AUSTRALIAN PRODUCT INFORMATION – THYROGEN (THYROTROPIN ALFA) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Thyrotropin alfa.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Thyrotropin alfa 1.1 mg

3 PHARMACEUTICAL FORM

THYROGEN is supplied as a sterile, non - pyrogenic, white to off - white, lyophilised product, intended for intramuscular (IM) administration after reconstitution with Sterile Water for Injection. Each vial of THYROGEN contains 1.1 mg thyrotropin alfa.

After reconstitution with 1.2 mL of Sterile Water for Injection, the thyrotropin alfa concentration is 0.9 mg/mL. The pH of the reconstituted solution is approximately 7.0.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

THYROGEN is indicated for:

1. 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.

2. therapeutic use in post - thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine.

4.2 DOSE AND METHOD OF ADMINISTRATION

A two - injection regimen is recommended for THYROGEN administration.

The two - injection regimen is THYROGEN 0.9 mg intramuscularly (IM), followed by a second 0.9 mg IM injection 24 hours later.

After reconstitution with 1.2 mL Sterile Water for Injection, 1.0 mL solution (0.9 mg thyrotropin alfa) is administered by intramuscular injection to the buttock.

Each vial, after reconstitution with 1.2 mL of Sterile Water for Injection, should be inspected visually for particulate matter or discolouration, before use. Any vials exhibiting particulate matter or discolouration should not be used.

For radioiodine imaging or treatment, radioiodine administration should be given 24 hours following the final THYROGEN injection. Diagnostic scanning should be performed 48 hours after radioiodine administration (72 hours after the final administration of THYROGEN), whereas post - therapy scanning may be delayed additional days to allow background activity to decline.

For serum Tg testing, the serum sample should be obtained 72 hours after the final intramuscular injection of THYROGEN.

The following parameters utilised in the second Phase III study are recommended for diagnostic radioiodine scanning with THYROGEN:

- A diagnostic activity of 148 MBq ^{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.
- Scanning times for single (spot) images of body regions should be 10 - 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).

To reduce microbiological hazard, use as soon as practicable after reconstitution / preparation. If storage after reconstitution is necessary, hold at 2° - 8°C for not more than 24 hours, and avoid microbial contamination.

Product is for single use in one patient only. Discard any residue.

Injection material should not be mixed with other substances.

4.3 CONTRAINDICATIONS

There are no known contraindications to the use of THYROGEN.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

THYROGEN may be used as an adjunctive diagnostic tool to detect recurrent or residual cancer in combination with radioiodine. Thyroid hormone withdrawal Tg testing with radioiodine imaging remains the standard diagnostic modality to assess the presence, location and extent of thyroid cancer.

The use of THYROGEN in conjunction with Tg testing alone (without radioimaging) should be restricted to patients at low risk of disease recurrence, that is those patients with no clinical evidence of disease who have suppressed serum Tg levels during thyroid hormone suppression therapy.

The use of THYROGEN should be directed by physicians knowledgeable in the management of patients with thyroid cancer.

Even when THYROGEN - stimulated Tg testing is performed in combination with radioiodine imaging, there remains a meaningful risk of missing a diagnosis of thyroid cancer or of underestimating the extent of disease.

THYROGEN - stimulated Tg levels are generally lower than, and do not correlate with, Tg levels after thyroid hormone withdrawal.

A newly detectable Tg level or a Tg level rising over time after THYROGEN, or a high index of suspicion of metastatic disease, even in the setting of a negative or low - stage THYROGEN radioiodine scan, should prompt further evaluation such as thyroid hormone withdrawal to definitively establish the location and extent of thyroid cancer. Note that none of the 31 patients studied with undetectable THYROGEN - stimulated Tg levels (< 2.5 ng/mL) had metastatic disease therefore an undetectable THYROGEN - stimulated Tg level suggests the absence of clinically significant disease (see Section 5.1 **CLINICAL TRIALS**).

