**PUBLIC SUMMARY DOCUMENT**

**Product:** Thyrotropin alfa-rch, powder for injection, 1.1 mg, 2 vials, Thyrogen®

**Sponsor:** Genzyme Australasia Pty Ltd

**Date of PBAC Consideration:** July 2006

## 1. Purpose of Application

The submission requested an authority required listing for thyrotropin alfa-rch for the treatment of post-thyroidectomy patients, in combination with radioactive iodine, to ablate thyroid remnant tissue.

## 2. Background

This drug had not previously been considered by the PBAC.

## 3. Registration Status

Thyrogen is registered with the TGA on 14 August 2001 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 suppression therapy, and for therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine.

## 4. Listing requested and PBAC's View

Authority required
For therapeutic use in post thyroidectomy patients without known metastatic disease, maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine in adults 18 years and older.

The PBAC's view was that limiting use to one treatment per patient per lifetime was seen as appropriate.

## 5. Clinical place for the proposed therapy

The primary treatment for the majority of papillary or follicular thyroid carcinomas is total or near total thyroidectomy, followed by radioiodine ablation of the remaining glandular tissue.

Current medical practice is for post-operative thyroid cancer patients to undergo remnant ablation procedure with radioiodine whilst in a hypothyroid state. Inducing hypothyroidism acts to elevate endogenous TSH, which is turn optimises the uptake of radioiodine into the thyroid remnant.

Thyrotropin is a source of exogenous TSH, which enhances radioiodine uptake while allowing patients to remain in a euthyroid state and avoids the need for thyroid hormone

withholding or withdrawal that would otherwise be required to elevate endogenous TSH prior to radioiodine ablation.

## 6. Comparator

The submission nominated preparation for radioiodine ($^{131}$I) ablation in post-thyroidectomy patients by a period of hypothyroidism for 4–6 weeks prior to ablation (induced by withholding or withdrawing thyroid hormone therapy) as the comparator. The PBAC confirmed the comparator was appropriate.

## 7. Clinical Trials

The submission presented a single randomised non-inferiority trial in a post-thyroidectomy patient population prior to $^{131}$I ablation of remnant thyroid tissue, comparing 0.9mg/ml of thyrotropin alfa - rch once per day for two days (rhTSH stimulation of $^{131}$I uptake) + thyroid hormone therapy, with the withholding of thyroid hormone therapy (endogenous TSH stimulation of $^{131}$I uptake) for 4-6 weeks.

| Trial/First author | Publication title | Publication citation |
|---|---|---|
| THYR-008-00/ Pacini F, et al, 2005 | 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: 926-932, 2006 |

## 8. Results of Trials

The submission indicated that there was equivalently successful ablation at month 8 whole body scan between the two trial arms, on the basis of a lack of statistically significant difference using a post hoc re-analysis of the intention-to-treat population for the pre-specified primary outcome. Similar interpretation and analysis was applied to ablation success as measured by thyroglobulin level. The submission did not interpret the results with respect to the non-inferiority criterion or to the per protocol population, as pre-specified in the trial report. This was conducted as part of the evaluation process.

The pre-specified non-inferiority criteria in the primary analysis were met for the criterion of “no visible uptake or uptake <0.1% in thyroid bed” and for the post hoc criterion of serum Tg <2ng/mL.

Utilities used in the trial-based economic analysis and the model were derived from the secondary outcome of quality of life (QoL), measured by the SF-36 survey of general health status in this trial. All statistical analysis was post hoc.

Patients withheld from thyroid hormone therapy had a substantial decrease in QoL at week 4, compared to patients receiving thyrotropin alfa – rch + thyroid hormone therapy. The difference between the two treatment groups in the mean change from baseline in week 4 SF-36 scores was statistically significant in five of the eight SF-36 domains, with the thyrotropin alfa – rch + thyroid hormone therapy patients (euthyroid group) having a better QoL. The mean baseline SF-36 scores in both groups were not provided in the trial

report or in the submission, but were provided in the Pre-Sub-Committee response. The SF-36 was also a subjective instrument and as patients were unblinded to their treatment allocation in this trial it cannot be excluded that the results may be biased.

The mean residence time of $^{131}$I in the whole body was higher in the group with endogenous TSH-stimulated $^{131}$I uptake (24.0±7.63h) than in the group with rhTSH-stimulated uptake (17.3±3.89h). All statistical analyses were conducted post hoc and without adjustment for multiple comparisons. Despite this, it appeared that $^{131}$I was cleared faster from the body in patients with rhTSH-stimulated uptake, compared to patients with endogenous TSH-stimulated uptake. This may allow a shorter hospital stay.

In the pre-treatment period (from randomisation until ablation) in the group withheld from thyroid hormone, 12/30 (40%) of patients experienced 30 adverse events. Headache and nausea were the most common events (3 patients each). During this period 13/33 (39.4%) of patients allocated to the euthyroid group experienced 36 adverse events, of which asthenia and fatigue were the most common (3 patients each). None of these patients experienced serious adverse events related to the trial medication. It was clear that hypothyroidism in the group withheld from thyroid hormone only clinically manifested as a slight increase in headache and nausea, compared to the euthyroid group. The adverse event rate and serious adverse event rate were similar in both groups.

Following thyrotropin alfa – rch administration in the euthyroid group, and ablation treatment in the group withheld from thyroid hormone, 26 (78.8%) and 22 (73.3%) patients, respectively, experienced at least 1 treatment-emergent adverse event until Month 8 or the last observation. No deaths occurred during the trial. The adverse events of eight patients in each group were considered possibly, probably, or definitely related to use of the study medication. The most frequently reported treatment-related adverse events in the endogenous TSH-stimulated arm were fatigue, nausea and skeletal pain. In the rhTSH-stimulated arm, the most frequently reported adverse events were nausea, fatigue and taste loss. Treatment period adverse events appeared similar in both treatment groups in the trial.

