

(Logo) Thyrogen

thyrotropin alfa for injection

DESCRIPTION

Thyrogen[®] (thyrotropin alfa 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 synthesized 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 synthesized as a mixture of glycosylation variants. Unlike pituitary TSH, which is secreted as a mixture of sialylated and sulfated forms, thyrotropin alfa is sialylated but not sulfated. 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 is 4-12 IU/mg using this cell-based bioassay. The specific activity of thyrotropin alfa is determined relative to an internal Genzyme reference material that was calibrated against the World Health Organization (WHO) human pituitary derived TSH reference standard NIBSC 84/703 using an *in vitro* bioassay that measures the amount of cAMP produced by a bovine thyroid microsome preparation in response to rhTSH.

Thyrogen is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product, intended for intramuscular (IM) administration after reconstitution with Sterile Water for Injection, USP. Each vial of Thyrogen contains 1.1 mg thyrotropin alfa (4-12 IU/mg), 36 mg Mannitol, 5.1 mg Sodium Phosphate, and 2.4 mg Sodium Chloride.

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

Thyrotropin alfa (recombinant human thyroid stimulating hormone) is a heterodimeric glycoprotein produced by recombinant DNA technology. It has comparable biochemical properties to 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 (T₃) and thyroxine (T₄).

In patients with thyroid cancer, a near-total or total thyroidectomy is usually performed. Thyroidectomy is usually followed by radioiodine treatment to remove any remnant of normal thyroid tissue and microscopic residues of malignant tissue. Prior to radioiodine remnant ablation, serum TSH elevation is necessary to promote uptake of radioiodine by thyroid cells or thyroid cancer cells. Elevation of TSH may be achieved by withholding of synthetic thyroid hormone medication after thyroidectomy, with subsequent rise of endogenous pituitary thyroid stimulating hormone; or by administration of thyrotropin in the setting of synthetic thyroid hormone administration. After remnant ablation, 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 tumor growth. Thereafter, patients are followed for the presence of remnants, or of residual or recurrent cancer, by thyroglobulin (Tg) testing, usually with radioiodine imaging. This follow-up testing is most effective when conducted under TSH stimulation, achieved either by thyroid hormone withdrawal or administration of thyrotropin. Thyroid hormone withdrawal results in hypothyroidism with subsequent elevation of endogenous pituitary TSH; when thyrotropin is used, patients remain on thyroid hormone suppressive therapy and are euthyroid.

Pharmacokinetics

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 3 and 24 hours after injection (median of 10 hours). The mean apparent elimination half-life was 25 ± 10 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.

Clinical Trials

Clinical Trials of Thyrogen as an Adjunctive Diagnostic Tool:

Two phase 3 clinical trials were conducted in 358 evaluable patients with well-differentiated thyroid cancer to compare 48-hour radioiodine (¹³¹I) whole body scans obtained after Thyrogen to whole body scans after thyroid hormone withdrawal. One of these trials also compared Tg levels obtained after Thyrogen to those on thyroid hormone suppressive therapy, and to those after 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 Tg value was obtained 72 hours after the final Thyrogen injection, and this value was used in the analysis (see DOSAGE AND ADMINISTRATION).

Diagnostic Radioiodine Whole Body Scan Results

Table 1 summarizes the scan data in patients with positive scans after withdrawal of thyroid hormone from the diagnostic phase 3 studies:

Table 1: Scan Data in Patients with Positive Scans

| | # scan pairs by disease category | #(%) scan pairs in which Thyrogen scan <u>detected</u> disease seen on withdrawal scan | #(%) scan pairs in which Thyrogen scan <u>did not detect</u> disease seen on withdrawal scan |
|------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| <u>First Phase 3 Study (0.9 mg IM qd x 2)</u> | | | |
| positive for remnant or cancer in thyroid bed | 48 | 39(81) | 9(19) |
| metastatic disease | 15 | 11(73) | 4(27) |
| total positive withdrawal scans ^a | 63 | 50(79) | 13(21) |
| <u>Second Phase 3 Study (0.9 mg IM qd x 2)</u> | | | |
| positive for remnant or cancer in thyroid bed | 35 | 30(86) | 5(14) |
| metastatic disease | 9 | 6(67) | 3(33) |
| total positive withdrawal scans ^a | 44 | 36(82) | 8(18) |
| <u>Second Phase 3 Study (0.9 mg IM q 72 hrs x 3)</u> | | | |
| positive for remnant or cancer in thyroid bed | 41 | 35(85) | 6(15) |
| metastatic disease | 14 | 12(86) | 2(14) |
| total positive withdrawal scans ^a | 55 | 47(85) | 8(15) |

