7,369.65	0.189	$39,077.07
MBS additional costs increased by 20% in THT-withdrawal arm	$7,389.49	0.189	$39,182.26
T3 costs removed	$7,396.59	0.189	$39,219.88
T4 cost reduced by 20%	$7,375.29	0.189	$39,106.96
T4 cost increased by 20%	$7,383.85	0.189	$39,152.36
Life time cost of cancer reduced by a further 20%	$7,386.64	0.189	$39,167.15
Life time cost of cancer increased by 20% (to original value)	$7,372.50	0.189	$39,092.17
Life time cost of cancer entirely removed (set to $0.00)	$7,414.92	0.189	$39,317.10
Model probabilities			
Thyrogen sensitivity reduced to 86% and specificity set to 95% at 10 months (i.e. as reported in Table 11 MSAC 2002 assessment)(NB. this ignores the imperfect reference standard issue)	$7,762.80	0.152	$51,197.23
Thyrogen *and* THT-withdrawal stimulated sensitivity reduced to 86% and specificity set to 95% at 10 months (i.e. as reported in Table 11 MSAC 2002 assessment) *(NB. this ignores the imperfect reference standard issue)*	$7,424.96	0.190	$39,181.36
Thyrogen and THT-withdrawal diagnostic sensitivity and specificity at 28 months set to 100% *(NB. this ignores the imperfect reference standard issue)*	$7,419.67	0.192	$38,602.35
Assumes only 50% of patients with a positive unstimulated Tg test are referred to Thyrogen stimulated ablation, the remainder undergo watchful waiting	$6,007.27	0.176	$34,197.72
Unstimulated Tg sensitivity and specificity set to 100% *(NB. this ignores the imperfect reference standard issue)*	$4,508.88	0.167	$26,930.19

Scenario	Incremental cost	Incremental outcome	ICER (cost per QALY)
Base-case	***$7,379.57***	***0.189***	***$39,129.66***
Unstimulated Tg sensitivity and specificity decreased by an absolute 10% points (i.e. sensitivity decreased to 47% and specificity decreased to 69%) *(NB. this ignores the imperfect reference standard issue)*	$8,449.10	0.199	$42,370.13
Probability of patient being disease positive at 10 months reduced by absolute 10% points (i.e. from 25% to 15%)	$7,239.69	0.187	$38,689.64
Probability of patient being disease positive at 10 months increased by absolute 10% points (i.e. from 25% to 35%)	$7,519.45	0.190	$39,562.88
Probability of patient being disease positive at 28 months halved (i.e. from 5% to 2.5%)	$7,263.30	0.184	$39,396.22
Probability of patient being disease positive at 28 months increased by an absolute 10% points (i.e. from 5% to 15%)	$7,884.99	0.205	$38,283.71
Probability of disease progression in disease negative non-compliant patients set equal to low risk disease negative patients that have had two sequential negative tests (i.e. an annual probability of 0.01375 or biennial probability of 0.02730 applied).	$7,408.14	0.184	$40,190.88
Probability of cancer death in all patients decreased by 20%	$7,420.60	0.182	$40,753.04
Probability of cancer death in all patients increased by 20%	$7,339.32	0.195	$37,652.38
Probability of cancer death in compliant disease negative patients decreased by 20%	$7,400.09	0.194	$38,108.39
Probability of cancer death in compliant disease negative patients increased by 20%	$7,359.18	0.183	$40,200.38
Probability of cancer death in compliant disease positive patients decreased by 20%	$7,390.15	0.189	$39,203.39
Probability of cancer death in compliant disease positive patients increased by 20%	$7,369.04	0.189	$39,056.51
Probability of cancer death in non-compliant disease negative patients decreased by 20%	$7,377.81	0.181	$40,735.43
Probability of cancer death in non-compliant disease negative patients increased by 20%	$7,381.33	0.196	$37,653.52

Scenario	Incremental cost	Incremental outcome	ICER (cost per QALY)
Base-case	***$7,379.57***	***0.189***	***$39,129.66***
Probability of cancer death in non-compliant disease positive patients decreased by 20%	$7,378.07	0.185	$39,827.81
Probability of cancer death in non-compliant disease positive patients increased by 20%	$7,381.04	0.192	$38,468.41
Probability non-compliant in THT withdrawal arm set to 20% (i.e. as in original MSAC evaluation published in 2002)	$7,152.31	0.211	$33,902.60
Probability non-compliant in THT withdrawal arm increased by 20% (i.e. from 14.4% to 17.28%)	$7,263.50	0.200	$36,313.22
Probability non-compliant in THT withdrawal arm decreased by 20% (i.e. from 14.4% to 11.52%)	$7,493.97	0.177	$42,262.64
Utility weights			
Difference in utility for Thyrogen arm versus THT-withdrawal in Pre-test and Test diagnostic phase reduced by 20% (i.e. rhTSH Pre-test and Test annual utility weight reduced to 0.7698)	$7,379.57	0.183	$40,386.19
Difference in utility for Thyrogen arm versus THT-withdrawal in Pre-test and Test diagnostic phase increased by 20% (i.e. rhTSH Pre-test and Test annual utility weight increased to 0.8362)	$7,379.57	0.194	$37,948.97
Removing incremental benefit of rhTSH in the second-post test period by setting second post-test utility in THT arm to parity with Thyrogen arm (i.e. second annual post test utility increased from 0.795 to 0.825)	$7,379.57	0.179	$41,330.28
Utility for a patient undergoing regular monitoring increased from 0.85 to 0.90 AND utilty for a patient that has had two negative stimulated tests and is no longer being monitored increased from annual weight of 0.880 to 0.930	$7,379.57	0.202	$36,487.61
Utility for a patient undergoing regular monitoring decreased from 0.85 to 0.80 AND utilty for a patient that has had two negative stimulated tests and is no longer being monitored decreased from annual weight of 0.880 to 0.830	$7,379.57	0.175	$42,184.20

Scenario	Incremental cost	Incremental outcome	ICER (cost per QALY)
Base-case	***$7,379.57***	***0.189***	***$39,129.66***
Disutility due to cancer decreased by 20% (i.e. from annual weight of -0.330 to -0.264)	$7,379.57	0.188	$39,175.99
Disutility due to cancer increased by 20% (i.e. from annual weigth of -0.330 to -0.396)	$7,379.57	0.189	$39,083.45
Discount rate			
3% costs and effects	$8,798.01	0.241	$36,521.81
0% costs and effects	$12,666.62	0.389	$32,555.21
Other sensitivity analyses			
Exploratory analysis: adding the cost of ultrasound (MBS Item: 55032 = $109.10) to diagnostic tests that do not include WBS (i.e. 28 month stimulated Tg test and unstimulated Tg scans). Assuming increased sensitivity and decreased specificity when ultrasound is combined with Tg tests. 28-month stimulated Tg test sensitivity increased from 81% to 91% and specificity decreased from 100% to 90%; unstimulated Tg testing sensitivity increased from 57% to 67% and specificity decreased from 79% to 69%).	$9,230.43	0.209	$44,103.84
Exploratory analysis: adding the cost of ultrasound (MBS Item: 55032 = $109.10) to diagnostic tests that do not include WBS (i.e. 28 month stimulated Tg test and unstimulated Tg scans). Assumes perfect sensitivity and specificity when ultrasound is combined with Tg tests. 28-month stimulated Tg test sensitivity increased from 81% to 100% and specificity remaining at 100%; unstimulated Tg testing sensitivity and specificity set to 100%	$4,372.27	0.169	$25,862.69
Multivariate sensitivity analyses			

Scenario	Incremental cost	Incremental outcome	ICER (cost per QALY)
Base-case	***$7,379.57***	***0.189***	***$39,129.66***
Thyrogen sensitivity reduced to 86% and specificity set to 95% at 10 months (i.e. as reported in Table 11 MSAC 2002 assessment) AND Probability non-compliant in THT withdrawal arm decreased by 20% (i.e. from 14.4% to 11.52%) AND Difference in utility for Thyrogen arm versus THT-withdrawal in Pre-test and Test diagnostic phase reduced by 20% (i.e. rhTSH Pre-test and Test annual utility weight reduced to 0.7698)	$7,877.20	0.134	$58,590.46
Thyrogen sensitivity and specificity equal to THT-withdrawal AND Probability non-compliant in THT withdrawal arm increased by 20% (i.e. from 14.4% to 17.28%) AND Difference in utility for Thyrogen arm versus THT-withdrawal in Pre-test and Test diagnostic phase increased by 20% (i.e. rhTSH Pre-test and Test annual utility weight increased to 0.8362)	$7,263.50	0.206	$35,278.34

A perfect reference standard test is one which correctly identifies the patient's true disease status in all cases. In many clinical circumstances there is no perfect reference standard that can unequivocally determine a patient's disease state. This is the case for patients undergoing monitoring for well differentiated thyroid cancer. The previous MSAC evaluation report used THT-withdrawal stimulated testing (i.e. the comparator) as a proxy for a perfect reference standard, despite the fact it is not 100% accurate at determining the true disease state of the patient. Therefore, by definition, in these analyses, THT-withdrawal stimulated testing will appear to have 100% diagnostic accuracy. Furthermore, any other testing method that is compared to this test will, by definition, appear to have less than perfect diagnostic accuracy. Consequently, the diagnostic accuracy results from the MSAC Evaluation Report, which indicated that Thyrogen-stimulated testing had a slightly lower sensitivity and specificity than THT-withdrawal-stimulated testing, represent a worst case scenario for Thyrogen. Indeed, the reverse could well be the case. A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation preparatory methods is that they have similar diagnostic accuracy. This is reflected by the high level of concordance seen between THT-withdrawal and Thyrogen-stimulation reported in the literature (Haugen *et al* 1999: 87% for serum Tg alone and 89.4% for dxWBS alone). In the event that these tests do not agree, the patient's true disease state will be best reflected by Thyrogen-stimulated testing in some cases and by THT-withdrawal stimulation in others. In fact, this is the conclusion drawn in a systematic review of Thyrogen published since the last MSAC review (Eustatia-Rutten *et al* 2004).

The conclusion that Thyrogen and THT-withdrawal stimulation preparatory methods have equivalent diagnostic accuracy is further supported by the leading clinical practice guidelines for the management of thyroid cancer published around the world (Pacini *et al* 2006a, Cooper *et al* 2006/2009, Pacini *et al* 2010). These expert groups recommended Thyrogen as a viable alternative to THT-withdrawal and these recommendations are based on a comprehensive literature search and careful analysis of all available data, as well as expert clinical opinion.

The value of Thyrogen lies principally in the important patient benefits of avoiding the signs, symptoms and significant morbidity of hypothyroidism and improving overall patient quality of life. Historically, THT-withdrawal has been the principal method of achieving the TSH stimulation required for follow-up monitoring in differentiated thyroid cancer. However, the acute adverse

effects associated with withdrawal-induced hypothyroidism have a significant impact on the patient and, in turn, wider society.

In a study by Schroeder *et al* (2006), SF-36 data from the pivotal randomised controlled trial of Thyrogen in the diagnostic setting were re-analysed. During this process, an important error was identified which was significantly affecting the original calculation of SF-36 scores reported by Haugen and colleagues (1999). The error was corrected and the SF-36 scores reported in Schroeder *et al* (2006) were then converted into utility weights for the purposes of economic evaluation (data on file). Patients rendered hypothyroid by the withdrawal of THT had a mean utility of 0.637, however when patients were maintained on THT prior to Thyrogen administration and WBS, mean utility was maintained at 0.803, a difference of 0.166 ($p < 0.0001$). This difference was identical to that observed between the Thyrogen and THT-withdrawal arms in the pivotal trial for ablation (Pacini *et al* 2006). The magnitude of disutility observed in both trials is not surprising given the clinical aim of THT- withdrawal is to increase serum TSH levels as rapidly as possible to the same target (>30 mU/L) that renders patients profoundly hypothyroid.

The effects of short-term hypothyroidism due to THT-withdrawal are profound and can lead to the development, as well as the exacerbation, of a range of physical and psychological morbidities. The use of Thyrogen means that individuals no longer have to suffer these morbidities, as they are maintained euthyroid throughout the diagnostic follow-up period.

12.1 Assessing the evidence for the clinical impact of the test

It is important to note that this application is a re-submission. Much of the information requested for this part of the application was also presented in the 2002 application. Importantly, many parts of the clinical argument for the safe and effective diagnostic use of Thyrogen have been previously accepted by the MSAC. Nevertheless, there is relevant information published since the 2002 MSAC Application (1043) that supports:

- The equivalent diagnostic accuracy of Thyrogen-stimulated compared with THT-withdrawal stimulated testing to detect thyroid remnant or cancer recurrence in patients with differentiated thyroid cancer.

- The quality of life and health-related quality of life benefits associated with the use of Thyrogen as opposed to the debilitating signs and symptoms of hypothyroidism subsequent to THT-withdrawal.

This application is not seeking a listing for either of the diagnostic testing methods (i.e. serum Tg measurement and dxWBS), rather an expanded MBS listing for Thyrogen, which is used to prepare patients for these tests.

CLINICAL EVIDENCE

The evidence base to support the diagnostic use of Thyrogen has increased since the publication of the initial MSAC Assessment Report. The MSAC Assessment report concluded that Thyrogen-stimulated testing has a relatively high sensitivity, specificity and accuracy in comparison with the reference standard (THT-withdrawal stimulated serum Tg and dxWBS). Importantly, the report makes it clear that interpreting the diagnostic effectiveness of Thyrogen relative to the comparator is difficult when the comparator serves as the reference standard and is recognised as arbitrary and imperfect. By this definition, it is impossible for Thyrogen serum Tg testing and dxWBS to have a better diagnostic accuracy than THT-withdrawal serum Tg testing and dxWBS. If a perfect reference standard were available, such that the patient's true disease state was known with certainty, Thyrogen stimulated testing may well prove to have an equivalent diagnostic accuracy to THT-withdrawal stimulated testing. In fact, this is what is implied in the clinical practice guidelines and consensus statements outlined below.

Pivotal diagnostic evidence

Clinical practice guidelines

Since the publication of the initial MSAC Assessment report in 2002, there have been a number of evidence-based clinical practice guidelines and consensus reports developed by expert clinicians and societies throughout the world that describe best practice management for patients with thyroid cancer. A summary of these guidelines and their recommendations in relation to TSH-stimulated diagnostic follow-up is outlined in **Table 34**.

The authors have concluded that the evidence supports that Thyrogen or THT-withdrawal can be used interchangeably to stimulate TSH in differentiated thyroid cancer patients undergoing follow-up with serum Tg testing or dxWBS. Leading organisations and associations throughout the world, and their associated clinicians, believe that Thyrogen and THT-withdrawal provide equivalent diagnostic accuracy when used to prepare patients for dxWBS or serum Tg testing.