The decisions whether to perform a THYROGEN radioiodine scan in conjunction with a THYROGEN serum Tg test and whether and when to withdraw a patient from thyroid hormone are complex. Pertinent factors in these decisions include the sensitivity of the Tg assay used, the THYROGEN-stimulated Tg level obtained, and the index of suspicion of recurrent or persistent local or metastatic disease. In the clinical trials, combination Tg and scan testing did enhance the diagnostic accuracy of THYROGEN in some cases (see Section 5.1 **CLINICAL TRIALS**).

THYROGEN should be administered intramuscularly only. It should not be administered intravenously.

Clinicians employ a wide range of ^{131}I administered activities to achieve remnant ablation. Published studies on the use of THYROGEN to achieve remnant ablation have used ^{131}I activities of 30 mCi to 110 mCi, and the Genzyme study employed 100 mCi in all patients. Multiple factors contribute to the decision about what activity of ^{131}I should be administered for a given patient, such as the size of the remnant tissue (e.g. a function of aggressiveness of the surgeon) and the perceived risk of the patient for thyroid cancer recurrence (e.g. a function of patient age, primary tumour type and size, extent of disease). Activities of ^{131}I in the 100 mCi range or above achieve remnant ablation more frequently than do lower activities but may be associated more often with complications of ^{131}I treatment, such as salivary gland pain and swelling, persistent dry mouth, dry eyes or altered taste. Clinicians must weigh the risks and benefits when selecting an activity of ^{131}I to achieve remnant ablation for a given patient.

In clinical trials with thyrotropin alfa, which produces a short - term increase in TSH levels, no case of tumour growth has been reported. In thyroid cancer patients, several cases of stimulated tumour growth have been reported during withdrawal of thyroid hormones for diagnostic procedures due to the subsequent prolonged elevation of TSH levels. There is a low risk of tumour stimulation when THYROGEN is used as an adjunct to radioiodine therapy to achieve remnant ablation.

In the clinical trials performed, the combination of whole body scanning and thyroglobulin testing after THYROGEN administration increased the detection rate for remnant thyroid tissue or cancer when compared to either diagnostic test alone. False negative results may occur with THYROGEN as with other diagnostic modalities. If a high index of suspicion for

metastatic disease persists, a confirmatory withdrawal diagnostic or post - therapy whole body scan and thyroglobulin test should be considered.

Caution should be exercised when THYROGEN is administered to patients who have been previously treated with bovine TSH and, in particular, to those patients who have experienced hypersensitivity reactions to bovine TSH.

THYROGEN is known to cause a transient but significant rise in serum thyroid hormone concentration. Therefore, caution should be exercised in patients with a known history of heart disease and with significant residual thyroid tissue. One case of fatal myocardial infarction has been reported in a patient with residual thyroid tissue and a history of heart disease. The event was considered related to THYROGEN - induced hyperthyroidism.

Thyroid cancer patients with metastatic disease present in confined spaces such as the brain and spinal cord, orbit or disease infiltrating the neck, may be subject to local oedema or focal haemorrhage at the site of these metastases. Due to the elevation of TSH levels after THYROGEN administration, the patients with metastatic disease may experience symptoms after administration including acute hemiplegia, hemiparesis, pain, or swallowing difficulty. Pre - treatment with corticosteroids should be considered in these patients prior to the administration of THYROGEN.

There is a theoretical possibility that THYROGEN, like hormone withdrawal may lead to stimulated tumour growth. However any changes in tumour size reportedly seen with THYROGEN are more likely to be due to oedematous or haemorrhagic changes.

Thyroglobulin (Tg) antibodies will confound the Tg assay and render the Tg levels uninterpretable. Therefore, in such cases, even with a negative or low - stage THYROGEN radioiodine scan, consideration should be given to evaluating patients further with, for example, a confirmatory thyroid hormone withdrawal scan to determine the location and extent of thyroid cancer.