^a Across all studies, uptake was detected on the Thyrogen scan but not observed on the scan after thyroid hormone withdrawal in 5 patients with remnant or cancer in the thyroid bed.

Across the two clinical studies, the Thyrogen scan failed to detect remnant and/or cancer localized to the thyroid bed in 16% (20/124) of patients in whom it was detected by a scan 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 Tg Testing Alone and in Combination with Diagnostic Whole Body Scanning: 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 Tg was ≥ 2.5 ng/mL in 69% (40/58) of patients after 2 doses of Thyrogen, and in 80% (53/66) of patients after 3 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 2 doses of Thyrogen and 94% (62/66) of patients after 3 doses of Thyrogen.

Thyrogen Tg Testing Alone and in Combination with Diagnostic Whole Body Scanning in Patients with Confirmed Metastatic Disease:

Metastatic disease was confirmed by a post-treatment scan or by lymph node biopsy in 35 patients. Thyrogen 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 confirmed metastatic disease, the Thyrogen Tg levels were below 10 ng/mL in 27% (3/11) of patients after 2 doses of Thyrogen and in 13% (3/24) of patients after 3 doses of Thyrogen. The corresponding thyroid hormone withdrawal Tg levels in these 6 patients were 15.6 – 137 ng/mL. The Thyrogen scan detected metastatic disease in 1 of these 6 patients (see INDICATIONS AND USAGE, Considerations in the Use of Thyrogen).

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.

Clinical Trials of Thyrogen as an Adjunct to Radioiodine Therapy to Achieve Thyroid Remnant Ablation:

A randomized prospective clinical trial comparing the rates of thyroid remnant ablation achieved after preparation of patients either with hypothyroidism or Thyrogen has been performed. Patients (n = 63) with low-risk well-differentiated thyroid cancer underwent near-total thyroidectomy, then were equally randomized to the Hypothyroid group (serum TSH > 25 μ U/mL) or thyroxine replacement (Euthyroid group; serum TSH < 5 μ U/mL). Patients in the Euthyroid group then received Thyrogen 0.9 mg IM daily on two consecutive days, and then radioiodine 24 hours after the second dose of Thyrogen. All patients received 100 mCi 131 I $\pm 10\%$ with the intent to ablate any thyroid remnant tissue. The primary endpoint of the study, which was the success of ablation, was assessed 8 months later by a Thyrogen-stimulated radioiodine scan. Patients were considered successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1%. Table 2 summarizes the results of this evaluation.

Table 2: Results from the Remnant Ablation Clinical Trial

| Group ^a | Mean Age (Yr) | Gender (F:M) | Cancer Type (Pap:Fol) | Ablation Criterion (Measure at 8 Months) | |
|--------------------|---------------|--------------|-----------------------|------------------------------------------|----------------------------------------------|
| | | | | Thyroid Bed Activity <0.1% | No Visible Thyroid Bed Activity ^b |
| THW (N=28) | 43 | 24:6 | 29:1 | 28/28 (100) | 24/28 (86) |
| rTSH (N=32) | 44 | 26:7 | 30:3 | 32/32 (100) | 24/32 (75) |

^a 60 per protocol patients with interpretable scan data.

95% CI for difference in ablation rates, rTSH minus THW, = -6.9% to 27.1%.

^b Interpretation by 2 of 3 reviewers.

95% CI for difference in ablation rates, rTSH minus THW, = -30.5% to 9.1%.