Table 34 International clinical practice guidelines and effectiveness of diagnostic follow-up using Thyrogen

Guideline	Findings in relation to diagnostic follow-up with Thyrogen
Asia Pacific Region: A Report and Clinical Practice Guideline	TSH stimulation, either endogenously after withdrawal of thyroid hormone therapy or after administration of **recombinant TSH**, is essential for both radioiodine imaging and increasing the sensitivity of serum thyroglobulin monitoring for residual disease. The principal benefit of recombinant TSH is avoidance of the almost universal morbidity associated with temporary thyroid hormone withdrawal.
European Society of Medical Oncology (ESMO)	At 6–12 months the follow-up is aimed to ascertain whether the patient is free of disease. This follow-up is based on physical examination, neck US, basal and **rhTSH-stimulated** serum Tg measurement with or without diagnostic WBS. (Pacini *et al*, 2010, page 46).
American Thyroid Association (ATA)	In the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted following thyroid hormone withdrawal **or stimulation using rhTSH** (Cooper *et al* 2009, page 1186). There is good evidence that a Tg cutoff level above 2 ng/mL following **rhTSH stimulation** is highly sensitive in identifying patients with persistent tumor (Cooper *et al* 2009, page 1188) Recommendation 45 In low-risk patients who have had remnant ablation and negative cervical US and undetectable TSH-suppressed Tg within the first year after treatment, serum Tg should be measured after thyroxine withdrawal **or rhTSH stimulation** approximately 12 months after the ablation to verify absence of disease. Recommendation rating: **A** (Cooper *et al* 2009, page 1188). Recommendation 47 DxWBS, either following thyroid hormone withdrawal **or rhTSH**, 6–12 months after remnant ablation may be of value in the follow-up of patients with high or intermediate risk of persistent disease…Recommendation rating: **C** (Cooper *et al* 2009, page 1189).
Latin American Thyroid Society	In patients with low-risk thyroid carcinoma, serum Tg and Tg-Ab measurement following L-T4 withdrawal **or rhTSH administration** should be performed around 12 months after surgery. A Tg cut-off level of 2 ng/mL after rhTSH stimulation is highly sensitive to identify patients with persistent tumour (Pitoia, 2009, page 890). An increase in TSH levels should be obtained before administration of ^{131}I for diagnosis or therapeutic purpose. High TSH levels can be achieved after three to four weeks of thyroid hormone withdrawal… . **Another option is the administration of rhTSH** (0.9 mg intramuscularly) for two consecutive days, followed by ^{131}I on the third day. Serum Tg should be measured on the fifth day, when performed after rhTSH administration, and before radioiodine administration, when performed after withdrawal (page 892)
European Association of Nuclear Medicine (EANM)	An alternative to THW for attaining TSH elevation is **rhTSH administration**. In Europe and elsewhere, this drug has been approved for use in adults as preparation for serum Tg testing, dxWBS or both or for radioiodine ablation (Luster *et al*, 2008, page 1946). dxWBS should not take place sooner than 72 h after radioiodine administration during THW or sooner than 72 h **after the second injection of rhTSH**. (page 1951)
British Thyroid Association	Recommendations for the use of rhTSH-stimulated Tg in routine follow-up: TSH stimulation for measurement of serum Tg (or for WBS) can be achieved by thyroid hormone withdrawal **or by administration of rhTSH**. (British Thyroid Association and Royal College of Physicians, 2007; Pitoia *et al*, 2009 page 28)

Guideline	Findings in relation to diagnostic follow-up with Thyrogen
European Thyroid Association	TSH stimulation can be achieved by two alternative methods: 1. Thyroid hormone withdrawal: LT4 treatment is withdrawn for 4–5 weeks… 2. **rhTSH injections**: rhTSH (0.9 mg) is injected i.m. for consecutive days (days 1 and 2) and ^{131}I is administered on the day after the second injection (day 3). Role of diagnostic ^{131}I whole body scan: TSH stimulation is obtained with prolonged thyroid hormone withdrawal **or with rhTSH injections**. (Pacini *et al*, 2006a, page 154)
France- Society for endocrinology	**rhTSH** is recommend for all "first control" at 6-12 months with ultrasonography (Vantyghem *et al*, 2007, page 19 and 20)
Portugal- Society of endocrinology, diabetes and metabolism	Traditionally, differentiated thyroid cancer follow-up protocols include periodical measurement of thyroglobulin and whole-body whole body scan with radioactive iodine, for which treatment with levothyroxine is interrupted. DFTC follow-up protocols based on measurement of thyroglobulin after **stimulation with rhTSH** have recently been put forward. Preparation for treatment with ^{131}I in most cases involves inducing hypothyroidism, which is done by prolonged suspension of thyroid hormone medication. **The availability of recombinant human TSH (rhTSH) has paved the way for its use in preparing for radioactive iodine treatment**. (Rodrigues *et al*, 2005, page 9).

Systematic review

Since the publication of the MSAC Evaluation Report, a systematic review has been conducted which examined serum Tg measurements in the follow-up of differentiated thyroid carcinoma (Eustatia-Rutten *et al* 2004). The authors conducted a literature search of Medline from 1975 to 2003 using the search terms 'thyroid carcinoma' and 'thyroglobulin'. Seven articles were included for the analysis of the diagnostic accuracy of Thyrogen-stimulated serum Tg testing. The review used the Tg cut-off values and reference standard tests that were reported in the original articles. The study reported the sensitivity of serum Tg using Thyrogen stimulation as 92.5% ± 1.8. The specificity of Thyrogen-stimulated Tg testing was slightly lower than after THT-withdrawal stimulated testing (88.0% ± 1.3). The use of variable and imperfect reference standard tests may explain the slightly lower specificity observed for Thyrogen-stimulated testing.

Characteristics of the comparative diagnostic studies

There were six comparative studies identified in the literature search describing the diagnostic use of Thyrogen for the follow-up of patients with differentiated thyroid cancer. Quality of the included studies was assessed using the NHMRC dimensions and levels of evidence for diagnostic accuracy studies (**Table 35** and **Table 36**).

Table 35 NHMRC dimensions of evidence

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

Source: NHMRC 2000

Table 36 NHMRC levels of evidence

Level	Diagnostic accuracy
I	A systematic review of Level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among consecutive patients with a defined clinical presentation †
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among non-consecutive patients with a defined clinical presentation†
III-2	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	Diagnostic case-control study †
IV	Study of diagnostic yield (no reference standard) ‡‡

Source: NHMRC 2005

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes.

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews.

† Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Hierarchies adapted and modified from: NHMRC 2000; Bandolier 1999; Lijmer *et al* 1999.

A summary of the included study characteristics and a quality appraisal is provided in **Table 37**. There were three studies classified as Level II evidence (Haugen *et al*, 1999; Ladenson *et al*, 1997 and Pacini *et al*, 2001), two as Level III-2 (Mazzaferri and Kloos 2002; Meier 1994) and one classified as Level III-3 evidence (Robbins *et al* 2001). Four of the comparative studies identified

were prospectively designed and two were retrospective in design. Three studies reported blinding of the dxWBS evaluation and no studies reported blinding of the serum Tg tests; however, Tg is an objective measure and therefore less susceptible to observer bias. Due to the nature of THT-withdrawal, it was not possible to blind the patients to the diagnostic modes used. Therefore, all the studies identified were performed in an open-label fashion.

The study by Haugen *et al* (1999) provides evidence for the effectiveness of Thyrogen-stimulated serum Tg testing and WBS compared to THT withdrawal and serum Tg testing and WBS. The TGA recommended dosage and schedule of Thyrogen (0.9 mg once per day for two days) was used only in Arm 1 of the study. Arm II did not use a TGA approved dosing regimen and therefore the results from this arm have been excluded from the analysis. The study by Ladenson *et al* (1997) also provides pivotal evidence on the clinical effectiveness of Thyrogen when used with dxWBS as an adjunct diagnostic agent. The study also measured serum Tg in a small sub-group of patients. However, this was performed in an inconsistent manner and at a suboptimal time point (24 hours after Thyrogen administration); therefore the serum Tg data reported in this study were excluded.

The Mazzaferri and Kloos (2002) study was a retrospective-cohort study designed to determine the diagnostic accuracy of Thyrogen stimulated serum Tg alone. Patients must have been free of disease and had ≥1 undetectable or low serum Tg measurement on THT to qualify for inclusion. A combination of variable reference standards were applied to assess the efficacy of Thyrogen as an adjunct to serum Tg. In general, the clinical assessments were more thorough as the Thyrogen-stimulated serum Tg level increased. The variation in the reference standard is likely to introduce partial verification bias and differential reference bias into the study results (Lijmer *et al*, 1999). Therefore, the results of this study were excluded from further consideration in the effectiveness analysis of Thyrogen. The study by Pacini *et al* (2001) was a prospectively designed, open-label trial conducted in 72 consecutive patients with undetectable on-T4 serum Tg levels. The study provides evidence on the effectiveness and diagnostic accuracy of Thyrogen-stimulated serum Tg alone.

The study by Robbins (2001) was a retrospective, open-label, parallel cohort design. Accordingly it is classified as Level III-3 evidence in the NHMRC levels of evidence. Patients were assigned to the study arms by need (patients who could not produce sufficient endogenous TSH, or those unable to tolerate hypothyroidism) or by patient choice in a non-randomised manner and as such the study is likely to have been subject to considerable bias. Therefore, the results of this study were excluded from the pivotal evidence of Thyrogen effectiveness and been included as supportive evidence only. The Meier *et al* (1994) study was a phase I/II dose ranging study with sequential diagnostic measurements. Patients were randomised to seven different dosing regimens (10 U/day (1, 2 or 3 days), 20 U/day (1 or 2 days), 30 U/day (1 day) or 40 U/day (1 day). Due to the low number of patients receiving the TGA approved dose of Thyrogen (N=3), this study was also excluded from the efficacy assessment.

Table 37 Pivotal diagnostic comparative studies

Author (year)	Study design	Population characteristics	Bias[a]	Level
Haugen *et al* (1999)	Prospective, randomised, open-label, evaluator-blinded (only for dxWBS not Tg), with sequential diagnostic measurements. Patients were randomised to two different dosing regimens (Arm I- 2 x Thyrogen 24 hours apart; Arm II- 3 x Thyrogen 72 hours apart, followed by THT-withdrawal)	N=229 enrolled, 226 completed Arm I (N=117) (74F; 43M); Arm II (N=112) (74F; 38M) Mean age: Arm I (44±15); Arm II (50±16) Cancer type: papillary (N=142); papillary/follicular (N=40); follicular (N=39); hurthle cell (N=8) Inclusion criteria: Patients with differentiated thyroid cancer, all but one had undergone a total or near total thyroidectomy. 83% had received prior radioiodine therapy. None of the patients had a concurrent major medical disorder.	Blinding of evaluators: Yes for WBS Selection bias: Consecutive recruiting of patients not reported Verification bias: No Withdrawal rate: 1.3%	II
Ladenson *et al* (1997)	Prospective, evaluator-blinded, open-label with sequential diagnostic measurements. Patients received Thyrogen stimulated WBS ± Tg, then THT-withdrawal stimulated WBS ± Tg. Thyrogen group received 0.9 mg Thyrogen on two consecutive days before the administration of ^{131}I.	N=152 enrolled, 127 completed (90F; 37M) Mean age: 44 yrs (20–84 yrs) Cancer type: papillary (N=112); follicular (N=12); hurthle cell (N=3) Inclusion criteria: Patients with differentiated thyroid cancer for whom radioiodine scanning was indicated. All but one patient has undergone total or subtotal thyroidectomy, and most had received radioiodine therapy.	Blinding of evaluators: Yes. Three reviewers blinded to diagnostic regimen Selection bias: Partial. Consecutive patients but large drop-out rate. Verification bias: No Withdrawal rate: 16.4%	II
Mazzaferri and Kloos (2002)	Retrospective cohort, open-label, with a combination of variable reference standards Patients received Thyrogen and Tg, then a range of other clinical assessments as the reference standard, not administered uniformly.	N=107 (88F; 19M) Median age: 36.3 yrs (10.9–85.3 yrs) Cancer type: typical papillary carcinoma (N=89); follicular (N=12); hurthle cell (N=6) Inclusion criteria: Patients with papillary or follicular thyroid cancer without anti-Tg antibodies who had undergone Thyrogen testing between January 8, 1999, and March 23, 2001. Must have been free of disease and had ≥1 undetectable or low serum Tg measurement on THT.	Blinding of evaluators: NA Selection bias: No Verification bias: NA Withdrawal rate: NA	III-2
Pacini *et al* (2001)	Prospective, open-label, with sequential diagnostic measurements Patients received Thyrogen-stimulated Tg,	N=72 (51F; 21M) Mean age: 39.4 yrs (17–78 yrs) Cancer type: papillary (N=66); follicular (N=6) Inclusion criteria: undetectable (<1	Blinding of evaluators: Not reported. Selection bias: No. Consecutive patients.	II

Author (year)	Study design	Population characteristics	Bias[a]	Level
	then THT-withdrawal stimulated WBS and Tg. Thyrogen group received 0.9 mg Thyrogen 24 and 48 hours before the administration of ^{131}I.	ng/ml) serum Tg, on L-T_4 suppressive therapy, and negative anti-Tg antibodies at the time of inclusion	Verification bias: No. All patients received Thyrogen stimulated Tg and THT-withdrawal stimulated Tg + WBS. Withdrawal rate: 0%	
Robbins *et al* (2001)	Retrospective, open-label, non-randomised, parallel cohort Thyrogen group received 0.9 mg Thyrogen 24 and 48 hours before the administration of ^{131}I.	N=128 (Thyrogen); 161 (THT-withdrawal) Mean age: 45.6 (Thyrogen); 44.2 (THT-withdrawal) Cancer type: papillary (N=239); follicular (N=21); hurthle cell (N=16) Inclusion criteria: all individuals referred to Nuclear Medicine section of the Memorial Hospital for Cancer, New York between January 1, 1998 and December 31, 1999.	Blinding of evaluators: No Selection bias: Yes. Non randomised parallel groups Verification bias: NA Withdrawal rate: NA	III-3
Meier *et al* (1994)	Prospective, multicentre, dose ranging study with sequential diagnostic measurements. Randomised to seven different dosing regimens (10U/day (1, 2 or 3 days), 20 U/day (1 or 2 days), 30U/day (1 day) or 40U/day (1 day) Sequential diagnostic testing; firstly Thyrogen with neck and WBS, then TSH-withdrawal with neck and WBS.	N=19 (13F; 6M) Median age: 42 yrs (22–62 yrs) Cancer type: papillary (N=17); follicular (N=2) Inclusion criteria: Not reported	Blinding of evaluators: Yes, independent review of scans conducted Selection bias: it was not reported whether patients were consecutively recruited Verification bias: No, all patients received both tests Withdrawal rate: 0%	III-2

[a] Due to the nature of hypothyroidism, blinding of the participants is not possible
Selection bias: if patients were not consecutively selected
Verification bias: when all patients don't receive the reference standard test (i.e. WBS and/or serum Tg)

In the included studies, in almost all situations, the comparator is the same as the reference standard. This is problematic for the measurement of diagnostic accuracy because, by definition, the reference test identifies the patients 'true' disease status, and therefore when the reference test is also the comparator, it is impossible for the index test (the new test) to be better than the comparator test. The new Health Technology Assessment guidelines for co-dependent technologies recognise this situation and recommend that in this circumstance the concordance between tests is an important determinant of comparative diagnostic performance and, therefore, should be reported.

In the analysis conducted here, a positive classification was assigned to all patients with a THT-withdrawal serum Tg ≥ 2 ng/mL or a dxWBS classification ≥ class 1 (i.e. including uptake limited to thyroid bed (class 1) and uptake outside the thyroid bed (>1)). A summary of the reference standard used in the study, the index test used in the current analysis, the reference standard used in the current analysis and the data available for each included study is provided in **Table 38**.