Use in renal impairment

Information from post - marketing surveillance as well as published information suggest that elimination of THYROGEN is significantly slower in dialysis - dependent end - stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels. ESRD patients who receive THYROGEN may have markedly elevated TSH levels for up to two weeks after treatment, which may lead to increased risk of headache and nausea. There are no studies of alternative activity schedules of THYROGEN in patients with ESRD to guide dose reduction in this population.

The safety and efficacy of THYROGEN in patients with impaired renal function has not been evaluated. In patients with significant renal impairment, the activity of ^{131}I should be carefully selected by the nuclear physician.

Use in the elderly

Results from controlled trials for the diagnostic indication, indicate no difference in the safety and efficacy of THYROGEN between adult patients less than 65 years and those greater than

65 years. There is only limited data available on the use of THYROGEN in the treatment of patients greater than 65 years.

Careful evaluation of the risk - benefit relationships should be assessed for high - risk elderly patients with functioning thyroid tumours and/or patients with heart disease, (e.g., valvular heart disease, cardiomyopathy, coronary artery disease and prior or current tachyarrhythmia) undergoing THYROGEN administration.

Paediatric use

The safety and effectiveness of THYROGEN use in children below the age of 18 years has not been assessed.

Effects on laboratory tests

The effect of THYROGEN on other laboratory tests has not been determined.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Formal interaction studies between THYROGEN and other medicinal products have not been performed. In clinical trials, no interactions were observed between THYROGEN and the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) when administered concurrently.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies have not been performed with THYROGEN to evaluate the effects on fertility.

Use in pregnancy (Category B2)

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Animal embryofoetal toxicity studies have not been conducted with THYROGEN. It is also not known whether THYROGEN can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. THYROGEN should not be used during pregnancy.

Use in lactation

It is not known whether the drug is excreted in human or animal milk. Patients given THYROGEN should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reaction data were derived from post - marketing surveillance and clinical trials. The percentages in the table below represent adverse reactions experienced by 481 thyroid cancer patients who participated in the clinical trials for THYROGEN. Most patients received 2 intramuscular injections, 0.9 mg of thyrotropin alfa per injection, 24 hours apart.

The safety profile of patients who received THYROGEN as adjunctive treatment for radioiodine ablation of thyroid tissue remnants who have undergone a thyroidectomy for well - differentiated thyroid cancer did not differ from that of patients who received THYROGEN for diagnostic purposes.

The most common adverse drug reactions (>5%) reported in clinical trials were nausea (11.9%) and headache (7.3%). Drug reactions reported in ≥1% of patients in the combined trials are summarised below. In some studies, an individual patient may have participated in both the Euthyroid Phase (THYROGEN) and Hypothyroid Phase (withdrawal).

**Table 1 - Summary of Adverse Drug Reactions*
During Euthyroid Phase In All Clinical Trials (≥1%)**

Preferred Term	Euthyroid Phase 481 Patients n (%)
	AE MedDRA Term
Very Common Adverse Drug Reactions (≥10%)	
Nausea	57 (11.9)
Common Adverse Drug Reactions (≥1% and <10%)	
Headache	35 (7.3)
Fatigue	16 (3.3)
Vomiting	14 (2.9)
Dizziness	12 (2.5)
Paraesthesia	8 (1.7)
Asthenia	7 (1.5)
Diarrhea	6 (1.2)

* Adverse drug reactions refer to adverse experiences that are determined to have a causal relationship as determined by a healthcare provider and/or the sponsor.

In addition, uncommon adverse reactions (≥0.1% and <1%) reported in at least 2 patients in clinical trials included influenza, paraesthesia, feeling hot, ageusia, diarrhoea, dysgeusia, and

neck pain. THYROGEN administration may cause transient (< 48 hours) influenza - like symptoms also called flu - like symptoms (FLS), which may include fever (> 38^{o}C), chills/shivering, myalgia/arthralgia, fatigue/asthenia/malaise and headache (non - focal) 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: these are urticaria, rash, pruritus, flushing and respiratory signs and symptoms.