Abbreviations: fol = follicular, pap = papillary, THW = thyroid hormone withdrawal

The mean radiation dose to blood was 0.266±0.061 mGy/MBq in the Euthyroid group and 0.395±0.135 mGy/MBq in the Hypothyroid group (P<0.0001). Radioiodine residence time in remnant tissue was 0.9±1.3 hours in the Euthyroid group and 1.4±1.5 hours in the Hypothyroid group. It is not known whether this difference in radiation exposure would convey a clinical benefit.

A follow-up study was conducted on patients who previously completed the initial study. The main objective of the follow-up study was to confirm the status of thyroid remnant ablation by using Thyrogen-stimulated radioiodine static neck imaging after a median follow-up of 3.7 years (range 3.4 to 4.4 years) following radioiodine ablation. Thyroglobulin testing was also performed.

Sixty-one male and female thyroidectomized patients who participated in the original study (Table 2) were planned for inclusion in this follow-up study. Fifty-one patients were enrolled in this study; 48 received Thyrogen for remnant neck/whole body imaging and/or Tg testing (three patients underwent the collection of medical history portion of the study but did not undergo stimulated neck/WB scanning or testing). Patients were still considered to be successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1% (Table 3).

Table 3: Summary of Thyroid Remnant Ablation During the 3.7-Year Follow-Up of Patients Treated in the Initial Study

| Uptake in Thyroid Bed | Former THW ^a Group (n=18) N (%) | Former rTSH Group (n=25) N (%) |
|---------------------------------------------------|-----------------------------------------------|-----------------------------------|
| No Visible Uptake in Thyroid Bed or Uptake < 0.1% | 18 (100) | 25 (100) |

^a THW = Thyroid Hormone Withdrawal

Of note, 9 patients (distributed similarly in both treatment groups: 5 former Hypothyroid and 4 former Euthyroid patients) received ¹³¹I (approximately 100 mCi (3.7 GBq) or more) during the period between the end of the initial study and the initiation of this follow-up study. When considering only the patients who did not receive radioiodine during the period between studies, 100% of patients in both treatment subgroups (15 former Hypothyroid and 22 former Euthyroid patients) were successfully ablated according to the predefined study criteria.

Successful ablation also can be inferred when the Thyrogen-stimulated serum Tg level is < 2 ng/mL, although a lower Tg level might also be used as a criterion by some experts. The presence of antithyroglobulin antibodies can render results of thyroglobulin assays uninterpretable. A total of 17 patients in the former Hypothyroid group and 20 patients in the former Euthyroid group had antithyroglobulin antibody levels <5 units/mL. Of these patients, 16/17 (94%) of patients in the former Hypothyroid group and 19/20 (95%) of patients in the former Euthyroid group had stimulated serum thyroglobulin levels of <2 ng/mL.

No patient had a definitive cancer recurrence during the 3.7 years of follow-up. Overall, 48/51 patients (94%) had no evidence of cancer recurrence, 1 patient had possible cancer recurrence (although it was not clear whether this patient had a true recurrence or persistent tumor from the regional disease noted at the start of the initial study), and 2 patients could not be assessed.

In summary, in this study and its follow-up study, Thyrogen was noninferior to thyroid hormone withholding for elevation of TSH levels as adjunctive therapy to radioiodine for post-surgical ablation of remnant thyroid tissue.