Table 38 Included study reference standards and test outcomes available

Study	Reference standard reported in publication	Index test used in this assessment	Reference standard used in this assessment	Thyrogen			THT-withdrawal		
				Tg + dxWBS	Tg alone	dxWBS alone	Tg + dxWBS	Tg alone	dxWBS alone
Haugen *et al* (1999)	THT-withdrawal stimulated serum Tg ≥ 2 ng/mL and/or dxWBS ≥ 1	Thyrogen-stimulated serum Tg ≥ 2 ng/mL *or* dxWBS ≥ 1	THT-withdrawal stimulated serum Tg ≥ 2 ng/mL *or* dxWBS ≥ 1	✓	✓	✓	✓	✓	✓
Ladenson *et al* (1997)	THT-withdrawal stimulated dxWBS ≥ 1	Thyrogen-stimulated dxWBS ≥ 1	THT-withdrawal stimulated dxWBS ≥ 1	×	× [a]	✓	×	× [a]	✓
Pacini *et al* (2001)	THT-withdrawal stimulated dxWBS ≥ 1 and/or serum Tg > 1 ng/mL	Thyrogen-stimulated serum Tg ≥ 1 ng/mL	THT-withdrawal stimulated serum Tg ≥ 1 ng/mL *or* dxWBS ≥ 1	×	✓	×	✓	✓	✓
Mazzaferri and Kloos (2002)	*Variable*	***Not used***		✓	✓	✓	*b*	*b*	✓
Robbins et al (2001)	*Composite of all clinical information*	***Not used***		✓	✓	✓	✓	✓	✓
Meier et al (1994)	*THT-withdrawal stimulated serum Tg or dxWBS ≥ 1*	***Not used***		✓	✓	✓	✓	✓	✓

Abbreviations: Tg, Thyroglobulin; THT, thyroid hormone withdrawal; WBS, whole body scan

[a] Serum Tg was not uniformly measured and measured at an inappropriate time point

[b] Tests varied between patients; these included physical examination, chest x-ray, diagnostic WBS, post-therapy WBS, neck ultrasound, fine needle cytology, surgical pathology, and whole body positron emission tomography

Diagnostic accuracy: overview

The effectiveness measure used for this assessment was the diagnostic accuracy of Thyrogen-stimulated serum Tg testing and dxWBS compared with THT-withdrawal stimulated serum Tg testing and dxWBS. The accepted methodology for investigating the accuracy of new diagnostic tests is to compare the diagnosis made with the new test with the true disease status. However, it is often not feasible to determine the disease status of a patient unequivocally. Therefore, in many disease states a proxy measure, such as another diagnostic test or clinical judgement, must be used. The best available measure of disease is called the reference standard. Both the Thyrogen result and the comparator result must be independently compared to the reference standard to assess accuracy, before the difference in accuracy between Thyrogen and the comparator can be determined (MSAC Assessment Report 2002). Currently, the best available indicators of the presence of thyroid remnants or thyroid cancer in patients who had near-total thyroidectomy are an elevated serum Tg or a positive dxWBS.

The study by Haugen *et al* (1999) provides the primary evidence for the assessment of diagnostic accuracy of Thyrogen-stimulated serum Tg testing and dxWBS compared to THT-withdrawal stimulated serum Tg testing and dxWBS. The study by Ladenson *et al* (1997) provides evidence for the diagnostic accuracy of Thyrogen-stimulated dxWBS alone. There were a number of shortcomings in this study, most notably a significantly lower WBS retention of radioiodine after Thyrogen stimulation compared with THT-withdrawal (Haugen *et al* 1999). Clearance of radioiodine is decreased by about one third during the hypothyroid withdrawal phase compared with the euthyroid Thyrogen phase, leading to a two-fold increase in whole body retention of radioiodine at 48 hours after the radioiodine dose. Subsequent studies have used a slower scanning speed and minimum total count number for each image rather than scanning for a defined period of time, thereby minimising potential count-poor scans after Thyrogen administration.Also a minimum dose of radiodine 131 (4 mCi) was specified for the Haugen study. When lower doses are applied, it was hypothesized that there would be insufficient uptake under rhTSH because of the differences in kinetics. Finally, a standardised, objective method for assessing scans was introduced.

In Ladenson *et al* (1997), the analysis of Thyrogen-stimulated serum Tg alone has not been used because Tg was not prospectively defined or uniformly measured. Pacini *et al* (2001) examines the diagnostic accuracy of Thyrogen-stimulated serum Tg alone, compared with THT-withdrawal stimulated serum Tg with or without dxWBS.

Unfortunately, in the study by Mazzaferri and Kloos (2002), an assortment of reference tests were applied; consequently it was considered that results may have been biased (partial verification bias and differential reference bias) and so the results of the study have not been reported here. They are, however, described in the supportive evidence section which follows. The study by Robbins *et*

al (2001) compared Thyrogen and THT-withdrawal stimulated Tg with or without WBS. The design was a retrospective parallel cohort study (i.e. different patients in each arm), which is inappropriate for accurately assessing the comparative accuracy of Thyrogen and therefore this study has been excluded. Meier *et al* (1994) has been excluded from the results because of small sample size and use of a dosing regimen (in most patients) that is not consistent with the TGA approved dosing regimen for Thyrogen.

Pivotal diagnostic evidence: concordance

Haugen *et al* (1999)

Serum Tg alone

Of the 229 patients in the study, 35 (15%) had detectable serum Tg antibodies. Only those who had undergone previous ablation of thyroid tissue (<1% in the thyroid bed) and had negative serum Tg antibodies were studied further. A serum Tg of ≥ 2 ng/mL was chosen as the cut-off value to indicate the presence of thyroid tissue. One hundred and five patients had a serum Tg level of 2 ng/mL or more after THT-withdrawal stimulation. Overall, serum Tg ≥ 2 ng/mL was concordant between Thyrogen and THT-withdrawal-stimulated patients in 91/105 (87%) cases.

To evaluate the ability of Thyrogen-stimulated serum Tg levels to detect thyroid remnant or cancer, 46 patients with withdrawal or post-therapy radioiodine uptake in the thyroid bed (class 1) and 30 patients with metastatic disease defined as post-therapy scans with uptake outside the thyroid bed (class ≥ 2) had Tg measurements after Thyrogen stimulation and after THT-withdrawal stimulation. Tg levels of 2 ng/mL or more and 5 ng/mL or more were used as cut-off values for disease detection. An elevated Tg was detected after Thyrogen-stimulation in 52% and 35% using these cut-off values. In comparison, an elevated Tg was detected after THT-withdrawal in 56% and 43% at the 2 and 5 ng/mL cut-off levels, respectively. For patients with cancer outside the thyroid bed, an elevated Tg level was detected after Thyrogen-stimulation in 100% and 97% of these patients with metastatic disease at these cut-off values. These results suggest that Thyrogen can be used interchangeably with THT-withdrawal for patients requiring a serum Tg test during follow-up.

dxWBS alone

The primary efficacy endpoint of the Haugen *et al* (1999) study was concordance of Thyrogen-stimulated and THT-withdrawal stimulated testing based on diagnostic ^{131}I imaging. If both of the patient's scans were identified to have the same clinically relevant location and extent of thyroid remnant or cancer, the two scans were rated with an equal class and considered concordant. If one dxWBS from the pair detected thyroid remnant or cancer but the other scan did not, the scans were considered discordant. A higher classification rating was given to the dxWBS that revealed the presence of thyroid remnant or thyroid cancer that was not seen on the other scan.

The concordance between Thyrogen-stimulated dxWBS and THT-withdrawal stimulated dxWBS is shown in **Table 39**. Scans were concordant between the two testing methods in 101/113 (89.4%) patients. The Thyrogen-stimulated scan showed a higher or concordant uptake classification to the THT-withdrawal stimulated scan in 104/113 (92.0%) patients. There were nine scans considered superior in the THT-withdrawal stimulated group. The difference in the number of superior scans with THT-withdrawal preparation compared with Thyrogen preparation was not significant.

Table 39 Concordant scans for the Thyrogen phase and THT-withdrawal phase

Thyrogen-stimulated dxWBS	**THT-withdrawal stimulated dxWBS**		
	Positive	Negative	
Positive	48	3	51
Negative	9	53	62
	57	56	113
Concordance (%)			
Concordant scans	89.4%		
Discordant scans	10.6%		

Source: Haugen *et al* (1999): Table 3, page 113

Metastatic disease was defined as disease outside the thyroid bed on a diagnostic or post-therapy scan, and/or an elevated serum Tg (≥10 ng/mL) during THT-withdrawal in the absence of a positive diagnostic scan at the time of the study. Based on this definition, 49 patients (22%) had metastatic disease. Ten of these patients had an elevated serum Tg as the only evidence of disease. Thirty-nine patients (80%) had concordant scans, 2 (5%) had superior Thyrogen scans, and 8 (16%) had superior withdrawal scans. There was no significant difference in the number of superior Thyrogen or withdrawal scans within either study arm or between arms I and II.

dxWBS and Tg

Due to insufficient data reported in the Haugen *et al* (1999) study the concordance rate between Thyrogen-stimulated testing and THT-withdrawal-stimulated testing using both serum Tg and dxWBS was unable to be calculated. Given the high rates of concordance between the two methods of patient preparation in serum Tg alone and dxWBS alone, the concordance for the two tests combined is expected to also be high.

Pacini *et al* (2001)

Serum Tg alone

A study by Pacini and colleagues (2001) examined the concordance of Thyrogen-stimulated testing and THT-withdrawal stimulated testing in 72 consecutive patients. Of 41 patients with a negative Tg result (< 1.0 ng/mL) after Thyrogen administration, 36 patients (88%) were also negative based on their THT-withdrawal Tg results (**Table 40**). Of 31 patients with a positive Thyrogen-stimulated Tg result, 100% were shown to be concordant with THT-withdrawal stimulated serum Tg.

Therefore the overall concordance was 67/72 (93.1%). This suggests that Thyrogen and THT-withdrawal can be used interchangeably to achieve the TSH stimulation required for accurate serum Tg diagnostic tests.

Table 40 Concordance results of THT-withdrawal stimulated Tg and Thyrogen-stimulated Tg

		THT-withdrawal stimulated Tg (ng/ml)		
		> 1.0	<1.0	No. cases
Thyrogen stimulated peak Tg (ng/ml)	< 1.0	5	36	41
	> 1.0	31	0	31
No. of cases		36	36	72

Source: Pacini *et al* (2001), Figure 3, page 5688.

Ladenson *et al* (1997)

DxWBS alone

In the Ladenson *et al* (1997) study 152 patients were prospectively enrolled and assessed by sequential diagnostic testing with Thyrogen preparation and THT-withdrawal preparation. Two dxWBS with ^{131}I were obtained in each patient, the first scan was performed after administration of Thyrogen while the patient continued THT, and the second was performed after THT-withdrawal. Reviewers evaluating the scans were blinded to the treatment allocation. The numbers and locations of the foci of uptake were compared within each pair of scans to classify the two scans as concordant or discordant. If a pair of scans was discordant, the scan with the greater number of foci or the more widespread distribution of foci was considered superior (Ladenson *et al* 1997).

There were a number of shortcomings in this study, most notably a significantly lower WBS retention of radioiodine after Thyrogen stimulation compared with THT-withdrawal (Haugen *et al* 1999). Clearance of radioiodine is decreased by about one third during the hypothyroid withdrawal phase compared with the euthyroid Thyrogen phase, leading to a two-fold increase in whole body retention of radioiodine at 48 hours after the radioiodine dose. Subsequent studies have used a slower scanning speed and minimum total count number for each image rather than scanning for a defined period of time, thereby minimising potential count-poor scans after Thyrogen administration.

The concordance between Thyrogen-stimulated dxWBS and THT-withdrawal stimulated dxWBS was moderate. Among the 127 patients qualifying for inclusion in the efficacy evaluable population analysis, the reviewers rated the scans obtained after administration of Thyrogen as equivalent in 106 patients (83.5%) or superior in 3 patients (2.3%) to those obtained after THT-withdrawal stimulated dxWBS. The rates of concordant and discordant pairs of scans were similar whether or not the patient had received ^{131}I therapy previously (Ladenson clinical study report 1997).

Supportive diagnostic evidence: diagnostic accuracy with an imperfect reference standard

Haugen *et al* (1999)

DxWBS and serum Tg

The results of the within patient comparison indicated that Thyrogen and THT-withdrawal were comparable in stimulating ^{131}I uptake for effective diagnostic imaging as no statistically significant differences were found in uptake between the two methodologies. Seventy-eight patients in Arm I (TGA approved Thyrogen dosage regimen) of the study underwent both a dxWBS and serum Tg test after preparation with Thyrogen and via THT-withdrawal. The diagnostic performance of Thyrogen-stimulated testing compared with THT-withdrawal stimulated testing is shown in **Table 41**. This analysis of Thyrogen-stimulated testing demonstrates relatively high sensitivity, specificity, and accuracy in comparison to the (albeit artificial) reference standard. Altering the serum Tg positive cut-off level has a modest effect on the accuracy of Thyrogen. It is also important to note that Thyrogen detected all (100%) of patients with metastatic disease.

As explained previously, in these analyses, THT-withdrawal stimulated testing will appear to have 100% diagnostic accuracy. Therefore, any other testing method that is compared to this will appear to have less than perfect diagnostic accuracy. Consequently these results, which have been replicated from the 2002 MSAC Evaluation Report, represent a worst case scenario for Thyrogen. Indeed the opposite could well be the case. A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation is that they have similar diagnostic accuracy. This is reflected by the high level of concordance between THT-withdrawal and Thyrogen-stimulation. Where these tests do not agree, the patient's true disease state will be best reflected by Thyrogen-stimulated testing in some cases and by THT-withdrawal stimulation in others, seen in both Haugen *et al* 1999 and Ladenson *et al* 1997.

Table 41 Thyrogen/THT-withdrawal dxWBS and serum Tg effectiveness in all patients (as presented in MSAC Evaluation Report)

Trial	Reference standard	Testing mode	Serum Tg assay and dxWBS positive definition	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen *et al* (1999) [a]	THT-withdrawal stimulated serum Tg ≥ 2ng/mL *or* WBS ≥ 1	Thyrogen-stimulated dx WBS and Tg	≥ 2 ng/mL WBS ≥ 1	86%	95%	89%	98%	70%
		THT-withdrawal stimulated dxWBS and Tg	≥ 2 ng/mL[b] WBS ≥ 1	100%	100%	100%	100%	100%
		Thyrogen-stimulated dx WBS and Tg	≥ 5 ng/mL WBS ≥ 1	82%	95%	85%	98%	64%
		THT-withdrawal stimulated dxWBS and Tg	≥ 5 ng/mL WBS ≥ 1	91%	100%	93%	100%	79%

Source: Haugen *et al* (1999), Clinical Study Report and MSAC Evaluation Report 2002
Abbreviations: Tg, Thyroglobulin; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value; WBS, whole body scanning
[a] who tested positive for Tg antibodies were excluded from the evaluation of *Thyrogen* accuracy
[b] this measure is identical to the reference standard, so 100% accuracy is implicit

Serum Tg alone

Diagnostic accuracy measures for Haugen *et al* (1999) were calculated using THT-withdrawal stimulated testing as the reference standard. When interpreting the results it is important to remember that the assignment of this measure as a positive reference standard is arbitrary, and that because THT-withdrawal stimulated testing is not 100% accurate at detecting the patient's true disease status, this reference standard is imperfect. Nevertheless, for consistency with the MSAC evaluation report, the results of the analyses are shown in **Table 42**.