Enlargement of residual thyroid tissue or metastases can occur following treatment with THYROGEN. This may lead to acute symptoms which depend on the anatomical location of the tissue. For example, hemiplegia, hemiparesis and/or loss of vision have occurred in patients with CNS metastases. Laryngeal oedema, pain at the site of the metastasis and respiratory distress requiring tracheotomy have also been reported after THYROGEN administration. It is recommended that pre - treatment with corticosteroids be considered for patients in whom local tumour expansion may compromise vital anatomic structures.

Mild hypersensitivity reactions consisting of urticaria, rash, pruritus, flushing and respiratory signs and symptoms have been reported in rare cases. However, in clinical trials, no patients have developed antibodies to thyrotropin alfa, either after single or repeated (27 patients) THYROGEN use.

Local oedema, focal haemorrhage or swallowing difficulty have been reported in thyroid cancer patients with metastatic disease in confined spaces such as the brain and spinal cord or disease infiltration of the neck. One case of acute visual loss was reported 24 hours after THYROGEN administration in a patient with metastases to the optic nerve. In addition, one case of laryngeal oedema requiring tracheotomy was reported 24 hours after THYROGEN administration in a patient with metastases to the paratracheal area. Pre - treatment with corticosteroids may be considered under such circumstances.

One case of fatal myocardial infarction has been reported in a patient with residual thyroid tissue and a history of heart disease, who received THYROGEN (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Post - Marketing Surveillance

Post - marketing surveillance indicates that the types of events most frequently reported are similar to those seen in the clinical trials (including headache, fatigue, nausea, vomiting, dizziness, paresthesia, asthenia, diarrhoea, and injection site reactions (e.g., discomfort, pain, and pruritus at the injection site)). Sudden rapid and painful enlargement of locally recurring papillary carcinoma has been reported 12 - 48 hours after THYROGEN administration. The enlargement was accompanied by dyspnoea, stridor or dysphonia. Rapid clinical improvement occurred following glucocorticoid therapy. There have also been several reports of hypersensitivity reactions (including urticaria, rash, pruritus, flushing, headache, fatigue, vomiting, dizziness, paresthesia, asthenia, diarrhoea, and respiratory signs and symptoms such as wheezing and bronchospasm) reported in post - marketing setting.

Very rare cases of stroke have been reported from world-wide post marketing experience.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

There has been no reported experience of overdose in humans. However, in clinical trials, three patients experienced symptoms after receiving higher doses than those recommended. Two patients had nausea after a 2.7 mg IM dose, and in one of these patients, the event was accompanied by weakness, dizziness and headache. Another patient experienced nausea, vomiting and hot flushes after a 3.6 mg IM dose. In addition, one patient experienced symptoms after receiving THYROGEN intravenously. This patient received 0.3 mg THYROGEN as a single intravenous bolus and, 15 minutes later, experienced severe nausea, vomiting, diaphoresis, hypotension (BP decreased from 115/66 mm Hg to 81/44 mm Hg) and tachycardia (pulse increased from 75 to 117 bpm).

For general advice on management of overdose, contact the Poisons Information Centre, telephone number 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Pituitary and Hypothalamic Hormones and Analogues, Anterior Pituitary Lobe Hormones and Analogues; ATC code: H01AB01

Mechanism of action

Thyrotropin alfa (recombinant human thyroid stimulating hormone) is a heterodimeric glycoprotein produced by recombinant DNA technology. It has comparable biochemical properties to those of the human pituitary TSH. Binding of thyrotropin alfa to TSH receptors on normal thyroid epithelial cells or on well - differentiated thyroid cancer tissue stimulates iodine uptake and organification, and synthesis and secretion of thyroglobulin (Tg), triiodothyronine (T_3) and thyroxine (T_4).