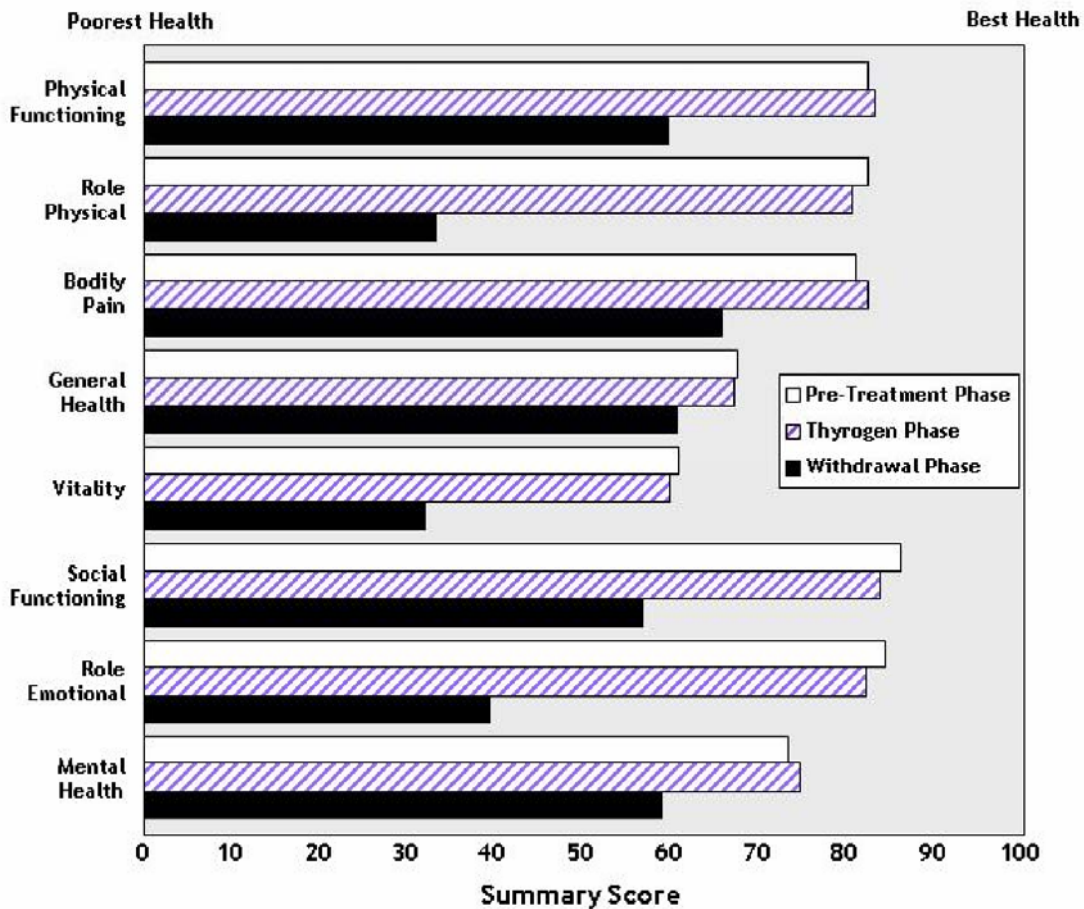
Several publications describe studies or series of patients in which Thyrogen was used as an adjunct to radioiodine for the ablation of thyroid remnant tissue. Some publications¹⁻⁴ found comparable rates of remnant ablation whether patients were prepared using hypothyroidism or Thyrogen, whereas another publication⁵ found that hypothyroidism had a better rate of success than Thyrogen, although in that study the radioiodine was administered 48 hours rather than 24 hours after the second dose of Thyrogen. Follow-up for 2.5 years of patients undergoing ablation at Memorial Sloan-Kettering has shown that use of Thyrogen results in a low rate of tumor recurrence that is comparable to the rate

seen after use of withdrawal from thyroxine.⁶

Quality of Life:

Quality of Life (QOL) was measured during both the diagnostic study and the ablation of thyroid remnant study, using the SF-36 Health Survey, a standardized, patient-administered instrument assessing QOL across eight domains measuring both physical and mental functioning. In the diagnostic study and in the remnant ablation study, following Thyrogen administration, little change from baseline was observed in any of the eight QOL domains of the SF-36. Following thyroid hormone withdrawal in the diagnostic study, 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 (Figure 1). In the remnant ablation study, following thyroid hormone withdrawal, statistically significant negative changes were noted in five of the eight QOL domains (physical functioning, role physical, vitality, social functioning and mental health). The difference between treatment groups was statistically significant ($p < 0.05$), favoring Thyrogen over thyroid hormone withdrawal.