## 9. Clinical Claim

The submission described thyrotropin alfa – rch + thyroid hormone therapy as (1) being significantly more effective (comprising equivalent efficacy with respect to ablation success, but greater effectiveness with respect to ability to maintain euthyroid status and quality of life) than the main comparator, and (2) having similar or less toxicity (comprising less retention of radiation and comparable other adverse events).

*For PBAC's views see Recommendation and Reasons.*

## 10. Economic Analysis

A preliminary economic evaluation was presented, in the form of a cost-comparison. Outcome data were not provided. The justification for this departure from usual practice was that as the claim of greater effectiveness is multi-factorial (comprising equivalent efficacy with respect to ablation success but greater effectiveness with respect to ability to maintain euthyroid status and quality of life) the value of a trial-based preliminary economic evaluation was limited. The sponsors also stated that a trial-based cost-

effectiveness analyses would have been meaningless given the identical primary outcome (100% ablation success). The PBAC considered that the choice of a cost-comparison approach was not valid. Without an estimate of the ICER under trial conditions it was unclear as to what the impact of modelling had been. The Pre-PBAC Response provided a trial-based preliminary economic evaluation with an incremental cost per extra QALY gained in the range $15,000 - $45,000.

A modelled economic evaluation was presented. The choice of the cost-utility approach was valid. All costs in the base case analysis were said to be calculated from the perspective of the total healthcare system, with a sensitivity analysis investigating productivity losses. The Markov model had 5 health states and 2 treatment arms (rhTSH-stimulated $^{131}$I uptake, through use of thyrotropin alfa – rch in a euthyroid state; and endogenous TSH-stimulated $^{131}$I uptake through withdrawal of thyroid hormone therapy). The model had a six-month duration, with a weekly cycle length. Utilities were derived from the key THYR-008-00 trial, with SF-36 quality of life scores transformed to quality weights using the method of Brazier et al. (1998). The resources included were drug costs, cost of tests to monitor TSH and thyroglobulin levels (needed to determine when to initiate $^{131}$I ablation), treatment administration costs (eg specialist and GP consults, hospital stay) and diagnostic services (cost of whole body scan following ablation). The base case modelled incremental cost per extra QALY gained was $17,331, but when recalculated during the evaluation increased slightly to $17,625. Sensitivity analyses ranged from $9,535–$28,101 per QALY.

**11. Estimated PBS Usage and Financial Implications**

The likely number of patients per year accounting for market share as necessary was < 10,000 in Year 2010, while the financial cost per year to the PBS was < $10 million in Year 2010.

**12. Recommendation and Reasons**

The PBAC confirmed that withholding the hormone treatment prior to radioiodine ablation in post-thyroidectomy patients was the appropriate comparator. Limiting use to one treatment per patient per lifetime was seen as appropriate.

The PBAC accepted effectiveness had been demonstrated in the key trial by thyrotropin alfa-rch meeting the pre-specified non-inferiority criteria in the primary efficacy outcome for the criterion of “no visible uptake or uptake <0.1% in thyroid bed” and for the post hoc criterion of serum Tg <2 ng/mL.

Therefore, the PBAC considered that the only differences between thyrotropin alfa-rch and the comparator would stem from possible quality of life differences. The PBAC noted the pre-specified, secondary outcome, QoL assessments were subjective, as noted below, and unblinded to treatment allocation and any clinical differences were not reflected in the adverse event profiles of the two treatment groups.

The difference between the two treatment groups in the mean change from baseline in week 4 SF-36 scores was statistically significant in five of the eight SF-36 domains, with the thyrotropin alfa – rch + thyroid hormone therapy patients (euthyroid group) having a better QoL. The mean baseline SF-36 scores in both groups were not provided in the trial

report or in the submission but were provided in the Pre-Sub-Committee response. The SF-36 is also a subjective instrument and as patients were unblinded to their treatment allocation in this trial it cannot be excluded that the results may be biased. However, the PBAC considered it would seem likely that the patients who were intentionally rendered hypothyroid (through withholding thyroid hormone for a 4-6 week period) would have had a poorer QoL for those weeks than those who were able to remain euthyroid. One other possible health benefit, that of reduced exposure to $^{131}$I may reduce the risk of secondary malignancy, was not considered plausible by the PBAC.

The PBAC noted that the presentation in the submission of preliminary economic evaluation in the form of a cost-comparison did not allow for the impact of modelling to be easily assessed. The Pre-PBAC response undertook a preliminary economic evaluation which showed that the incremental cost-effectiveness ratio is in the range of $15,000 - $45,000/QALY gained.

The argument that faster clearance of $^{131}$I will reduce hospital stay by one day was not adequately supported by evidence. The PBAC considered it would be helpful if data could be presented on proportion of patients actually discharged at various time points rather than extrapolate this from the mean exposure to $^{131}$I. The uncertainty in this figure and the sensitivity of the ICER to the costs of a radioactive bed stay raises the possibility that the ICER could be much higher.

The PBAC rejected the application on the basis of an uncertain quality of life improvement and uncertain cost-effectiveness.

## 13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 14. Sponsor's Comment

Genzyme does not agree with the PBAC's view that there is uncertain quality of life benefit and uncertain cost-effectiveness and plans to re-submit with additional evidence to clarify these uncertainties.