Table 42 Thyrogen/THT-withdrawal stimulated serum Tg effectiveness

Trial	Reference standard	Testing mode	Serum Tg assay positive definition	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen *et al* (1999) [a]	THT-withdrawal stimulated serum Tg ≥ 2ng/mL *or* WBS ≥ 1	Thyrogen-stimulated Tg	≥ 2ng/mL	71%	100%	78%	100%	54%
		THT-withdrawal stimulated Tg	≥ 2ng/mL	81%	100%	85%	100%	63%
		Thyrogen-stimulated Tg	≥ 5ng/mL	65%	100%	74%	100%	50%
		THT-withdrawal stimulated Tg	≥ 5ng/mL	70%	100%	78%	100%	52%

Source: MSAC Evaluation Report 2002
Abbreviations: Tg, thyroglobulin; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value.
[a]Patients who tested positive for Tg antibodies were excluded.
[b]Data not available to calculate statistical significance.

Pacini *et al* (2001)

Serum Tg alone

The diagnostic accuracy of Thyrogen-stimulated serum Tg testing was compared with THT-withdrawal stimulated serum Tg testing. It should be noted that the results for this study as presented in the MSAC Evaluation Report were incorrect. The results have been corrected and are presented in **Table 43**. The sensitivity of Thyrogen-stimulated serum Tg was 100%, specificity 73%, PPV 74% and NPV 100%. The 100% NPV result indicates that Thyrogen-stimulated Tg did not miss any cases of disease detected by THT-withdrawal-stimulated Tg and dxWBS. Overall, Thyrogen-stimulated serum Tg and THT-withdrawal stimulated serum Tg have comparable diagnostic accuracy. However, both Thyrogen-stimulated and THT-withdrawal stimulated serum Tg alone have lower diagnostic accuracy than a reference standard that incorporates both serum Tg and dxWBS.

Table 43 Thyrogen/THT-withdrawal stimulated serum Tg diagnostic accuracy (corrected)

Trial	Reference standard	Testing mode	Serum Tg assay positive definition	Sensitivity	Specificity	Accuracy	PPV	NPV
Pacini (2001)[ab]	THT-withdrawal stimulated dxWBS ≥ class 1 and/or serum Tg > 1 ng/mL	Thyrogen-stimulated serum Tg	>1 ng/mL	100%	73%	85%	74%	100%
		THT withdrawal stimulated serum Tg	> 1 ng/mL	100%	83%	92%	86%	100%

Abbreviations: Tg, thyroglobulin;, THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value.
[a]Patients who tested positive for Tg antibodies were excluded.
[b]Data not available to calculate statistical significance.

Since the publication of these results, the functional sensitivity of Tg testing has been markedly improved due to improvements in the assay such that the accuracy of serum Tg testing alone is likely to be considerably higher, particularly in patients who have undergone a previous negative dxWBS and serum Tg and are considered low-risk for disease recurrence (Cooper *et al*, 2009). According to the ATA clinical practice guidelines, in the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted following THT-withdrawal or stimulation using Thyrogen (Cooper *et al*, 2009). Again, it must be noted that interpreting the diagnostic effectiveness of Thyrogen-stimulated testing relative to the comparator is difficult when the assignment of the comparator as the reference standard is arbitrary and this reference standard is imperfect.

Other supportive diagnostic evidence

A large retrospective study which looked at thyroid cancer recurrence in 289 post-thyroidectomy patients over a two year span also provides evidence for the efficacy of diagnostic testing with Thyrogen (Robbins, 2001). The study included patients who had either been given Thyrogen or undergone THT-withdrawal in preparation for testing using a combination of dxWBS and serum Tg. The study was designed with two parallel groups, meaning a different cohort of patients received Thyrogen to those that received THT-withdrawal, and therefore the groups were not directly comparable. Nevertheless, the mean ages, gender, median stimulated Tg levels and frequency of total thyroidectomy were similar between the two groups. The reference standard, rather than being the same as the comparator (THT-withdrawal), was a composite clinical measure consisting of multiple different tests and clinical judgment. When both the dxWBS and stimulated Tg were considered together as a combined test, the sensitivity and specificity between the Thyrogen-stimulated testing and THT-withdrawal stimulated testing groups was comparable (Robbins *et al* 2001). When both the dxWBS and stimulated Tg were negative, only one patient in

the Thyrogen group had metastatic disease, producing a NPV of 97%. This again supports the comparative accuracy of Thyrogen-stimulation to THT-withdrawal as the preparatory technique for patients requiring diagnostic follow-up.

There are also a number of non-comparative studies of Thyrogen that support its effectiveness as an adjunct diagnostic agent in the follow-up of patients with differentiated thyroid cancer. A retrospective chart review was conducted in Australia to determine if Thyrogen was equivalent to THT-withdrawal in terms of diagnostic accuracy (Wong *et al*, 2009). Ninety patients who had received the approved dose of Thyrogen were measured for remnant thyroid tissue and cancer using dxWBS and serum Tg tests. Serum Tg was defined as positive if ≥ 1.0 μg/L. Most patients in the study had a previously undetectable Tg and negative WBS following THT-withdrawal and hence were considered low-risk. Of the 85 patients with enough information for analysis, 64 (75%) had concordant negative Thyrogen-stimulated-Tg and Thyrogen-stimulated dxWBS results. Nineteen patients had negative dxWBS but positive Thyrogen-stimulated Tg and two patients had positive Thyrogen-stimulated dxWBS and negative Thyrogen-stimulated Tg. The study concluded that Thyrogen-stimulation was effective and safe in the management of thyroid cancer follow up and that dxWBS may be omitted in low risk patients (Wong *et al* 2009).

Another large study (N=104) examined the use of Thyrogen in patients who had refused to undergo or were contraindicated to THT-withdrawal (Giovanni *et al*, 2002). Patients with histologically proven differentiated thyroid cancer were evaluated with Thyrogen-stimulated serum Tg and dxWBS. Of the 86 patients with negative dxWBS, 40 had undetectable Thyrogen-stimulated serum Tg levels, 27 had barely detectable (< 1 ng/ml), 11 patients had Tg levels between 1 and 2 ng/ml and eight patients had Tg level > 5 ng/ml during TSH stimulation. In the 78 patients with Thyrogen-stimulated Tg < 2 ng/ml and negative dxWBS, no sites of recurrence were revealed by ultrasound of the neck and liver, chest radiograph, radionuclide bone scan, Tg and dxWBS after THT-withdrawal. The study concluded that Thyrogen is an effective alternative to THT-withdrawal for dxWBS and serum Tg testing in patients thyroidectomised for differentiated thyroid cancer.

David and colleagues (2001) investigated Thyrogen use in 33 patients with differentiated thyroid cancer who were undergoing serum Tg and dxWBS. All subjects had undergone total or near-total thyroidectomy and were on THT sufficient to suppress serum TSH concentrations. All patients had undergone one previous dxWBS 6-24 months before the study. Patients were divided into two groups depending on serum Tg concentrations on THT: Group A included 29 patients with Tg < 2 ng/ml; Group B included four patients with Tg values of > 2 ng/ml. In Group A, serum Tg concentrations remained < 2 ng/ml in 25 patients and increased after Thyrogen stimulation in four patients from 1.1 ± 0.14 ng/ml to 22.0 ± 5.75 ng/ml. Diagnostic WBS obtained after Thyrogen-stimulation showed no uptake in the patients who did not have a rise in the serum Tg value, whereas uptake was observed in two of the four patients who had a rise in serum Tg concentration

(> 2 ng/ml). In Group B, dxWBS showed ^{131}I uptake in three of four patients with Tg > 2 ng/ml. The study concluded that in differentiated thyroid cancer patients on THT, Tg measurements should be performed after Thyrogen administration and may have a higher diagnostic value in comparison with dxWBS for identifying patients with remnant thyroid tissue or cancer.

Wartofsky *et al* (2002) and Robbins *et al* (2002) came to a similar conclusion as that of David and colleagues (2001) in the study described above. The study by Wartofsky *et al* (2002) was a multicentre study examining 300 eligible patients who were considered to be at low risk of recurrence for differentiated thyroid cancer. Patients underwent Thyrogen-stimulation to increase serum Tg levels. After administration, 53 (18%) patients had elevations in Tg of at least 2 ng/ml, including 33 (11%) patients with increases of Tg from baseline of equal to or greater than 5 ng/ml. Patients with an initial advanced stage of disease were more likely to display elevations in Tg after Thyrogen. One third of patients with stage III disease displayed elevations in Tg of 2 ng/ml. The results indicated that Thyrogen-stimulated Tg testing without dxWBS may be a useful tool in the follow-up of patients with low-risk thyroid cancer. Robbins *et al* (2002) also concluded that Thyrogen-stimulated Tg was an effective diagnostic tool for those patients classified as low risk.

A study by Diaz-Soto *et al* (2011) examined 92 consecutive patients with differentiated thyroid cancer in whom Thyrogen-stimulated tests were performed during follow-up after initial treatment with total thyroidectomy followed by post-surgery thyroid ablation. There were 16 males and 76 females studied with a mean age of 49.2 years. All patients underwent unstimulated Tg using a Tg assay with a functional sensitivity of 0.5 ng/ml and a cut-off detection value of 0.2 ng/ml and Thyrogen-stimulated Tg. Only patients who had a positive basal Tg test received a Thyrogen-stimulated Tg test and therefore the results of the study are likely to be subject to verification bias. In addition, the Thyrogen-stimulated cut-off value for a positive test result was not pre-specified. A cut-off of 0.925 ng/ml was used to calculate diagnostic accuracy measures but was chosen after observing the results. Consequently, the results of this study are subject to severe limitations.

Those with an undetectable Tg (<0.5 ng/ml) (63/92; 68%) underwent Thyrogen-stimulated Tg with 6/63 (9.5%) considered positive (>0.925 ng/ml). Neck US showed suspicious images in three patients, all of whom had a Thyrogen-stimulated Tg above 2 ng/ml. Three patients with Thyrogen-stimulated Tg <2 ng/ml were closely followed and three years later remained free of disease, without a further increase in Tg level. This study showed that Thyrogen-stimulated Tg was more sensitive than unstimulated Tg, identifying three patients with recurrent disease that would have otherwise been undetected.

Fumarola *et al* (2010) undertook a prospective case series examining 66 consecutive patients with DTC, stage I to IV, who had previously undergone total thyroidectomy and radioiodine ablation. All patients underwent diagnostic follow-up with Thyrogen-stimulated Tg and neck US. The mean

age of patients at diagnosis was 46 years (19–80 years). All patients (n = 66) had basal Tg serum values < 0.25 ng/ml with no interfering Tg antibody and no suspicious imaging at neck US. After Thyrogen-stimulation, Tg serum levels were >0.25 ng/ml in 12 patients. All these patients were subsequently submitted to another dxWBS and the presence of local recurrence/remote metastasis was demonstrated in 7 (58.3%). In two patients, no disease was detected by neck US, WBS or TC-PET depite persistent Thyrogen-stimulated Tg >0.25 ng/mL. Three patients who had serum Thyrogen-stimulated Tg >0.25 ng/mL were lost to follow up. The results of this study suggest that Tg measurement after Thyrogen-stimulation and neck US is superior to unstimulated Tg in the follow-up of DTC.

Due to the importance of long-term diagnostic follow-up using dxWBS and serum Tg analysis in thyroid cancer management, for which TSH stimulation is integral in ensuring diagnostic accuracy, the use of Thyrogen for this purpose has been well-investigated. In further clinical studies its equal efficacy compared with THT-withdrawal is well-documented: several studies have confirmed the equal efficacy of Thyrogen and THT-withdrawal (Haugen *et al*, 1999; Ladenson *et al*, 1997; Pacini *et al*, 2001) and numerous others have confirmed the usefulness of Thyrogen for this purpose. In all, data from well over a thousand patients with differentiated thyroid cancer exists to support Thyrogen's use for preparing patients for diagnostic follow-up with comparable accuracy to THT-withdrawal (David *et al*, 2001; Haugen *et al*, 1999; Mazzaferri *et al*, 2002; Pacini *et al*, 2001; Robbins *et al*, 2001; Robbins *et al*, 2002; Wartofsky *et al*, 2002; Wong *et al*, 2009).

12.1.1 Is the test to be used for screening for a disease/condition (ie in asymptomatic subjects) or for diagnosis and /or management of a disease / condition in subjects who are known to have the disease?

Thyrogen is an agent used for the preparation of thyroid cancer patients for diagnostic follow-up testing following thyroidectomy. The test itself, and the clinician actions that follow, will remain the same.

12.1.2 Provide information about the technical aspects of the test to describe what factor it aims to measure, how is this related to the target condition and what is the appropriate reference standard test. Please provide the technical specifications of the test. If the test is interpreted using a quantitative measure, this includes cut-off points for positive, negative and indeterminate results.

In the majority of patients with thyroid cancer, (near) total thyroidectomy is performed and patients are placed on synthetic thyroid hormones supplements to replace endogenous hormone and to suppress serum levels of TSH in order to avoid TSH-stimulated tumour growth. In follow-up, patients are monitored using serial serum Tg measurements, dxWBS, or both. Serum Tg measurement helps to detect the presence or confirm the absence of thyroid cells since, if present, they secrete Tg. In dxWBS, any thyroid cells that are present in the body will take up the bulk of the radioiodine, and any gamma rays emitted by the radioactive portion of that radioiodine are detected by a gamma camera. Sufficient serum levels of TSH are required to optimise both radioiodine uptake in dxWBS, and Tg secretion.

Withdrawing THT has traditionally been required prior to monitoring in order to elevate endogenous TSH production. Thyrogen provides an exogenous source of human TSH meaning that patients no longer need to suffer from THT-withdrawal-induced hypothyroidism when undergoing monitoring by dxWBS or Tg. Thyrogen is administered intramuscularly in two 0.9 mg doses 24 hours apart. Serum Tg testing with or without diagnostic scanning should be performed 72 hours post final Thyrogen administration. The following parameters are recommended for diagnostic radioiodine scanning with Thyrogen. A diagnostic dose of approximately 148 MBq (4mCi) ^{131}I should be used. Whole body images should be acquired for a minimum of 30 minutes and/or should contain a minimum of 140,000 counts (Genzyme Corporation, 2010). Scanning times for single (spot) images of body regions should be 10 to 15 minutes or less if the minimum number of counts is reached sooner (i.e. 60,000 for a large field of view camera or 35,000 counts for a small field of view camera) (Genzyme Corporation, 2010). In serum Tg testing, although it varies between institutions, a serum Tg greater than 2 ng/mL is often used as a threshold for presence of tumour cells (Cooper *et al* 2009; Pacini *et al* 2006b).

A perfect reference standard test is one which correctly identifies the patient's true disease status in all cases. In many clinical circumstances there is no perfect reference standard that can unequivocally determine a patient's disease state. This is the case for patients undergoing monitoring for well differentiated thyroid cancer. The previous MSAC evaluation report used THT-withdrawal stimulated testing (i.e. the comparator) as a proxy for a perfect reference standard, despite the fact it is not 100% accurate at determining the true disease state of the patient. Therefore by definition, in these analyses, THT-withdrawal stimulated testing will appear to have 100% diagnostic accuracy. Consequently, any other testing method that is compared to this will

appear to have less than perfect diagnostic accuracy. Therefore, the diagnostic accuracy results from the MSAC Evaluation Report, which indicated that Thyrogen-stimulated testing had a slightly lower sensitivity and specificity than THT-withdrawal-stimulated testing, represents a worst case scenario for Thyrogen. A more realistic interpretation of the comparative diagnostic performance of THT-withdrawal and Thyrogen-stimulation is that they have similar diagnostic accuracy. This is reflected by the high level of concordance between THT-withdrawal and Thyrogen-stimulation reported in the literature. In the event where these tests do not agree, the patient's true disease state will be best reflected by Thyrogen-stimulated testing in some cases and by THT-withdrawal stimulation in others.