In patients with thyroid cancer, a near - total or total thyroidectomy is performed and patients are placed on synthetic thyroid hormone supplements to replace endogenous hormone and to suppress serum levels of TSH in order to avoid TSH - stimulated tumour growth. Thereafter, patients are followed up for the presence of remnants or of residual or recurrent cancer by thyroglobulin (Tg) testing while they remain on thyroid hormone suppressive therapy and are euthyroid, or by Tg testing and radioactive iodine imaging after thyroid hormone withdrawal. THYROGEN is an exogenous source of human TSH that offers an additional diagnostic tool in the follow - up of patients with a history of well - differentiated thyroid cancer.

Decreased iodide clearance, specifically ^{131}I, in hypothyroid patients as compared to euthyroid patients is well - documented. Hlad and Bricker (1954) demonstrated a direct correlation between a decrease in glomerular filtration rate and decreases in ^{131}I clearance.

Montenegro et al, (1996) studied renal function as assessed by creatinine clearance in 41 patients. Results demonstrated a 50% decrease in creatinine clearance (CrCl) when patients were hypothyroid versus euthyroid (90 ± 3 mL/min. versus 62 ± 4 mL/min. $p<0.05$). In clinical studies with THYROGEN, decreased clearance of ^{131}I during the hypothyroid state complicated comparisons between ^{131}I uptake observed in the thyroid bed when the patient was euthyroid after THYROGEN administration versus uptake while the patient was in a hypothyroid state.

Clinical trials

Studies on THYROGEN Use as an Adjunct Diagnostic Tool

Two Phase III clinical trials were conducted in 358 evaluable patients with well - differentiated thyroid cancer to compare 48 - hour radioiodine (^{131}I) whole body scans obtained after THYROGEN administration to whole body scans obtained after thyroid hormone withdrawal. In the second of these Phase III trials (n = 220 patients), the radioiodine imaging parameters were optimised. In addition, thyroglobulin (Tg) levels were measured at baseline (while patients were maintained on thyroid hormone suppressive therapy), and compared to Tg levels obtained after THYROGEN administration, as well as to Tg levels obtained following thyroid hormone withdrawal. All Tg testing was performed in a central laboratory using a radioimmunoassay (RIA) with a functional sensitivity of 2.5 ng/mL. Only successfully ablated patients (defined as patients who have undergone total or near -total thyroidectomy, with or without radioiodine ablation, and with < 1% uptake in the thyroid bed on a scan after thyroid hormone withdrawal) without detectable anti - thyroglobulin antibodies were included in the Tg data analysis. The maximum THYROGEN - stimulated Tg value was obtained 72 hours after the final THYROGEN injection, and this value was used in the analysis (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Diagnostic Radioiodine Whole Body Scan Results

In the second Phase III trial, two dose regimens of THYROGEN were examined: 0.9 mg injected intramuscularly (IM) every 24 hours for two doses or 0.9 mg injected IM every 72 hours for three doses. The administration of two or three doses of THYROGEN followed by radioiodine whole body scan detected remnant and/or cancer localised to the thyroid bed in 86% (30/35) and 85% (35/41) of patients, respectively, in whom remnant and/or cancer was detected by a scan after thyroid hormone withdrawal. In patients in whom metastatic disease was detected by a scan after hormone withdrawal, the scan following THYROGEN administration detected disease in 67% (6/9) and 86% (12/14) of patients after two and three doses of THYROGEN, respectively. The two dosing regimens were not statistically different from each other or from thyroid hormone withdrawal in stimulating radioiodine uptake for diagnostic imaging.

In the other Phase III trial a two dose regimen of THYROGEN was examined: 0.9 mg IM every 24 hours for two doses. The administration of THYROGEN followed by radioiodine whole body scan detected remnant and/or cancer localised to the thyroid bed in 81% (39/48) of patients, in whom remnant and/or cancer was detected by a scan after thyroid hormone withdrawal. In patients in whom metastatic disease was detected after hormone withdrawal, the scan following THYROGEN administration detected disease in 73% (11/15).