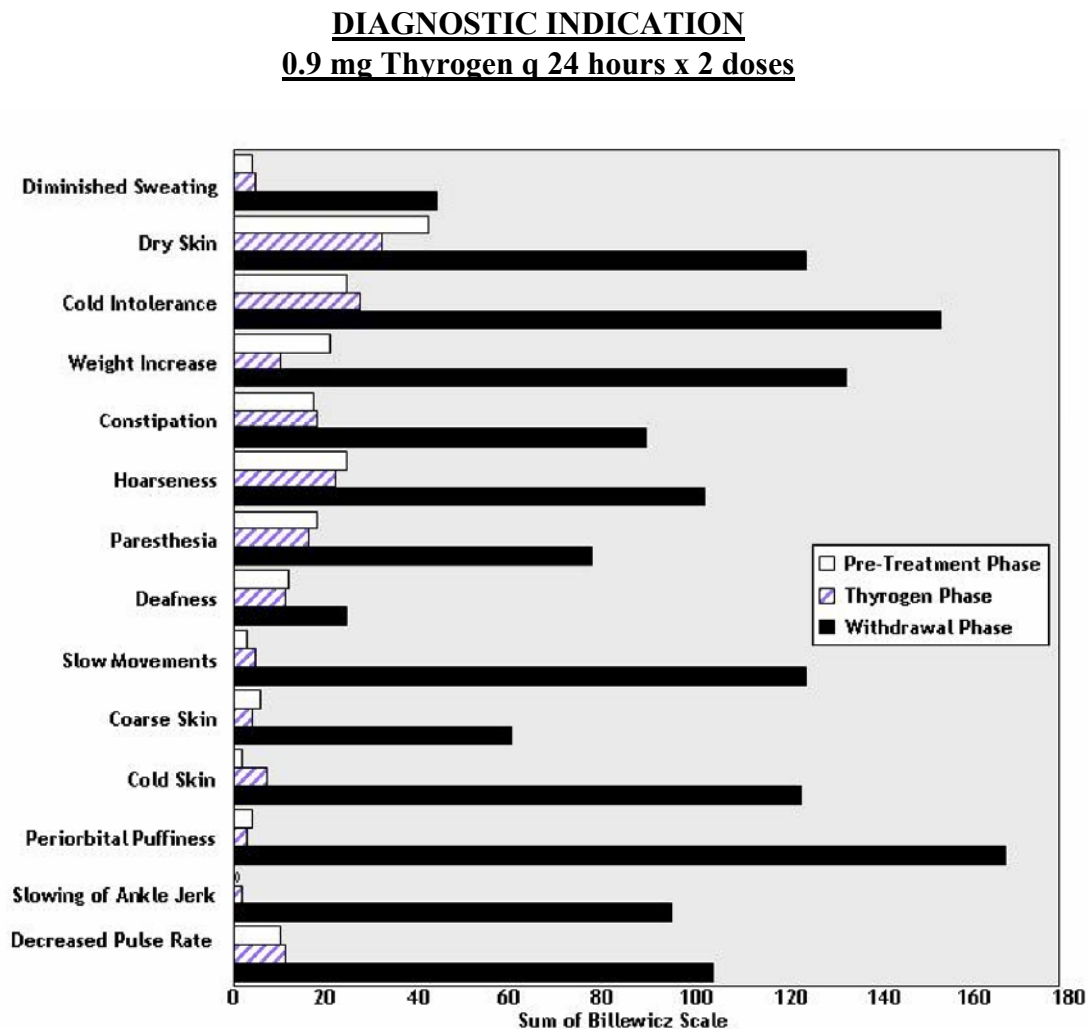
FIGURE 1 – SF-36 HEALTH SURVEY RESULTS
QUALITY OF LIFE DOMAINS
DIAGNOSTIC INDICATION



Hypothyroid Signs and Symptoms - Diagnostic Indication:

Thyrogen administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal as measured by the Billewicz scale. Statistically significant worsening in all signs and symptoms were observed during the hypothyroid phase ($p < 0.01$) (Figure 2).

FIGURE 2 – HYPOTHYROID SYMPTOM ASSESSMENT BILLEWICZ SCALE



INDICATIONS AND USAGE

Thyrogen (thyrotropin alfa for injection) is indicated for use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer.

Thyrogen (thyrotropin alfa for injection) is indicated for use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of metastatic thyroid cancer.

Potential Clinical Uses:

1. Thyrogen Tg testing may be used in patients with an undetectable Tg on thyroid hormone suppressive therapy to exclude the diagnosis of residual or recurrent thyroid

cancer (see CLINICAL PHARMACOLOGY, Clinical Trials, Thyroglobulin (Tg) Results).