12.1.3 Provide evidence of the effective management of the disease / condition being diagnosed / managed by the test.

Well differentiated thyroid cancer is regarded as slow-growing and potentially curable. Long-term prognosis is generally good, with 5-year survival rates from 1999 to 2003 in NSW of 89% for males and 95% for females (Tracey *et al*, 2008). Survival five years post diagnosis has been reported to decline with the extent of disease at diagnosis, emphasising the importance of early detection (Tracey *et al*, 2008). Survival in NSW in 2003 was 98.1% for localised disease, 93.3% for regional spread and 32.7% for distant metastases. Careful patient monitoring with serum Tg, with or without dxWBS is critical to detect persistent and recurrent disease at the earliest possible stage, because it is believed that early detection of recurrent disease offers the best opportunity for effective treatment (Cooper *et al*, 2009). Tests with high negative predictive value allow identification of patients unlikely to experience disease recurrence, so that less aggressive management strategies can be used and the patient can be reassured. This monitoring can be effectively carried out using Thyrogen as the exogenous source of TSH.

12.1.4 Provide any available evidence that the use of the test influences clinical decision making or health outcomes

Clinical decision making

This is not relevant to this submission as this application is not for the test *per se*, only the method of patient preparation. Thyrogen is an agent used to prepare a patient for a diagnostic test being used for periodic monitoring of the patient. Clinician actions subsequent to the test result will remain the same.

Health outcomes

Clinical consequences of THT withdrawal

The value of Thyrogen lies principally in the important patient benefits of avoiding the signs, symptoms and potentially significant morbidity of hypothyroidism and improving overall patient

quality of life. Historically, THT-withdrawal has been the principal method of achieving the TSH stimulation required for follow-up monitoring in differentiated thyroid cancer. However, the acute adverse effects associated with withdrawal-induced hypothyroidism have a significant impact on the patient and, in turn, wider society.

The effects of short-term hypothyroidism due to THT-withdrawal are profound and can lead to the development, as well as the exacerbation, of a range of physical and psychological morbidities (Bianchi *et al* 2004; Constant *et al* 2001; Dow, Ferrell and Anello 1997; Duntas and Biondi 2007). A summary of health impacts associated with THT-withdrawal induced hypothyroidism are presented in **Table 44**. Hypothyroidism may result in severe physical limitations, cognitive deficits, and emotional dysfunction, causing important debilitation and discomfort, safety risks, and a major disruption in family, social, and work life (Dow, Ferrell and Anello 1997).

Table 44 Summary of the clinical effects of withdrawal-induced hypothyroidism

Clinical area	Specific effect
Cerebrovascular	Cerebral blood flow abnormalities leading to: • Depression • Anxiety • Reduced/altered overall brain activity • Slowing of psychomotor speed
Cardiovascular	• Reduced heart rate at rest and during exercise • Increased systemic vascular resistance with reduced cardiac output • Reduced cardiac efficiency
Renal	Changes in: • Renal blood flow • Filtration rate • Absorptive capacity • Kidney structure
Lipids	• Reduced levels of enzyme involved in inverse cholesterol transport • Lower proportions of large-sized high-density lipoprotein (HDL) ('good' cholesterol) • Elevated levels of homocysteine (a cardiovascular risk factor)

Source: Bianchi *et al* 2004; Constant *et al* 2001; Dow, Ferrell and Anello 1997; Duntas and Biondi 2007

Withdrawal-induced hypothyroidism is overwhelmingly symptomatic, with many individuals experiencing several problems simultaneously. In a survey of 130 subjects, 92% experienced at least one symptom, 63% experienced two to five symptoms, and 25% experienced six or more of nine listed symptoms (Luster *et al*, 2005). Approximately two thirds of patients reported that hypothyroidism restricted or precluded activities of daily living and almost half sought medical attention for hypothyroid complaints (Luster *et al* 2005). These symptoms, including fatigue, difficulty concentrating, cold intolerance, weight gain, sleep disturbance, dry skin, constipation, hoarseness, and puffy face and hands have a considerable impact on functioning and quality of life.

Cardiovascular effects

Thyroid hormone deficiency is known to seriously affect the cardiovascular system. Adverse cardiovascular consequences induced by profound hypothyroidism include electrocardiogram abnormalities, reduced heart rate at rest and during exercise, impaired left ventricular diastolic function, impaired systolic function during effort, increased systemic vascular resistance with a reduced cardiac output, reduced cardiac efficiency and impaired endothelial function (Duntas and Biondi 2007).

Cerebrovascular effects

Hypothyroidism has consistently been associated with psychological disturbances including high levels of anxiety, depression and disability (Botella-Caaretero, 2003; Gulseren, 2006; Larisch, 2004; Tagay, 2005; Tagay, 2006). A link has been established between thyroid dysfunction and mood disorders, and it has been reported that patients hospitalised with hypothyroidism have a higher risk of readmission with depression (Duntas and Biondi 2007). Mood changes following THT-withdrawal may be partly due to cerebral blood flow abnormalities. Periods of hypothyroidism have been associated with slowing of psychomotor function, which may stem from brain cells inability to extract adequate amounts of oxygen and glucose from the blood (Duntas and Biondi 2007).

Effects on lipids

During periods of profound hypothyroidism, elevated levels of cholesterol and low density lipoprotein and quantitative changes that enhance its susceptibility to oxidation have been reported (Duntas and Biondi 2007). In two studies, elevated levels of homocysteine, a cardiovascular risk factor, were reported during severe hypothyroidism after withdrawal of thyroid therapy (Lien *et al* 2000 and Bicikova *et al* 2003). Although these lipid alterations are mostly reversible on restoration of euthyroidism, they should be avoided in patients with diffuse atherosclerosis and/or cardiovascular disease.

Effects on renal function

There have been studies reporting impaired renal clearance with hypothyroidism, with concomitant risk of impaired drug metabolism. In addition, hypothyroidism has been associated with changes in renal blood flow, filtration rate, absorptive capacity and kidney structure (Duntas and Biondi 2007). In the study by Bicikova *et al* (2003), a strong association was detected between creatinine, cholesterol, and homocysteine levels, suggesting that changes observed in lipids are partly due to alterations in renal function (Bicikova *et al* 2003). The elevated homocysteine levels significantly decreased after correction of hypothyroidism.

Compliance to follow-up

The undesirable consequences of THT-withdrawal have been suggested to negatively impact on thyroid cancer management itself by decreasing patient compliance to regular follow-up testing (Cohen *et al*, 2004). One study interviewed 48 consecutive patients with differentiated thyroid cancer to determine adherence to follow-up protocol following thyroidectomy. Physician questionnaires and/or patient interviews of the non-compliant patients indicated that the main reason for non-compliance was unwillingness to undergo hypothyroidism.

Health-related quality of life

Patient quality of life has been shown to be preserved with Thyrogen use compared to the sharp decline seen in patients undergoing THT-withdrawal. Consistent with this, Thyrogen is known to significantly improve a patient's preference based Health Related Quality of Life (utility) compared to THT-withdrawal, resulting in a substantial improvement in a patient's quality adjusted life years (QALYs). In Australia, this considerable impact of induced hypothyroidism on utility has been recognised by the PBAC leading to the reimbursement of Thyrogen through the PBS for use prior to radioiodine ablation.

These improvements in patient quality of life also decrease patient absenteeism and increase patient productivity. Importantly, avoiding the debilitating effects of hypothyroidism by using Thyrogen improves patient compliance to diagnostic follow up for recurrent disease, thereby facilitating early detection and treatment of recurrent disease.

In order to identify studies measuring quality of life in patients with thyroid cancer who are experiencing hypothyroidism, a systematic search of the literature was conducted. The Embase.com database, which includes both Embase and Medline, was searched and the resultant citations were screened for eligibility. The search strategy is described in **Table 45**.

Table 45 Embase.com utility literature search for patients with differentiated thyroid cancer

Date	Search terms	Results
21/11/2011 [Embase.com]	#1)'schroeder p.r.'/au	8
	#2) 'haugen b.r.'/au	78
	#3) 'luster m.'/au	99
	#4) 'leclere j.'/au	306
	#5) 'cost utility analysis'/exp OR 'cost utility analysis' OR 'cost utility'/exp OR 'cost utility' OR 'standard gamble' OR 'time trade off' OR 'time tradeoff' OR 'qaly'/exp OR 'qaly' OR 'quality adjusted life years'/exp OR 'quality adjusted life years' OR 'preference weights' OR 'preference based health related quality of life' OR 'preference based hrqol' OR 'cost utilities' OR 'utility weight' OR 'utility weights' OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'utility value' OR 'utility values' OR 'multiattribute utility' OR (tto NOT 'tobacco retrotransposon' NOT ('tea tree oil'/exp OR 'tea tree oil')) OR 'health utilities' OR 'health utility' OR sf6d OR aqol OR 'australian quality of life' OR 'assessment of quality of life instrument' OR 'euroqol' OR eq5d OR 'short form 6d' OR 'hui 3' OR 'hui iii' OR (utility OR utilities OR 'billewicz' AND ('quality of life'/exp OR 'quality of life'))	18,831
	#6) 'hypothyroidism'/exp OR hypothyroidism OR 'acute hypothyroidism'/exp OR 'acute hypothyroidism' OR 'hypothyreoidism'/exp OR hypothyreoidism OR 'hypothyreosis'/exp OR hypothyreosis OR 'hypothyroidea'/exp OR hypothyroidea OR 'hypothyroidosis'/exp OR hypothyroidosis OR 'hypothyrosis'/exp OR hypothyrosis OR 'primary hypothyroidism'/exp OR 'primary hypothyroidism' OR 'thyroid deficiency'/exp OR 'thyroid deficiency' OR 'thyroid gland failure'/exp OR 'thyroid gland failure' OR 'thyroid insufficiency'/exp OR 'thyroid insufficiency' OR 'hypothyroid' OR 'thyroid cancer' OR 'thyroid carcinoma' OR 'thyroid hormone withdrawal' OR 'rhtsh' OR 'recombinant human thyroid-stimulating hormone' OR 'thyrogen' OR 'thyroid hormone therapy' OR 'thyroxine'	119,825
	#7) 5 AND #6	62
	#8) #1 OR #2 OR #3 OR #4 OR #7	545
	#9) #8 AND [humans]/lim	431
	#10) #9 AND [english]/lim	**247**

Initially, the 247 citations identified were screened for inclusion using their title and abstract, and where necessary, full papers were retrieved to determine eligibility. In particular, the search aimed to identify studies that had compared health-related quality of life for patients undergoing ablation or diagnostic monitoring with Thyrogen compared to THT-withdrawal. Five studies were identified through the Embase.com utility literature search and an additional eight citations were retrieved from the previously described clinical study literature search or by hand searching reference lists. The thirteen identified citations are described in **Table 46**. Those studies that provide comparative quality of life evidence for patients stimulated with Thyrogen compared to THT-withdrawal have been discussed in detail in-text and are marked with a tick (✓).

Table 46 Clinical studies identified in the utility literature search

Citation	Discussed below
Botella-Carretero (2003) Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 10:601-10.	
Davids T (2006) Three-week thyroxine withdrawal: a thyroid-specific quality of life study. The Laryngoscope 116:250-3.	
Dueren C, Dietlein M, Luster M, Plenzig F, Steinke R, Grimm J, Groth P, Eichhorn W, Reiners C (2010) The use of thyrogen in the treatment of differentiated thyroid carcinoma: An intraindividual comparison of clinical effects and implications of daily life. Exp Clin Endocrinol Diabetes 118(8):513-9.	✓
Golger A (2010) Three-week thyroxine withdrawal thyroglobulin stimulation screening test to detect low-risk residual/recurrent well-differentiated thyroid carcinoma. J Endocrinol Invest 26:1023-31.	
Gulseren S (2006) Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. Archives of Medical Research 37:133-9.	
Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, Degroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon III HR, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD, Ridgway EC (1999) A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 84(11):3877-85.	✓
Ladenson PW, Braverman LE, Mazzaferri EL, Brucker-Davis F, Cooper DS, Garber JR, Wondisford FE, Davies TF, Degroot LJ, Daniels GH, Ross DS, Weintraub BD, Hay ID, Levis S, Reynolds JC, Robbins J, Becker DV, Cavalieri RR, Maxon HR, McEllin K, Moscicki R (1997) Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. New Engl J Med 337(13):888-96.	✓
Larisch R (2004) Depression and anxiety in different thyroid function states. Horm Metab Res 36:650-3.	
Luster M, Felbinger R, Dietlein M, Reiners C (2005) Thyroid hormone withdrawal in patients with differentiated thyroid carcinoma: A one hundred thirty-patient pilot survey on consequences of hypothyroidism and a pharmacoeconomic comparison to recombinant thyrotropin administration. Thyroid 15(10):1147-55.	✓
Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, Sherman S, Haugen B, Corone C, Molinaro E, Elisei R, Ceccarelli C, Pinchera A, Wahl RL, Leboulleux S, Ricard M, Yoo J, Busaidy NL, Delpassand E, Hanscheid H, Felbinger R, Lassmann M, Reiners C (2006) Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: Results of an international, randomized, controlled study. J Clin Endocrinol Metab 91(3):926-32.	✓ [a]
Schroeder PR, Haugen BR, Pacini F, Reiners C, Schlumberger M, Sherman SI, Cooper DS, Schuff KG, Braverman LE, Skarulis MC, Davies TF, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Weintraub BD, Ridgway EC, Ladenson PW (2006) A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab 91(3):878-84.	✓
Tagay S (2005) Health-related quality of life, anxiety and depression in thyroid cancer patients under short-term hypothyroidism and TSH-suppressive levothyroxine treatment. Eur J Endocrinol 153:755-63.	✓
Tagay S (2006) Health-related quality of life, depression and anxiety in thyroid cancer patients. Quality of Life Research 15:695-703.	✓