Across the two trials, the THYROGEN scan failed to detect remnant and/or cancer localised to the thyroid bed in 16% (20/124) of patients, in whom it was detected after thyroid hormone withdrawal. In addition, the THYROGEN scan failed to detect metastatic disease in 24% (9/38) of patients in whom it was detected by a scan after thyroid hormone withdrawal.

Thyroglobulin (Tg) Results

THYROGEN - stimulated Tg Testing Alone and in Combination with Diagnostic Radioiodine Imaging: Comparison with Results after Thyroid Hormone Withdrawal

In Tg antibody negative patients with a thyroid remnant or cancer as defined by a withdrawal Tg ≥ 2.5 ng/mL or a positive scan (after thyroid hormone withdrawal or after radioiodine therapy), the THYROGEN - stimulated Tg was ≥ 2.5 ng/mL in 69% (40/58) of patients after two doses of THYROGEN, and in 80% (53/66) of patients after three doses of THYROGEN. Across both dosage groups, 45% had a Tg ≥ 2.5 ng/mL on thyroid hormone suppressive therapy.

In these same patients, adding the whole body scan increased the detection rate of thyroid remnant or cancer to 84% (49/58) of patients after two doses of THYROGEN and 94% (62/66) of patients after three doses of THYROGEN.

THYROGEN - stimulated Tg Testing Alone and in Combination with Diagnostic Radioiodine Imaging in Patients with Confirmed Metastatic Disease

Metastatic disease was confirmed by a post - treatment scan or by lymph node biopsy in 35 patients. THYROGEN - stimulated Tg was ≥ 2.5 ng/mL in all 35 patients while Tg on thyroid hormone suppressive therapy was ≥ 2.5 ng/mL in 79% of these patients.

In this same cohort of 35 patients with metastatic disease, the Tg levels following administration of THYROGEN were ≥ 5 ng/mL in 97% (34/35) of patients and ≥ 10 ng/mL in 83% (29/35) of patients. Following hormone withdrawal, all 35 patients had Tg ≥ 10 ng/mL. The scan following THYROGEN administration detected metastatic disease in one of the six patients in whom the Tg level following THYROGEN administration was below 10 ng/mL.

As with thyroid hormone withdrawal, the intra - patient reproducibility of THYROGEN testing with regard to both Tg stimulation and radioiodine imaging has not been studied.

Quality of Life (Diagnostic Indication):

Quality of Life (QoL) was measured using the SF-36 Health Survey, a standardised, patient - administered instrument assessing QoL across eight domains measuring both physical and mental functioning. Following THYROGEN administration, little change from baseline was observed in any of the eight QoL domains of the SF-36. Following thyroid hormone withdrawal, statistically significant negative changes were noted in all eight QoL domains of the SF-36. The difference between treatment groups was statistically significant ($p<0.0001$) for all eight QoL domains, favoring THYROGEN over thyroid hormone withdrawal.

Hypothyroid Signs and Symptoms (Diagnostic Indication):

In two Phase III trials THYROGEN administration was not associated with any of the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal, such as cold intolerance, weight increase, constipation, slow movements, periorbital puffiness and decreased pulse rate. In comparison, a statistically significant worsening of all such signs and symptoms was observed in the hypothyroid phase after thyroid hormone withdrawal.

Pivotal Study on THYROGEN Use in Combination with Radioiodine to Achieve Thyroid Remnant Ablation