2. Thyrogen treatment may be used in combination with radioiodine (^{131}I) to ablate thyroid remnants following near-total thyroidectomy in patients without evidence of metastatic disease.
3. Thyrogen testing may be used in patients requiring serum Tg testing and radioiodine imaging who are unwilling to undergo thyroid hormone withdrawal testing and whose treating physician believes that use of a less sensitive test is justified.
4. Thyrogen treatment and testing may be used in patients who are either unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is medically contraindicated.

Considerations in the Use of Thyrogen:

1. **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. Therefore, thyroid hormone withdrawal Tg testing with radioiodine imaging remains the standard diagnostic modality to assess the presence, location and extent of thyroid cancer.**
2. Although Thyrogen appeared noninferior to thyroid hormone withholding in a study of postsurgical thyroid remnant ablation, long-term clinical outcome data are limited. Due to the relatively small clinical experience with Thyrogen in remnant ablation, it is not possible to conclude whether long-term thyroid cancer outcomes would be equivalent after use of Thyrogen or use of thyroid hormone withholding for TSH elevation prior to remnant ablation.
3. Clinicians employ a wide range of ^{131}I activities to achieve remnant ablation in patients who have been prepared by withholding of thyroid hormone. The primary study of Thyrogen for remnant ablation employed $100 \text{ mCi} \pm 10\%$ in all patients. Data are inadequate to determine if a lower dose of radioiodine would be effective when Thyrogen is used as an adjunct to radioiodine in postsurgical thyroid remnant ablation.
4. Thyrogen Tg levels are generally lower than, and do not correlate with Tg levels after thyroid hormone withdrawal (see CLINICAL PHARMACOLOGY, Thyroglobulin (Tg) Results).
5. 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. On the other hand, none of the 31 patients studied with undetectable Thyrogen Tg levels (< 2.5 ng/mL) had metastatic disease. Therefore, an undetectable Thyrogen Tg level suggests the absence of clinically significant disease (see CLINICAL PHARMACOLOGY, Clinical Trials).

6. 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 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 CLINICAL PHARMACOLOGY, Clinical Trials).
7. The signs and symptoms of hypothyroidism which accompany thyroid hormone withdrawal are avoided with Thyrogen (see CLINICAL PHARMACOLOGY, Clinical Trials, Quality of Life, Hypothyroid Signs and Symptoms).

PRECAUTIONS

(see INDICATIONS AND USAGE, Considerations in the Use of Thyrogen)

General

The use of Thyrogen (thyrotropin alfa for injection) should be directed by physicians knowledgeable in the management of patients with thyroid cancer.

There have been reports of deaths in which events leading to death occurred within 24 hours after administration of Thyrogen. A 77 year-old non-thyroidectomized patient with a history of heart disease and spinal metastases who received 4 Thyrogen injections over 6 days in a special treatment protocol experienced a fatal MI 24 hours after he received the last Thyrogen injection. The event was likely related to Thyrogen-induced hyperthyroidism. In post-marketing experience, there have been rare reports of events leading to death that occurred within 24 hours of administration of Thyrogen in patients with multiple serious medical problems. For patients for whom Thyrogen-induced hyperthyroidism could have serious consequences, hospitalization for administration of Thyrogen and post-administration observation should be considered. Such patients might include those with known heart disease, extensive metastatic disease, or other known serious underlying illness.

Thyroglobulin (Tg) antibodies may confound the Tg assay and render 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.

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

TSH antibodies have not been reported in patients treated with Thyrogen in the clinical trials, although only 27 patients received Thyrogen on more than one occasion.

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 when given to patients who have substantial thyroid tissue still *in situ*. Therefore, caution should be exercised in patients with a known history of heart disease and with significant residual thyroid tissue (see ADVERSE REACTIONS).

It is recommended that pretreatment with glucocorticoids be considered for patients in whom local tumor expansion may compromise vital anatomic structures (such as trachea, central nervous system, or extensive macroscopic lung metastases) (see ADVERSE REACTIONS).