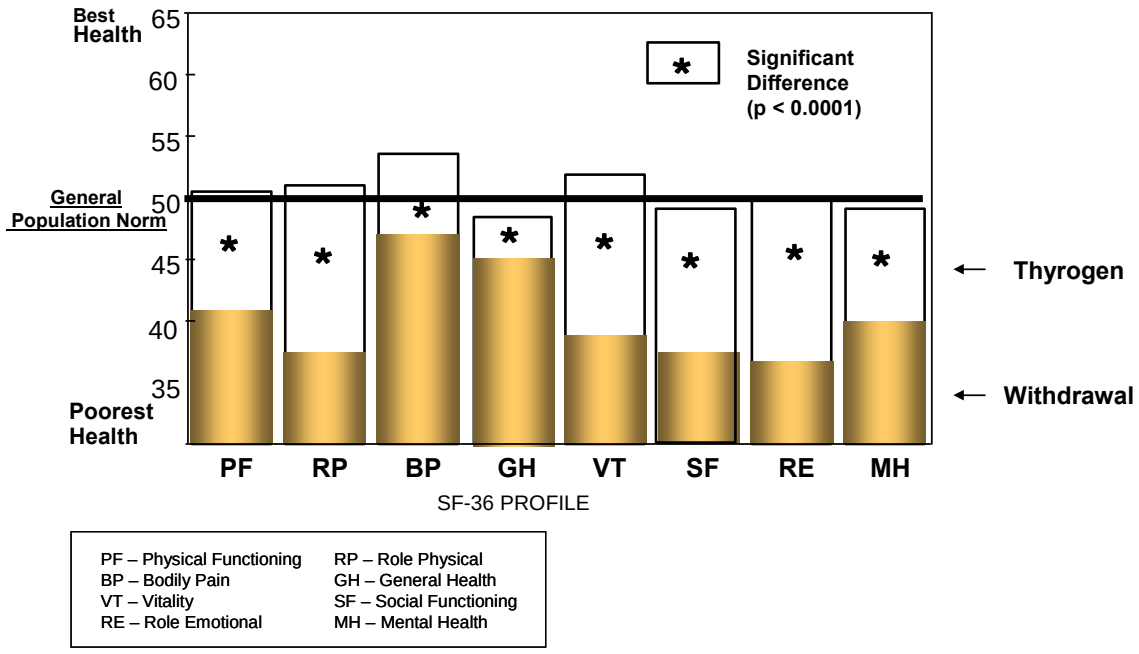
[a] Pivotal ablation study underpinning PBS listing of Thyrogen

Pivotal quality of life evidence

Haugen *et al* 1999 (Diagnostic)

The Haugen *et al* (1999) study provides pivotal head-to-head quality of life data for patients stimulated endogenously with THT-withdrawal, versus patients stimulated exogenously with Thyrogen. The quality of life results for this trial are re-reported in Schroeder *et al* (2006), where mistakes that occurred in the original reporting of SF-36 data by Haugen and colleagues (1999) were corrected. The SF-36 was administered to 228 patients at three time points: on THT, after Thyrogen and after THT-withdrawal. A comparison of patient scores for the THT-withdrawal and Thyrogen-stimulated group is shown in **Figure 17**. Patients SF-36 scores declined significantly from Thyrogen administration to THT-withdrawal in all eight HRQOL domains as well as the physical and mental summary responses ($p < 0.0001$). The largest decrease was seen in the role physical score ($p < 0.0001$). SF-36 scores while on THT versus Thyrogen did not differ significantly in seven of eight domains and PCS and MCS; with the exception being the social functioning domain.

Figure 17 SF-36 Scores for Thyrogen versus THT-withdrawal

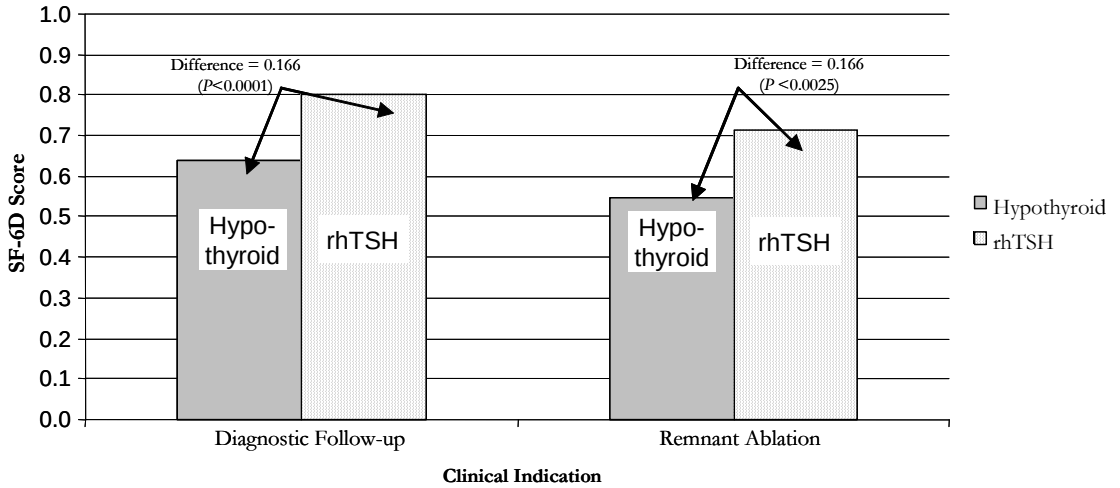


Source: Adapted from Schroeder *et al* 2006

For the purposes of the economic evaluation, these QOL data were also converted into utility weights, using the SF-6D method of Brazier *et al* (1998). Patients rendered hypothyroid by the withdrawal of THT in the diagnostic setting had a mean utility of 0.637, however when patients were maintained on THT prior to Thyrogen administration and WBS, mean utility increased to

0.803, a difference of 0.166 (P <0.0001) (**Figure 18**). This difference was identical to that observed between the Thyrogen and THT-withdrawal arms in the pivotal trial for ablation (Pacini *et al* 2006b). The magnitude of disutility observed in both trials is not surprising given the clinical aim of THT- withdrawal is to increase serum TSH levels as rapidly as possible to the same target (>30 mU/L) that renders patients profoundly hypothyroid.

Figure 18 Impact of Thyrogen-preparation upon quality of life (diagnostic withdrawal versus therapeutic withholding)



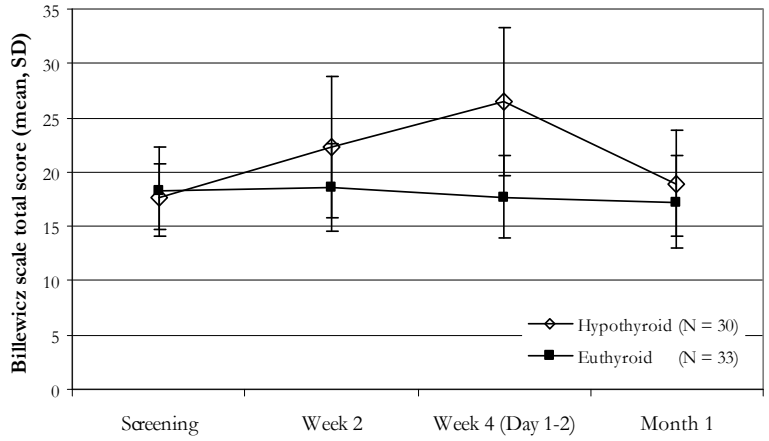
Source: Adapted from Schroeder *et al* 2006

Pacini *et al* (2006b) (Remnant ablation)

Pacini *et al* (2006b) provides the pivotal evidence for the difference in quality of life for patients prepared for ablation with Thyrogen and THT-withdrawal within a multicentre, open-label randomised controlled trial including 63 patients. This study in ablation is still highly relevant because the hypothyroid period induced prior to ablation exactly replicates the hypothyroid period prior to diagnostic accuracy testing - i.e. both target increased endogenous TSH to the same level. Symptoms of hypothyroidism and quality of life were assessed using the Billewicz scale and SF-36 scores at baseline, two weeks after randomisation, immediately before ^{131}I ablation, and one month after ablation. The Billewicz scale is used to measure the presence or absence of hypothyroid signs or symptoms. It is an observer-rated scale to serve as a diagnostic index for identifying clinical hypothyroidism specifically.

In general, the hypothyroid-stimulated arm showed increases in Billewicz scale mean total scores (i.e. a worsening of the condition) up to week 4, while these increases were not seen in the Thyrogen-stimulated arm (**Figure 19**). The differences between the two treatment arms at week 2 were statistically significant (95% CI, 1.004, 6.396; *post-hoc* analysis) and at week 4 were highly statistically significant (p<0.0001; 95% CI, 6.066, 11.534; *post-hoc* analysis). One month post-ablation, when the patients in the hypothyroid-stimulated arm were again on THT, their mean total scores were approaching the levels seen in the Thyrogen-stimulated arm.

Figure 19 QoL outcome: Billewicz scale total score (ITT population)



Source: Pacini *et al* (2006b)

The most common complaints of patients in the hypothyroid group, as opposed to the Thyrogen group, were cold intolerance (50 vs. 21%), weight increase (60 vs. 21%), constipation (43 vs. 3%), slow movements (50 vs. 12%), cold skin (47 vs. 12%), and periorbital puffiness (50 vs. 0%). The SF-36 results showed a significantly reduced quality of life for the hypothyroid-stimulated arm compared to the Thyrogen-stimulated arm in five of the eight SF-36 domains at week 4 (prior to ablation), despite comparable baselines. In fact, the quality of life of patients rendered hypothyroid worsened in 7/8 domains, whilst patients prepared with Thyrogen showed an improvement in 7/8 domains. Although SF-36 can be considered a subjective instrument, the results closely track the underlying change in the objective biochemical marker of hypothyroidism, serum TSH. The magnitude of the difference between arms is unlikely to have occurred by chance or to have been subject to bias as the exact magnitude of effect was also observed in the pivotal diagnostic trial, where the same patients received both methods of preparation (**Figure 18**).

For the purposes of the economic evaluation of Thyrogen for ablation, these QOL data were also converted into utility weights, using the SF-6D method of Brazier *et al* (1998) (**Table 47**). The results show that the utility values in the hypothyroid-stimulated arm during THT withdrawal in the pre-ablation period were significantly lower compared to the Thyrogen-stimulated arm ($P<0.01$). The hypothyroidism experienced during the THT withdrawal has considerable impact on the health utility of an individual (hypothyroid-stimulated 0.548, Thyrogen-stimulated 0.714, on a scale where 1.0 = perfect health and 0 = death). This impact continues into the initial post-ablation period, where there remains a utility benefit for patients on Thyrogen compared to those patients experiencing hypothyroidism subsequent to THT-withdrawal (Thyrogen-stimulated 0.637, hypothyroid-stimulated 0.712).

Table 47 Utility data: SF-6D utility values at week 4, pre-ablation, derived from SF-36 survey scores

	Hypothyroid-stimulated (N = 30) Mean	Thyrogen-stimulated (N = 31) Mean	Difference (95% CI)	*P*-value
Week 4, pre-ablation	0.548	0.714	0.166 (-0.25, -0.081)	<0.0025

Source: Adapted from THYR-008-00 clinical study report

Supportive quality of life evidence

Ladenson *et al* 1997

In the other pivotal diagnostic trial, a significant difference in hypothyroid symptoms, favouring Thyrogen compared to THT-withdrawal, was observed (Ladenson *et al*, 1997). Patients remained clinically euthyroid after Thyrogen while experiencing significantly more hypothyroid symptoms after THT-withdrawal. On all 37 items of the short form POMS scale, highly significant paired differences favouring Thyrogen were seen ($p < 0.0001$). Mean changes in mood score were also significant when the factors were grouped into six mood states. Similarly, the Billewicz scale indicated that Thyrogen resulted in a significant reduction in all 14 symptoms of hypothyroidism compared with THT-withdraw. A total of 94% of patients showed better quality of life as determined by the Billewicz scale after administration with Thyrogen compared with THT-withdrawal.

Dueren *et al* 2010

An observational study was conducted in Germany to examine the differences in HRQOL between those undergoing THT-withdrawal stimulation and those undergoing Thyrogen-stimulation in preparation for dxWBS and serum Tg testing (Dueren *et al*, 2010). Patients were assessed 3–6 months post-thyroidectomy after a period of THT-withdrawal and again after 6–12 months in a euthyroid state after administration with Thyrogen. Quality of life was measured by the SF–12® health survey and clinical symptoms using patient interview and a modified version of the Billewicz scale. The SF-12® sum score in the patients prepared by THT-withdrawal for physical and mental symptoms was 48.8 ± 23.0% and 49.4 ± 23.1%, compared with Thyrogen patients whose scores were significantly higher (75.6 ± 18.8% and 73.5 ± 17.5%, respectively). There was also a significant improvement in all clinically reported symptoms (sleeping disorder, lethargy, hoarseness, cold intolerance, weight gain, constipation, lack of concentration) in patients receiving Thyrogen compared to those stimulated using THT-withdrawal ($p<0.0001$) (**Table 48**).

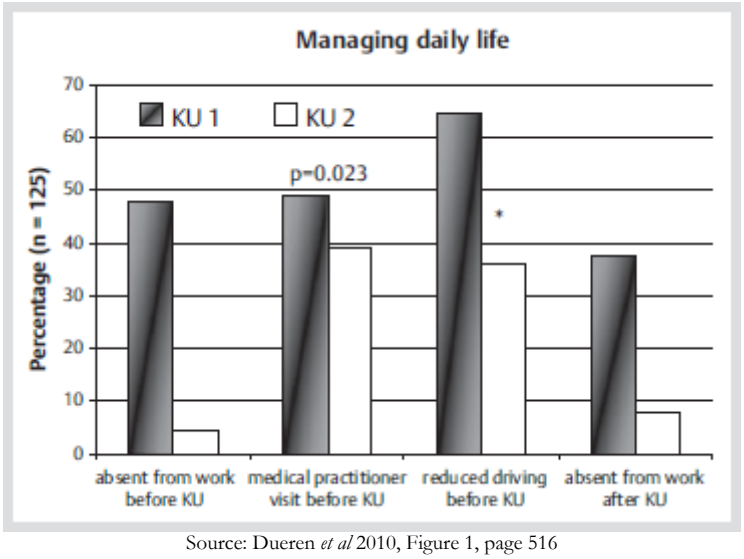
Table 48 Prevalence of diverse, definitive present, symptoms (%) for patients prepared with THT-withdrawal and Thyrogen

	THT-withdrawal N (%)	Thyrogen N (%)	p-value
Sleeping disorder	64 (50.4)	8 (6.3)	<0.0001
Lethargy	98 (77.2)	7 (5.6)	<0.0001
Hoarseness	43 (33.9)	7 (5.5)	<0.0001
Cold intolerance	59 (46.8)	6 (4.7)	<0.0001
Weight gain	72 (56.7)	5 (3.9)	<0.0001
Constipation	25 (19.8)	5 (3.9)	<0.0001
Lack of concentration	61 (48.0)	5 (3.9)	<0.0001

Source: (Dueren *et al* 2010, page 515

The study also measured the effect on people's daily activities though measures such as absence from work, medical practitioner visits and reduced driving behaviour (**Figure 20**). Results indicated that absenteeism from work, medical practitioner visits and reductions in driving were all significantly improved in patients in the KU2 (Thyrogen) group compared to those in the KU1 (THT-withdrawal) group. The need for additional medication during both modalities was also explored. Under THT-withdrawal, 20.8% of the patients needed additional pharmaceuticals and 36 different classified drugs were used. Under a euthyroid state after exogenous stimulation with Thyrogen, 11.2% of the patients needed additional medication and 17 different drugs were in use. Patients were also asked for their preferred health state and 127/128 preferred to be euthyroid after Thyrogen administration.

