PUBLIC SUMMARY DOCUMENT

Product: Thyrotropin alfa-rch, powder for injection, 1.1 mg, 2 vials (1 kit), Thyrogen®

Sponsor: Genzyme Australasia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The sponsor sought a Section 85 Authority required listing for therapeutic use in preparation for radioiodine ablation of thyroid remnant tissue.

2. Background

This was the second submission to PBAC. At its July 2006 meeting the PBAC rejected an application for the preparation of patients for ablation of thyroid tissue on the basis of an uncertain quality of life improvement and uncertain cost-effectiveness.

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 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.

There is a Public Summary Document for the thyrotropin-alfa application to the July 2006 PBAC meeting at:

http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-mtjuly06

3. Registration Status

Thyrogen® is registered by the Therapeutic Goods Administration (TGA) for:

- Use with serum thyroglobulin (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.

4. Listing Requested and PBAC's View

Authority required

For therapeutic use in adult post thyroidectomy patients without known metastatic disease who are/will be maintained on hormone suppression therapy, in the ablation of thyroid remnant tissue in combination with radioactive iodine. PBS-subsidised use is limited to once per lifetime.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Thyrotropin is a source of exogenous thyroid stimulatory hormone (TSH), which enhances radioiodine uptake while allowing patients to remain in a euthyroid state and avoids the need for thyroid hormone withdrawal that would otherwise be required to elevate endogenous TSH prior to radioiodine ablation.

6. Comparator

The submission nominated a period of hypothyroidism for 4–6 weeks prior to ablation (induced by withholding/withdrawing thyroid hormone therapy) as the comparator. The PBAC confirmed that the comparator was appropriate.

7. Clinical Trials

There was one change to the trial data presented in the previous submission, namely a new analysis of the primary outcome. Details of the trials submitted follow:

Trial/First author	Protocol title/Publication title	Publication citation
THYR-008-00-00	A Randomized, Controlled, Open-Label, Multi-National Pilot Study of Thyroid Remnant Ablation Comparing the Safety and Ablation Rate Following ^{131}I Administration Using Thyrogen versus the Safety and Ablation Rate Following ^{131}I Administration in the Hypothyroid State – Final Report	
Pacini et al (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 2006; 91(3):926-32.
Hanscheid et al (2006)	Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal.	Journal of Nuclear Medicine: official publication, Society of Nuclear Medicine 2006; 47:648-54.

8. Results of Trials

The results of previous trials have been reported in the July 2006 Public Summary Document (PSD).

The re-submission represented the per protocol analyses of: thyroid remnant ablation at Month 8 follow-up (primary efficacy outcome); and the number of patients with serum Tg levels <2ng/mL or <1ng/mL at Month 8 as presented previously.

The re-submission represented the secondary outcome, quality of life (QoL) as measured by the SF-36 survey of general health status and the utility values calculated from these QoL data using the SF-6D method of Brazier et al (1998). All statistical analysis was post hoc.

There were statistically significant differences in the mean change from baseline in Week 4 SF-36 scores for five of the eight SF-36 domains, favouring thyrotropin alfa – rch + thyroid hormone therapy.

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 QoL) than the main comparator, and (2) having similar or less toxicity (comprising less retention of radiation and comparable other adverse events).

See Recommendation and Reasons for PBAC's views.

10. Economic Analysis

An updated preliminary economic evaluation was presented.

The submission calculated a trial-based incremental cost/extra QALY gained value of $75,000 - $105,000.

An updated modelled economic evaluation was also presented.

In the pre-PBAC response the sponsor presented a revised base case incremental cost effectiveness ratio of between $15,000 - $45,000 per extra QALY gained.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/ year (accounting for market share as necessary) would be < 10,000 by 2011 (in Year 5).

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be < $10 million in 2011 (Year 5).

12. Recommendation and Reasons

The PBAC recommended listing to prepare for radioiodine ablation on the basis of acceptable cost-effectiveness compared to withdrawing thyroid hormone therapy and thus inducing a longer period of hypothyroidism of 4-6 weeks prior to ablation.

The PBAC had previously (July 2006 PBAC meeting) considered that effectiveness had been demonstrated in the key trial, by thyrotropin alfa meeting the pre-specified non-inferiority criteria in the primary efficacy outcome, and considered that the only differences between thyrotropin alfa and the comparator would stem from possible quality of life (QoL) differences in the pre-ablation period.

The PBAC noted the re-submission represented QoL as measured by the SF-36 survey of general health status and utility values using the SF-6D method of Brazier et al. The SF 36 results showed there were statistically significant changes from baseline in Week 4 SF-36 scores for five of the eight SF-36 domains favouring thyrotropin alfa + thyroid hormone therapy. The PBAC noted that SF-36 values were derived using the 4-week recall version (rather than the 1-week recall version). However, there was some concern that patients were unblinded, and that the Week 4 values may overestimate the average utility impact over the 4-week period, noting that the physiological changes take some time to develop and thus to manifest symptomatically. Nevertheless, the PBAC also noted the pre-PBAC Response provided the results of a treatment survey advising that the time between surgery and ablation is actually 6 weeks or longer in more than 62% of patients, not 10% as used in the submission. On the basis of this survey, the revised base case ICER was reduced, though still between $15,000 - $45,000 per extra QALY gained.

The PBAC considered that while there was also uncertainty around the time points post-surgery when QoL was affected due to withdrawal of thyroid hormone therapy, it appeared the four weeks preceding ablation were the most relevant.

The PBAC accepted there was an advantage in the weighted average time to discharge of 1.56 days for patients given thyrotropin alfa + thyroid hormone therapy versus 2.04 days for patients withheld from thyroid hormone therapy, which would be realisable under current hospital discharge practices.

Therefore, while taking into account uncertainties associated with QoL, the PBAC concluded the incremental cost per extra QALY gained, while uncertain, was acceptable.

Recommendation
THYROTROPIN ALFA-rch, powder for injection, 1.1 mg, 2 vials (1 kit)

Restriction:	Authority required Ablation of thyroid remnant tissue, in combination with radioactive iodine, in a post thyroidectomy adult aged 18 years of older without known metastatic disease. This drug is only PBS-subsidised for one treatment in a patient's lifetime.
Maximum Quantity:	1 (equivalent to 2 vials)
Repeats:	nil

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 Australasia welcomes the recommendation by the PBAC to list thyrotropin alfa-rch on the pharmaceutical benefits scheme.