Careful evaluation of benefit risk relationships should be assessed for high risk elderly patients with functioning thyroid tumors undergoing Thyrogen administration. This may result in palpitations or cardiac rhythm disorder (see ADVERSE REACTIONS).

Elimination of Thyrogen is significantly slower in dialysis-dependent end stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels (see ADVERSE REACTIONS).

Drug-Drug 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 (T₃) and thyroxine (T₄) when administered concurrently.

The use of Thyrogen allows for radioiodine imaging while patients are euthyroid on triiodothyronine (T₃) and/or thyroxine (T₄). Data on radioiodine ¹³¹I kinetics indicate that the clearance of radioiodine is approximately 50% greater in euthyroid patients than in hypothyroid patients, who have decreased renal function. Thus radioiodine retention is less in euthyroid patients at the time of imaging and this factor should be considered

when selecting the activity of radioiodine for use in radioiodine imaging.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed with Thyrogen to evaluate the carcinogenic potential of the drug. Thyrogen was not mutagenic in the bacterial reverse mutation assay. Studies have not been performed with Thyrogen to evaluate the effects on fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with Thyrogen.

It is also not known whether Thyrogen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thyrogen should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Thyrogen is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Geriatric Use

Results from controlled trials indicate no difference in the safety and efficacy of Thyrogen between adult patients less than 65 years and those greater than 65 years of age.

ADVERSE REACTIONS

Adverse reaction data were derived from post-marketing surveillance and clinical trials. The percentages in Table 4 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 events (>5%) reported in clinical trials were nausea (11.9%) and headache (7.3%). Events reported in $\geq 1\%$ of patients in the combined trials are summarized in Table 4. In some studies, an individual patient may have participated in both the Euthyroid Phase (Thyrogen) and Hypothyroid Phase (withdrawal).

Table 4: Summary of Adverse Events by Euthyroid Phase and Hypothyroid Phase in All Clinical Trials ($\geq 1\%$)

| Preferred Term | Euthyroid Phase 481 Patients n (%) | Hypothyroid Phase 418 Patients n (%) |
|----------------------------|------------------------------------------|--------------------------------------------|
| Nausea | 57 (11.9) | 13 (3.1) |
| Headache | 35 (7.3) | 5 (1.2) |
| Fatigue | 16 (3.3) | 4 (1.0) |
| Hypercholesterolemia | 0 (0.0) | 13 (3.1) |
| Vomiting | 14 (2.9) | 3 (0.7) |
| Dizziness | 12 (2.5) | 0 (0.0) |
| Paraesthesia | 8 (1.7) | 0 (0.0) |
| Asthenia | 7 (1.5) | 0 (0.0) |
| Insomnia | 7 (1.5) | 0 (0.0) |
| Blood Cholesterol Abnormal | 0 (0.0) | 6 (1.4) |
| Diarrhea | 6 (1.2) | 0 (0.0) |
| Nasopharyngitis | 5 (1.0) | 0 (0.0) |
| Thyroglobulin Present | 5 (1.0) | 0 (0.0) |

Post-marketing experience indicates that Thyrogen administration may cause transient (<48 hours) influenza-like symptoms [also called flu-like symptoms (FLS)], which may include fever (>100°F/38°C), chills/shivering, myalgia/arthralgia, fatigue/asthenia/malaise, headache (non-focal), and chills.

Very rare manifestations of hypersensitivity to Thyrogen have been reported in clinical trials, post-marketing settings and in a special treatment program involving patients with advanced disease: these are urticaria, rash, pruritus, flushing, and respiratory signs and symptoms.

In clinical trials no patients have developed antibodies to thyrotropin alfa, either after single or repeated (27 patients) use of the product.