Figure 20 Differences in managing daily activities



Source: Dueren *et al* 2010, Figure 1, page 516

Tagay *et al* 2005

A cross-sectional study by Tagay and colleagues (2005) compared the quality of life, anxiety, depression, and physical complaints of 130 patients rendered hypothyroid by withdrawal of THT,

with 100 control patients who remained euthyroid under TSH-suppressive levothyroxine treatment. Additionally, both groups were compared against a general reference population. Patients who were hypothyroid had significantly worse HRQOL compared to patients treated with levothyroxine with regard to the following SF-36 domains: physical functioning (63.8 ± 28.8 versus 78.4 ± 24.3, respectively; $p<0.001$), role-physical (41.8 ± 39.9 versus 74.4 ± 36.2, respectively; $p<0.001$), bodily pain (72.2 ± 29.2 versus 82.4 ± 26.8, respectively; $p<0.05$), vitality (44.2 ± 9.7 versus 49.9 ± 9.6, respectively; $p<0.001$) and role-emotional (50.2 ± 45.1 versus 77.5 ± 36.6, respectively; $p<0.001$). Those patients rendered hypothyroid had significantly more signs and symptoms of hypothyroidism than subjects who remained on levothyroxine treatment. There were no differences between the two groups with regards to depression, anxiety or mood.

Tagay *et al* (2006)

A second study by Tagay and colleagues (2006) compared 136 patients who had been thyroidectomised for differentiated thyroid cancer, to 2911 individuals from a general German reference population. Subjects in the study were rendered hypothyroid by withdrawal of THT for 4 weeks. Their quality of life, anxiety, depression and physical complaints during the period of hypothyroidism were compared to general population norms. In all domains of SF-36, patients who were rendered hypothyroid reported significantly reduced HRQL compared to the general population reference group. The summary PCS score and MCS score were 44.3 ± 9.5 and 40.8 ± 10.2 in the patients who were rendered hypothyroid, compared to 50.2 ± 10.2 and 51.5 ± 8.1 in the control group ($p\leq 0.001$ and $p \leq 0.001$, respectively). Around 63% of study subjects were diagnosed with borderline or definite anxiety, however, mean depression scores were in the normal or non-clinically relevant range.

Luster *et al* (2005)

Another study examined 130 patients to elucidate clinical and quality of life effects of hypothyroidism secondary to THT-withdrawal (Luster *et al* 2005). A 13-item questionnaire was mailed to patients to determine the type of symptoms, duration, impact on daily activities and medical resource utilisation associated with hypothyroidism. Hypothyroidism was found to be multi-symptomatic with 120 (92%) experiencing at least one symptom, 82 (63%) 2–5 symptoms and 33 (25%) experiencing 6 or more of the 9 listed symptoms. Patients reported fatigue (82%), difficulty concentrating (52%), intolerance of cold (51%), weight gain (45%), sleep disturbances (40%), dry skin (36%), constipation (29%), hoarseness (28%), and puffy face and hands (28%). Two thirds of patients noted restrictions on performing or inability to perform activities of daily living during hypothyroidism with only one third able to drive motor vehicles while hypothyroid.

The study also examined health care resource utilisation of patients experiencing a period of hypothyroidism following THT-withdrawal (Luster *et al* 2005). Almost 40% of patients took additional prescription or over-the-counter medications to relieve hypothyroid symptoms.

Medications included sleeping pills, headache tablets, and cardiovascular agents. Almost half of the participants answering the relevant questions reported utilising a primary care and/or specialist physician and/or hospital because of hypothyroid complaints. Thirty-eight (38%) of 101 patients answering the question consulted a primary care physician, 20 (20%) on at least 2 occasions. Twenty-nine (31%) of 95 patients answering the question visited a specialist physician, 11 (12%) on multiple occasions. Hypothyroid symptoms necessitated an outpatient or inpatient hospital visit other than at the Nuclear Medicine Clinic in 29 (29%) of 99 patients answering this question.

Borget *et al* (2007)

The significant debilitation to patients resulting from THT-withdrawal has been shown to result in reduced productivity and increased sick leave. A study by Borget *et al* (2007) collected hospital data prospectively and retrospectively to examine the difference for patients who had been followed-up using Thyrogen versus THT-withdrawal. The authors found that Thyrogen treatment reduced the length of sick leave by 8.1 days when compared to THT-withdrawal (3.1 days and 11.2 days respectively). In addition, Thyrogen was associated with significantly less productivity loss.

Overall, the use of Thyrogen obviates the clinical and economic consequences of hypothyroidism thus offsetting the cost of Thyrogen, whilst also promoting compliance with diagnostic follow-up protocol and allowing patients to maintain daily functioning. By allowing patients to stay euthyroid, Thyrogen results in significant quality of life benefits compared to a period of hypothyroidism, subsequent to THT-withdrawal.

Safety

In the previous MSAC evaluation of Thyrogen, it was concluded that 'In general, the adverse events associated with the use of Thyrogen appear to be mild in nature.' Since the previous MSAC submission for the diagnostic use of Thyrogen, the drug has undergone government assessment for its therapeutic use. This independent government evaluation concluded that Thyrogen was safe and efficacious for therapeutic use.

In brief, Thyrogen is typically well-tolerated with short-lived and generally mild adverse effects. The most common of these adverse effects include: nausea (approximately 10% incidence), headache (approximately 7% incidence) and asthaenia (approximately 3% incidence). No serious adverse events (life-threatening or requiring hospitalisation) were related to Thyrogen administration. Thyrogen administration may also cause transient (<48 hours) influenza-like symptoms, which may

include fever, chills/shivering, myalgia/arthralgia, fatigue/asthenia/malaise and headache and chills. Very rare manifestations of hypersensitivity to Thyrogen have been reported in both clinical, post-marketing settings and in special treatment groups with advanced disease, such as urticaria, rash, pruritis, flushing and respiratory signs and symptoms. Enlargement of residual thyroid tissue or metastases has been reported to occur following treatment with Thyrogen. This may lead to acute symptoms which depend on the anatomical location of the tissue. It is recommended that pre-treatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.

The adverse events associated with Thyrogen administration should be considered in the context of adverse events associated with profound hypothyroidism secondary to THT-withdrawal.

12.2 Assessing the evidence for the performance of the test.

Evidence relating to the performance of Thyrogen as a preparatory agent for TSH-stimulated serum Tg, dxWBS, or both, versus the diagnostic performance of THT-withdrawal stimulated serum Tg, dxWBS, or both, is provided in **Section 12.1**.

12.2.1 Reports on the performance of the test:

(a) a copy of the literature search undertaken to identify evidence which supports the technical performance including sensitivity and specificity of the test (this should describe the search strategies used to retrieve the relevant clinical studies in the published and unpublished literature).

Please refer to **Section 9** for a copy of the full literature search results.

(b) a list of the studies that support the technical performance of the test (for example, validation studies, studies estimating sensitivity and specificity etc).

A list of included studies that support the technical performance of Thyrogen-stimulated testing is provided in **Section 9** of this application.

(c) a list of reports from regulatory authorities or expert panels/professional societies.

An expert report on the use of Thyrogen in Australia is included with this submission in **Section 14**. In brief the report states:

'It is the view of the undersigned experts in the management of thyroid cancer that the current reimbursement availability criteria for Thyrogen (thyrotropin-alfa, rhTSH) on the Medicare Benefits Scheme (MBS) are inappropriately restrictive. This report is written in support of a re-evaluation of eligibility criteria using current evidence, much of which has been published subsequent to the original MBS decision.'

The expert clinicians add that: '*Due to the existing restrictive MBS criteria, the majority of thyroid cancer patients do not currently qualify for subsidised Thyrogen, and thus must endure a period of thyroid hormone withdrawal to enable appropriate follow-up of thyroid cancer. These patients would have improved short and long-term outcomes from having access to Thyrogen.'*

12.2.2 Validity, accuracy, reliability and applicability

The pivotal clinical evidence supporting the expanded listing of Thyrogen on the MBS is provided in **Section 12.1**.

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CONFIDENTIAL

Availability of Thyrogen on the Medicare Benefits Scheme in Australia 2010

It is the view of the undersigned experts in the management of thyroid cancer that the current reimbursement availability criteria for Thyrogen (thyrotropin-alfa, rhTSH) on the Medicare Benefits Scheme (MBS) are inappropriately restrictive. This report is written in support of a re-evaluation of eligibility criteria using current evidence, much of which has been published subsequent to the original MBS decision.

Due to the existing restrictive MBS criteria, the majority of thyroid cancer patients do not currently qualify for subsidised Thyrogen, and thus must endure a period of thyroid hormone withdrawal to enable appropriate follow-up of thyroid cancer. These patients would have improved short and long-term outcomes from having access to Thyrogen.

This brief report will outline the current clinical body of evidence that supports the contention that Thyrogen should be reimbursed for use in the diagnostic indication for all patients, without the current restrictive eligibility criteria.

The efficacy of Thyrogen in diagnostic follow-up

The efficacy of Thyrogen in diagnostic follow-up is well established. Thyrogen has been licensed for this indication in Australia since 2001 and in Europe and North America for over 7 years. (November 1998 in the US and March 2000 in Europe)

The efficacy was first demonstrated in the pivotal Phase III study from Haugen *et al* (1999). In this prospective randomised study of 229 patients, Thyrogen-stimulated Tg and the diagnostic whole body scan (WBS) were able to detect all of the metastases that were noted in the same patients under thyroid hormone withdrawal. The authors concluded that Thyrogen is a safe and effective method for stimulation during follow-up.

In 2001, Robbins *et al* published data from their clinical experience of using Thyrogen in diagnostic follow-up at the Memorial Sloan-Kettering Cancer Centre in New York. This study compared patients undergoing testing under thyroid hormone withdrawal (n=161) to a second group undergoing Thyrogen stimulation (n=128). In total, 373 diagnostic WBS and stimulated Tg tests were performed on 289 patients. The diagnostic accuracy of testing under the two conditions was found to be comparable. Most importantly the false negative rate was very low in both cases thus the negative predictive value (NPV) was very high. The highest NPV (98%) was noted during Thyrogen testing when the diagnostic WBS was negative and the stimulated Tg level was low or undetectable. The authors concluded that use of Thyrogen is diagnostically equivalent to thyroid hormone withdrawal.

A third comparative study was published by Pacini *et al* in 2001. In this study, 72 patients underwent sequential diagnostic follow-up, firstly with Thyrogen and then with thyroid hormone withdrawal. Thyrogen-stimulated Tg was able to predict the presence of disease in all cases, leading the authors to conclude that when basal Tg is undetectable (measured while the patient is euthyroid on thyroxine, a state in which small amounts of Tg secretion from a tumour may be suppressed by the thyroxine therapy), Thyrogen stimulation of Tg with or without a scan is an informative test to

distinguish disease free patients from patients with disease requiring further diagnostic and/or therapeutic procedures.

Since the publication of these three comparative studies (in nearly 600 patients) several further confirmatory studies have been published.

Schlumberger *et at* published a review article of 10 such papers which describes well over 1500 patients; in all the studies the performance of Thyrogen was assessed using a variety of imaging modalities. Thyrogen is found to be highly efficacious in diagnostic follow-up in these studies. Many of these studies support the concept that diagnostic WBS is not required routinely in patients at low risk of recurrence (assuming that a near total thyroidectomy and adequate remnant ablation has been performed.)

The need for stimulated Tg during follow-up

The measurement of Tg without stimulation (basal Tg) avoids hypothyroidism and its attendant potential morbidity but has the crucial drawback that even using a modern assay (functional sensitivity around 1 μg/L), disease in the neck will be missed in about 1 in 5 cases. Basal Tg can also be undetectable in cases of distant metastases on occasion. Stimulation of Tg by Thyrogen allows for earlier or more sensitive detection of such cases**.**

One recent development is the production of highly sensitive serum Tg assays capable of reliable detection down to 0.1μg/L rather than the current assays which have a detection limit around 1.0 μg/L. Potentially such assays could preclude the need to stimulate Tg with Thyrogen to obtain an appropriate sensitivity in cancer detection. At present there is insufficient information to determine if this will indeed be the case and expert opinion is in favour of Thyrogen stimulated Tg and/or whole body radioiodine scans. There is no widespread availability of such highly sensitive Tg assays. The crucial point is that when such highly sensitive Tg assays are used there may be a substantial loss of specificity leading to an excessive number of false positives. Currently there is little published data to give guidance about how to deal with detectable but very low basal Tg values. Studies of ultra-sensitive Tg assays to date have suggested that the need for measurement of stimulated Tg may be reduced, but not eliminated. Further research in this area is required.

Eventually the requirements for repeated diagnostic scans and stimulated Tg during follow up will need to take into account the effect of the new paradigm of initial surgical management of thyroid cancer. Changed surgical approaches to the management of differentiated thyroid cancer have the potential to lead to a significant reduction in persistent disease in the long-term. The University of Sydney Endocrine Surgery Unit has published data demonstrating that the addition of routine level VI lymph node dissection to total thyroidectomy leads to a significant increase in the number of patients with a negative thyroglobulin at 6 month follow-up (73% vs 41%, $p<0.0001$) and an increase in the number of negative scans. If this surgical practice were to become widespread such a potential reduction in the presence of persistent disease will need to be factored into economic calculations of future requirement for diagnostic scans. At present this impact cannot be assessed. Adoption of our proposal on availability of Thyrogen will promote standardization of management protocols and will likely contribute to widespread adoption of best practice across all aspects of management including initial surgery.

The Clinical Consequences of Hypothyroidism

One of the main benefits of the use of Thyrogen is the elimination of the symptoms of hypothyroidism; the period of hypothyroidism can last for up to 10 weeks for every stimulated diagnostic follow-up session[i]. The elimination of the concomitant impairment of work performance and personal well-being during this time and the resultant eradication of a substantial disincentive to appropriate follow-up, will lead to the promotion of enhanced quality of treatment for thyroid cancer patients.

The physiological and potential pathological consequences of iatrogenic hypothyroidism in a number of major organs and body systems have been well documented in several carefully controlled studies. A recent review article by Duntas and Biondi provides an in depth summary of this data and provides commentary on the possible pathological consequences.

A number of body systems are profoundly affected by the hypothyroidism that results from thyroid hormone withdrawal. The most significant effects on specific body systems are as follows: *Cardiovascular:* a number of parameters show that cardiac contraction, work and oxygen consumption are significantly reduced while the systemic vascular resistance increases. ECG changes have also been noted. *Central nervous system:* cerebral blood flow is significantly reduced while psychomotor performance can be significantly affected. Marked levels of depressive affective disorder have been recorded. *Renal function*: kidney function is affected by hypothyroidism causing reduced creatinine clearance. *Other effects*: thyroid hormone withdrawal can reduce total body energy expenditure, slow gastric emptying, reduce the immune response and lead to a disturbance of anti-coagulation control in patients taking warfarin.

In addition to the potential morbidity associated with thyroid hormone withdrawal, the prolonged high TSH levels associated with this method of stimulation (TSH levels may be high for several weeks compared to days when Thyrogen is used) could-theoretically- increase the risk of rapid tumour growth or inflammatory change that can occur in some patients. This may be particularly important where the patient has metastatic disease in confined spaces such as in the CNS.

One alternative to full thyroid hormone withdrawal is the possible use of protocols for partial thyroid hormone withdrawal rather than the use of Thyrogen. While such protocols have been published and may have merit, they are insufficiently studied and have not yet been endorsed as a standard of care, particularly against the well-characterised, evaluated and reproducible Thyrogen protocol.

Guidelines for Thyroid Cancer Management

The use of Thyrogen should be subject to strict evidence-based guidelines. These guidelines are already well-developed internationally, and have led to the development of several national guidelines. The guidelines which are most reflective of Australian clinical practice and referenced by Australian clinicians are those developed by the American Thyroid Association (ATA), and the European Thyroid Association (ETA). Expert committees of the ATA and ETA, in accordance with evaluation of published evidence, have developed these guidelines independent of Genzyme Corp., the manufacturer of Thyrogen. Both the US and European guidelines support the use of Thyrogen in diagnostic follow-up on the basis that the available clinical evidence demonstrates that this approach has similar efficacy and accuracy to thyroid hormone withdrawal.