In a comparative study involving 60 evaluable patients, the rates of successful ablation of thyroid remnants with 100 mCi (3.7 MBq) radioiodine (^{131}I) in post -thyroidectomy patients with thyroid cancer were comparable for patients treated after withdrawal of thyroid hormone suppression therapy (THST) versus patients treated after THYROGEN administration. Success of remnant ablation was assessed with radioiodine imaging and with serum Tg testing at eight months after treatment. All 28 patients (100%) treated after withdrawal of THST and all 32 patients (100%) treated after THYROGEN administration had either no visible uptake of radioiodine in the thyroid bed or, if visible, thyroid bed uptake < 0.1% of the administered dose of radioiodine (14.3% in the hypothyroid group and 25% in the euthyroid group). The success of thyroid remnant ablation was also assessed by the criterion of THYROGEN - stimulated serum Tg level < 2 ng/ml eight months after ablation, but only in patients who were negative for interfering anti - Tg antibodies. Using this Tg criterion, 18/21 patients (86%) and 23/24 patients (96%) had thyroid remnants successfully ablated in the THST withdrawal group and the THYROGEN treatment group, respectively. When using a stricter criterion of Tg < 1 ng/mL, 86% of hypothyroid and 83% of euthyroid patients were assessed as having achieved successful ablation.

Table 2 - Summary of the Principal Results of the Pivotal Study on THYROGEN® Use in Combination with Radioiodine to Achieve Thyroid Remnant Ablation

Group[1]	**Mean Age (y)**	**Gender (F:M)**	**Cancer Type (papillary: follicular)**	**Ablation by various criteria [n/N (%)]**		
				Thyroid bed activity < 0.1%	Serum Tg < 2 ng/mL2	No visible thyroid bed activity3
THW4 (N = 28)	43	24:6	29:1	28/28 (100%)	18/21 (86%)	24/28 (86%)
rhTSH5 (N = 32)	44	26:7	32:1	32/32 (100%)	23/24 (96%)	24/32 (75%)
			95% CI for difference in ablation rates			
	rhTSH (test) minus THW (control)			N/A	[-6.9%, 27.1%]	[-30.5%, 9.1%]

Group[1]	Mean Age (y)	Gender (F:M)	Cancer Type (papillary: follicular)	Ablation by various criteria [n/N (%)]

[1]60 per protocol patients with interpretable scan data

[2]Analysis was limited to patients with no or only low levels of anti - Tg antibodies, below a pre - defined limit

[3]Interpretation by at least 2 out of 3 reviewers

[4]THW = thyroid hormone withdrawal group, i.e., hypothyroid or control group
[5]rhTSH = recombinant thyrotropin alfa group, i.e., THYROGEN/euthyroid or test group

Patients treated with THYROGEN experienced less radiation exposure to the blood since the radioiodine residence time was shorter in the euthyroid patients. Mean radiation dose to blood was 33% lower in these patients (0.266 ± 0.0613 mGy/MBq) than in the hypothyroid group (0.395 ± 0.1345 mGy/MBq).

Table 3 - Summary of ^{131}I Radioiodine Kinetics in Remnant Tissue (ITT Population)

Parameter	Hypothyroid				Euthyroid			
	n	mean (SD)	median	range	n	mean (SD)	median	range
Residence time in remnant (h)	29	1.4 (1.51)	0.8	0.0-5.9	33	0.9 (1.27)	0.4	0.0-6.6
Effective half - life in remnant (h)	29	48.0 (52.64)	26.9	16.0-192.5	33	67.6 (48.85)	51.1	17.3-192.5
Uptake in remnant tissue (%)	29	0.9 (1.05)	0.5	0.0-4.3	33	0.5 (0.70)	0.3	0.0-3.4
Area of remnant tissue in 48 h neck image (cm2)	30	18.8 (17.03)	18.9	-1.1-84.3	33	16.2 (10.42)	14.0	-0.7-48.8
^{131}I activity at week 4 (mCi)	30	102.9 (4.54)	102.2 (3.79 GBq)	92.8-114.8	33	102.4 (4.43)	102.5 (3.80 GBq)	93.8-111.2
^{131}I activity at month 8 (mCi)	29	4.1 (0.19)	4.1 (0.15 GBq)	3.9-4.5	33	4.2 (0.18)	4.2 (0.15 GBq)	3.6-4.5

Quality of Life (Remnant Ablation):

Quality of life was significantly reduced following thyroid hormone withdrawal, but maintained following THYROGEN treatment in five of the eight domains of a

patient - administered quality - of - life measurement instrument, the SF - 36 Health Survey (physical functioning, role physical, vitality, social functioning and mental health).