Four patients out of 55 (7.3%) with CNS metastases who were followed in a special

treatment protocol experienced acute hemiplegia, hemiparesis or pain one to three days after Thyrogen administration. The symptoms were attributed to local edema and/or focal hemorrhage at the site of the cerebral or spinal cord metastases. In addition, one case each of acute visual loss and of laryngeal edema with respiratory distress, requiring tracheotomy, with onset of symptoms within 24 hours after Thyrogen administration, have been reported in patients with metastases to the optic nerve and paratracheal areas, respectively. In addition, sudden, rapid and painful enlargement of locally recurring papillary carcinoma has been reported within 12-48 hours of Thyrogen administration. The enlargement was accompanied by dyspnea, stridor or dysphonia. Rapid clinical improvement occurred following glucocorticoid therapy. It is recommended that pretreatment with glucocorticoids be considered for patients in whom local tumor expansion may compromise vital anatomic structures.

There have been reports of deaths in which events leading to death occurred within 24 hours after administration of Thyrogen. A 77 year-old non-thyroidectomized patient with a history of heart disease and spinal metastases who received 4 Thyrogen injections over 6 days in a special treatment protocol experienced a fatal MI 24 hours after he received the last Thyrogen injection. The event was likely related to Thyrogen-induced hyperthyroidism. In post-marketing experience, there have been rare reports of events leading to death that occurred within 24 hours of administration of Thyrogen in patients with multiple serious medical problems. For patients for whom Thyrogen-induced hyperthyroidism could have serious consequences, hospitalization for administration of Thyrogen and post-administration observation should be considered. Such patients might include those with known heart disease, extensive metastatic disease, or other known serious underlying illness.

Information from post-marketing surveillance, as well as from the literature, suggests 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 several days after treatment, which may lead to increased risk of headache and nausea.

Post-marketing data include cases of atrial arrhythmias in elderly patients with pre-existing cardiac disease who received Thyrogen, and suggest that use of Thyrogen in this group should be considered carefully.

OVERDOSAGE

There has been no reported experience of overdose in humans. However, in clinical trials, three patients experienced symptoms after receiving Thyrogen doses higher 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 flashes 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).

DOSAGE AND 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, a 1.0 mL solution (0.9 mg thyrotropin alfa) is administered by intramuscular injection to the buttock.

For radioiodine imaging or remnant ablation, radioiodine administration should be given 24 hours following the final Thyrogen injection. Diagnostic scanning should be performed 48 hours after radioiodine administration, whereas post-therapy scanning may be delayed additional days to allow background activity to decline.

The following parameters utilized in the second Phase 3 study are recommended for diagnostic radioiodine scanning with Thyrogen:

- A diagnostic activity of 4 mCi (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, 35,000 counts for a small field of view).

For radioiodine ablation of thyroid tissue remnants, the activity of ^{131}I is carefully selected at the discretion of the nuclear medicine physician. Studies with Thyrogen were conducted using $100 \text{ mCi} \pm 10\%$ of ^{131}I . Data are inadequate to determine if a lower dose of radioiodine would be effective when Thyrogen is used as an adjunct to radioiodine in postsurgical thyroid remnant ablation.

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

INSTRUCTIONS FOR USE

Thyrogen (thyrotropin alfa for injection) is for intramuscular injection to the buttock. The powder should be reconstituted immediately prior to use with 1.2 mL of Sterile Water for Injection, USP. Each vial of Thyrogen and each vial of diluent, if provided, is intended for single use. Discard unused portion of the diluent.

Thyrogen should be stored at 2-8°C (36-46°F). Each vial, after reconstitution with 1.2 mL of the accompanying Sterile Water for Injection, USP, should be inspected visually for particulate matter or discoloration before use. Any vials exhibiting particulate matter or discoloration should not be used.

If necessary, the reconstituted solution can be stored for up to 24 hours at a temperature between 2°C and 8°C, while avoiding microbial contamination.

DO NOT USE Thyrogen after the expiration date on the vial. Protect from light.

HOW SUPPLIED

Thyrogen (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available either in a two-vial kit or a four-vial kit. The two-vial kit contains two 1.1 mg vials of Thyrogen (thyrotropin alfa for injection). The four-vial kit contains two 1.1 mg vials of Thyrogen, as well as two 10 mL vials of Sterile Water for Injection, USP.

NDC 58468-1849-4 (4-vial kit)

NDC 58468-0030-2 (2-vial kit)

Store at 2-8°C.

Rx ONLY

Thyrogen[®] (thyrotropin alfa for injection)

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
(800) 745-4447

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