Adoption of the ATA and ETA guidelines would be strongly supported by Australian expert clinicians (endocrinologists, nuclear medicine physicians, and endocrine/head and neck surgeons) who would be able to advise on developing guidelines appropriate and specific for Australia.

Compliance with Follow-up

At present, the development of symptomatic hypothyroidism is a disincentive for a significant number of thyroid cancer patients to undergo standard protocols of follow-up involving whole body radioiodine scans and blood sampling for TSH-stimulated serum thyroglobulin measurement.

An additional benefit of removing the inappropriately restrictive eligibility criteria for Thyrogen use would be an enhancement of adherence to evidence-based protocols for follow-up. This increased availability of Thyrogen may lead to an earlier diagnosis of recurrences and potentially a better clinical outcome for patients. These additional benefits to improve patient outcomes will prove more cost-effective to the overall Australian health system.

Pharmaco-economic Evidence

The cost of Thyrogen (AUD $1825) is sufficiently high to be a major cost barrier to personal funding and thus inequity of access for Australian citizens.

The pharmaco-economic value provided by Thyrogen in the diagnostic follow-up setting has been studied carefully. The two principal areas of pharmaco-economic value are avoidance of significant quality of life (QoL) impairment and a significant reduction in working days lost due to sick leave. The significant reduction of QoL in patients undergoing thyroid hormone withdrawal compared to the preservation of QoL during Thyrogen stimulation has been well documented[i].

Luster *et al* carried out a survey of 130 patients who had recently undergone thyroid hormone withdrawal. Patients were found to lose around 11 days of work. Using Thyrogen would have given a saving of around €326 per diagnostic WBS, taking into account the sick leave. More recently in a study from France, 292 patients undergoing either thyroid hormone withdrawal or Thyrogen stimulation completed detailed questionnaires about sick leave. Use of Thyrogen reduced sick leave by a mean of 8.1 days and reduced the costs of sick leave by over €1000.

Improvement of thyroid cancer follow-up by guideline-based care would have some potential cost-offsets. For instance, a whole-body radioiodine scan does not always need to be linked to Thyrogen administration, as measurement of stimulated serum thyroglobulin (Tg) in many circumstances is more sensitive for detection/exclusion of residual thyroid cancer, especially if a neck ultrasound is performed by an experienced operator. As the average cost of a diagnostic WBS is $554.80, this reduced requirement to perform DxWBS has the potential to offset some of the cost of Thyrogen. Furthermore both the ATA and ETA guidelines advise that diagnostic whole body radioiodine scans are not indicated in low risk patients, if free of disease both clinically and on high-quality neck ultrasonography, and with serum Tg < 1 μg/L on suppressive thyroxine therapy. Also, current Australian evidence supports this recommendation. Indeed repeated Thyrogen stimulation of serum Tg may be unnecessary in such patients. That said, DxWBS does continue to have a role, especially in cases where the patient has Tg antibodies (perhaps around 15% of cases), or if there is no access to expertise in neck ultrasound.

While increasing the availability of Thyrogen earlier in the course of evaluation and treatment of patients with thyroid cancer would obviously result in a greater initial expenditure for the MBS; when this is linked to appropriate protocols of care, the overall result would be better patient outcomes in both the short and long term and these improved patient outcomes would be linked to a reduced expenditure on repeated whole-body radioiodine scans. Furthermore, the need for repeated use of Thyrogen beyond the first few years would be low or nil for most patients.

Conclusion

Based on current clinical evidence and in the clinical setting as viewed by myself and colleagues, the availability criteria for the use of Thyrogen in diagnostic follow-up in Australia are far too restrictive. There is a very substantial evidence base to support the effectiveness of this form of stimulation both in terms of accuracy and in the avoidance of the deleterious effects of hypothyroidism. It will bring us in line with current best-practice management for thyroid cancer surveillance as per the ATA/ETA Guidelines and is moreover cost-effective. We feel confident that these accumulated data in Thyrogen are sufficient to demonstrate that it is safe and effective for the diagnostic follow-up of thyroid cancer.

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APPENDICES

APPENDIX 1: THYROGEN EXPERT OPINION SURVEY

This report describes the collection and collation of expert opinions. To ensure transparency, these results have been set out in the format suggested in Appendix 4 of the *Guidelines for preparing submissions* to the Pharmaceutical Benefits Advisory Committee (PBAC).

Introduction

A survey of experts has been conducted to seek information about the current diagnostic follow-up of patients with well differentiated thyroid cancer in Australia. In particular, the survey was conducted to confirm the applicability of estimates used in the economic model, which was submitted to the MSAC as part of the application for an expanded MBS listing for recombinant human thyroid stimulating hormone (rhTSH; Thyrogen®).

Methods

General description of survey methods

A complete copy of the survey is included in an appendix to this report. As described on the first page of the survey, the distribution, collection and collation of the survey was undertaken by an independent research agency (Health Technology Analysts Pty Ltd) on behalf of Genzyme Australasia. All responses were de-identified by the research agency, and only aggregated responses are provided herein. No doctors received reimbursement for the completion of the survey.

Criteria for selecting the experts

The survey was sent to a database of Australian endocrinologists, nuclear medicine specialists and physicians with an interest in treating thyroid cancer. All physicians had experience managing thyroid cancer and with the use of Thyrogen.

Number of experts approached and number who participated

The survey was sent to 46 clinicians that specialise in the treatment of patients with thyroid cancer in Australia. A total of 12 surveys were returned to Health Technology Analysts (26%) (**Table 49**). Of the 12 returned responses, 7 (58%) were from endocrinologists, 4 (33%) from nuclear medicine specialists and one (8%) from an endocrine surgeon.

Table 49 Number of clinicians

Clinicians contacted	Number of returned surveys
46	12 (26%)

Declaration of conflict of interest

None of the respondents declared a conflict of interest.

Background information provided to the respondents

Each survey included a brief description of the purpose of the questionnaire. This information was consistent with the evidence provided in the MSAC submission for Thyrogen. The reader is referred to the complete copy of the survey instrument presented with this report.

Method and medium used to collect opinions

The survey was emailed to a sample of experts, who were asked to complete all pages of the survey and return the surveys to the research agency by email or fax. No incentives were given to maximise the response rate to the survey.

The questions asked and whether iteration was used

The questions asked are provided in the attached copy of the survey. The survey was in the form of a self-administered questionnaire. Where responses from returned surveys were unclear, iteration was used in an attempt to clarify.

The number of responses received for each question

The total number of responses and the number of valid responses received for each question is shown in **Table 50**. The majority of respondents provided valid responses to the questions posed. A response was considered valid if it conformed to the requirements of the question (i.e. adding to 100% when specified) and if it was consistent with responses to previous questions. For example, for *question four*, respondents were asked to describe their current management of patients and how that would change with an expanded MBS listing for Thyrogen. In *question three*, they had been asked to specify what proportion of their Tg tests were currently performed using standard or ultrasensitive Tg. If they answered that 100% of tests were performed using **ultra-sensitive** Tg in *question three*, but then stated that a proportion of patients were currently being treated using **standard** Tg in *question four*, their response was marked as invalid. Similarly, if the response to *question two* was yes, *question five* was not to be answered. However, three respondents answered *question five*, despite having answered yes to *question two*.

Table 50 The number and validity of responses

Question	Responses	Valid responses
1	11	11
2	12	12
3	12	12
4	11	7
5	3	0
6	11	11

Data analysis

Data were analysed using Microsoft Excel 2007. Summary statistics were calculated for each question. The variability around the answers for each question is explored by presenting the 95% CI and the range of the results, where appropriate.

Results

Question 1

Table 51 presents the aggregate answers to *question 1* along with the variance measures around each of the values provided. The clinicians surveyed had a mean of 69 patients in their care per annum. The 11 respondents indicated they managed a total of 760 well-differentiated thyroid cancer patients for diagnostic testing per annum.

Table 51 *Question 1*: total number of thyroid cancer patients treated per year

Summary statistics	Total well-differentiated thyroid cancer patients
Mean	69
Lower 95% CI	40
Upper 95% CI	98
Minimum	10
Maximum	150
Total patients	760

Question 2

For *question 2*, respondents were asked whether they were aware of the sensitivity (1.0 μg/L versus 0.1 μg/L) of the thyroglobulin (Tg) assay, when they requested a Tg test be performed for diagnostic purposes. All respondents answered yes.

Question 3

Table 52 presents summary statistics for the responses to *questions 3a* and *3b*. The clinicians surveyed indicated that of the Tg tests they requested, 34% were performed using the standard Tg assay (1.0 μg/L), while 66% were performed using the ultrasensitive Tg assay (0.1 μg/L). There were 7 (58%) respondents that indicated their Tg tests were performed using ultrasensitive assays

for the majority of their patients, compared with 5 (42%) that stated the majority of their Tg tests were conducted using standard assay.

Table 52 *Question 3a and 3b*: percentage of standard Tg tests and ultrasensitive Tg tests

Summary statistics	Standard Tg assay	Ultrasensitive Tg assay
Mean [a]	34%	66%
Lower 95% CI [a]	31%	62%
Upper 95% CI [a]	37%	70%
Minimum	0%	0%
Maximum	100%	100%

[a] Mean, 95% CI were weighted by the number of patients treated by each clinician per annum
[b] The minimum and maximum were based on individual clinician responses (i.e. unweighted)

Question 4

The aim of *question 4* was two-fold: (i) to determine how Thyrogen was being used in current clinical practice and (ii) to determine how Thyrogen would be used under an expanded MBS listing that included all patients with well-differentiated thyroid cancer. A total of seven valid responses were obtained for *question 4*.

Respondents were asked what proportion of their patients were currently being managed with Thyrogen, THT-withdrawal stimulated diagnostic testing using any Tg ± WBS, using unstimulated standard Tg only and using unstimulated ultrasensitive Tg only. They were then asked what proportion of these patients would receive Thyrogen-stimulated testing and what proportion of patients would continue current testing if Thyrogen were to be approved for an expanded MBS listing.

As shown in **Table 5** the mean proportion of patients currently being treated with MBS reimbursed Thyrogen stimulated Tg ± WBS (i.e. patients medically contraindicated to hypothyroidism), weighted by the number of patients managed per annum, was 7.4%. As these patients are currently being treated with rhTSH their diagnostic follow up will not change with an expansion of the listing of rhTSH through the MBS.

The respondents indicated that unstimulated ultra-sensitive Tg was the most frequently used diagnostic testing strategy (55.6%), followed by unstimulated standard Tg (22.8%) and then THT-withdrawal stimulated Tg ± WBS (14.3%) (**Table 53**). Respondents indicated that 98.5% of patients who were being treated with THT-withdrawal stimulated diagnostic testing would be switched to Thyrogen-stimulated testing under the new proposed listing. They also suggested about half (50.5%) of all patients currently being treated with unstimulated standard Tg would receive Thyrogen-stimulated standard Tg under the proposed new MBS listing for Thyrogen. Importantly, responses suggested that *no patient* being managed with unstimulated ultrasensitive Tg would be

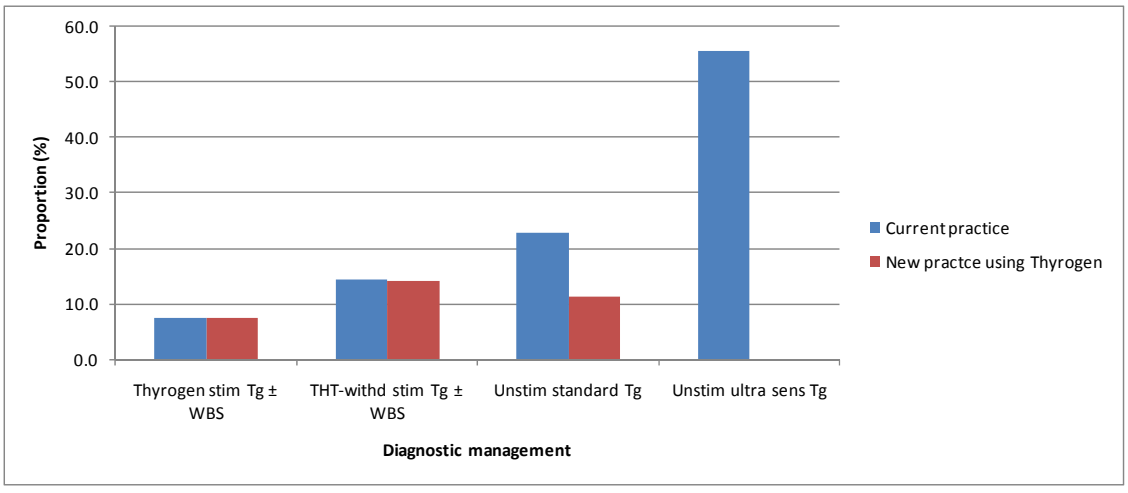
switched to Thyrogen-stimulated ultrasensitive Tg under the proposed new listing for Thyrogen (**Figure 21**).

Table 53 ***Question 4:*** **Current practice and change in practice if Thyrogen was to receive an expanded MBS listing**

	Current practice n/N (%)	New practice	
		Thyrogen-stimulated diagnostic testing n/N (%)	No change from current practice n/N (%)
4a. Currently receiving Thyrogen stimulated Tg ± WBS (ie medically contraindicated)	35/475 (7.4%)	35/35 (100.0%)	0/35 (0.0%)
4b. THT-withdrawal stimulated diagnostic testing	68/475 (14.3%)	67/68 (98.5%)	1/68 (1.5%)
4c. Unstimulated standard serum Tg testing only	109/475 (22.9%)	55/109 (50.5%)	54/109 (49.5%)
4d. Unstimulated ultrasensitive serum Tg only	264/475 (55.6%)	0/264 (0.0%)	264/264 (100.0%)

Note that rounding applies

Figure 21 Question 4: Current practice and change in practice if Thyrogen was to receive an expanded MBS listing



Question 5

If clinicians responded that they were aware of the sensitivity of the Tg assays they requested, which 100% of clinicians stated they were in *question 2*, they were not required to complete *question 5*. Three clinicians attempted *question five* inappropriately and therefore these results were considered invalid.

Question 6

The proportion of patients with well-differentiated thyroid cancer who do not comply with THT-withdrawal stimulated diagnostic testing due to the negative effects of hypothyroidism is shown in **Table 54**. The clinicians surveyed suggested that the mean proportion of patients who would be non-compliant, weighted by the number of patients treated per clinician per year, was 14.4%. However, there was significant variation with the range being 0%–100%.

Table 54 Non-compliance to follow-up with THT-withdrawal stimulated diagnostic testing

Summary statistics	Non-compliance to THT-withdrawal
Mean [a]	14.4%
Lower 95% CI [a]	13.3%
Upper 95% CI [a]	15.4%
Minimum [b]	0%
Maximum [b]	100%

[a] Mean, 95% CI were weighted by the number of patients treated by each clinician per annum
[b] The minimum and maximum were based on individual clinician responses (i.e. unweighted)

APPENDIX 2: LIST OF EXCLUDED CITATIONS AND REASON FOR EXCLUSION

Embase and Cochrane Library literature search: citations and reasons for exclusion (original search: 2010)

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