Hypothyroid Signs and Symptoms (Remnant Ablation):

Post hoc statistical analysis showed a statistically significant increase in hypothyroid signs and symptoms in the thyroxine withdrawal group using the Billewicz scale (difference in mean total score, $p<0.0001$). The difference between the two groups was largest for the following symptoms: cold intolerance, weight increase, constipation, slow movements, cold skin and periorbital puffiness.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of THYROGEN were studied in 16 patients with well -differentiated thyroid cancer given a single 0.9 mg IM dose. Mean peak concentrations of 116 ± 38 mU/L were reached between 13 ± 8 hours after injection (median of 10 hours). The mean apparent elimination half - life was 22 ± 9 hours. The organ(s) of TSH clearance in man have not been identified, but studies of pituitary - derived TSH suggest the involvement of the liver and kidneys (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

THYROGEN was not mutagenic in the bacterial reverse mutation assay.

Carcinogenicity

Long - term toxicity studies in animals have not been performed with THYROGEN to evaluate the carcinogenic potential of the drug.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

36 mg Mannitol

1.4 mg Monobasic Sodium Phosphate Monohydrate

3.7 mg Dibasic Sodium Phosphate Heptahydrate

2.4 mg Sodium Chloride

6.2 INCOMPATIBILITIES

Injection material should not be mixed with other substances.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

To reduce microbiological hazard, use as soon as practicable after reconstitution / preparation. If storage after reconstitution is necessary, hold at 2° - 8°C for not more than 24 hours, and avoid microbial contamination.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

THYROGEN powder for injection should be stored at 2° - 8°C. Refrigerate. Do not freeze.

DO NOT USE THYROGEN after the expiry date on the vial. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

THYROGEN is supplied as a kit containing two 5 mL vials of thyrotropin alfa per kit. Each vial, after reconstitution with Sterile Water for Injection, (1.2 mL), contains thyrotropin alfa 0.9 mg/mL.

The closure of each 5 mL glass vial consists of a grey, 20 mm siliconised butyl rubber stopper with an aluminium seal and a plastic flip - off cap.

The vials contain no antimicrobial agent and should be used only once.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

THYROGEN powder for injection contains a highly purified recombinant form of human thyroid stimulating hormone (TSH), a glycoprotein which is produced by recombinant DNA technology. Thyrotropin alfa is synthesised in a genetically modified Chinese Hamster ovary cell line.

Thyrotropin alfa is a heterodimeric glycoprotein comprised of two non - covalently linked subunits; an alpha subunit of 92 amino acid residues containing two N - linked glycosylation sites and a beta subunit of 118 residues containing one N - linked glycosylation site. The amino acid sequence of thyrotropin alfa is identical to that of human pituitary thyroid stimulating hormone.

Both thyrotropin alfa and naturally occurring human pituitary thyroid stimulating hormone are synthesised as a mixture of glycosylation variants. Unlike pituitary TSH, which is secreted as a mixture of sialylated and sulphated forms, thyrotropin alfa is sialylated but not sulphated. The biological activity of thyrotropin alfa is determined by a cell - based bioassay. In this assay, cells expressing a functional TSH receptor and a cAMP - responsive element coupled to a heterologous reporter gene, luciferase, enable the measurement of rhTSH activity by measuring the luciferase response. The specific activity of thyrotropin alfa using the cell - based bioassay is determined relative to an internal Genzyme reference standard that

was calibrated against the World Health Organisation (WHO) human TSH reference standard.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14 August 2001

10 DATE OF REVISION

12 April 2021

THYROGEN® is a registered trademark of Genzyme Corporation, USA.

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Update to ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and post-marketing surveillance section
All	Minor editorial changes to spelling and isotope notation