**Thyrogen** is indicated for use as an adjunctive treatment for radioiodine ablation of thyroid tissue who have previously undergone thyroidectomy. (1.1)

**Limitations of Use**:
- **Diagnostic**: Use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radiiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy. (1.1)
- **Ablation**: 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 distant metastatic thyroid cancer. (1.2)
- **Thyrogen Administration**: The effect of **Thyrogen** on long-term thyroid cancer outcomes has not been determined. 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.

**Dosage and Administration**:
- **Thyrogen** should be used by physicians knowledgeable in the management of patients with thyroid cancer. (2.1)

**Indications and Usage**
- **Thyrogen** is a thyroid stimulating hormone indicated for: **Ablation**: Use as an adjunctive treatment for radioiodine ablation of thyroid tissue remnants in patients who have previously undergone thyroidectomy. (1.1)
- **Diagnostic**: Use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radiiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy. (1.1)

**Warnings and Precautions**
- **Risk of Thyrogen-induced Hyperthyroidism**: Hospitalization for administration of **Thyrogen** and post-administration observation should be considered for patients at risk. (5.1)
- **Stroke**: In female patients as well as other neurologic events in patients with central nervous system metastases. (5.2) (5.3)
- **Sudden, rapid and painful enlargement in distant metastatic thyroid cancer**: (5.3)

**Adverse Reactions**
- The most common adverse reactions reported in clinical trials were nausea and headache. (6.1)

**Use in Specific Populations**
- **Renal Impairment**: Elimination of **Thyrogen** is significantly slower in dialysis-dependent end stage renal disease patients, resulting in prolonged elevation of TSH levels. (8.6)

See 17 for Patient Counseling Information

**Full Prescribing Information**

1. **Indications and Usage**
   - 1.1 **Adjunctive Diagnostic Tool for Serum Thyroglobulin Testing in Well Differentiated Thyroid Cancer**
   - 1.2 **Adjunct to Treatment for Ablation in Well Differentiated Thyroid Cancer**

2. **Dosage and Administration**
   - 2.1 **Recommended Dosage**
   - 2.2 **Reconstitution, Preparation, and Administration of Thyrogen**
   - 2.3 **Timing of Serum Thyroglobulin Testing Following Thyrogen Administration**
   - 2.4 **Timing for Remnant Ablation and Diagnostic Scanning Following Thyrogen Administration**

3. **Dosage Forms and Strengths**

4. **Contraindications**

5. **Warnings and Precautions**
   - 5.1 **Thyrogen-induced Hyperthyroidism**
   - 5.2 **Stroke**
   - 5.3 **Sudden Rapid Tumor Enlargement**

6. **Adverse Reactions**
   - 6.1 **Clinical Trials Experience**
   - 6.2 **Postmarketing Experience**

8. **Use in Specific Populations**
   - 8.1 **Pregnancy**
   - 8.3 **Nursing Mothers**
   - 8.4 **Pediatric Use**
   - 8.5 **Geriatric Use**
   - 8.6 **Renal Impairment**

10. **Overdosage**

11. **Description**

12. **Clinical Pharmacology**
   - 12.1 **Mechanism of Action**
   - 12.3 **Pharmacokinetics**

13. **Nonclinical Toxicology**
   - 13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
   - 13.2 **Animal Pharmacology and/or Toxicology**

14. **Clinical Studies**
   - 14.1 **Clinical Trials of Thyrogen as an Adjunctive Diagnostic Tool**
   - 14.2 **Clinical Trials of Thyrogen as an Adjunct to Radiiodine Therapy to Achieve Thyroid Remnant Ablation**
   - 14.3 **Quality of Life**

16. **How Supplied/Storage and Handling**

17. **Patient Counseling Information**

The supplied lyophilized powder must be reconstituted with Sterile Water for Injection. **Thyrogen** should be prepared, and administered in the following manner:

- Add 1.2 mL of sterile Water for Injection to the vial containing the **Thyrogen** lyophilized powder.
- Swirl the contents of the vial until all the material is dissolved. Do not shake the solution. The reconstituted **Thyrogen** solution has a concentration of 0.9 mg of thyrotropin alfa per mL.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. The reconstituted **Thyrogen** solution should be clear and colorless. Do not use if the solution has particulate matter or is cloudy or discolored.
- Withdraw 1 mL of the reconstituted **Thyrogen** solution (0.9 mg of thyrotropin alfa) and inject intramuscularly in the buttocks.

**Full Prescribing Information - Contents**

1. **Indications and Usage**
   - 1.1 **Adjunctive Diagnostic Tool for Serum Thyroglobulin Testing in Well Differentiated Thyroid Cancer**
   - 1.2 **Adjunct to Treatment for Ablation in Well Differentiated Thyroid Cancer**

2. **Dosage and Administration**
   - 2.1 **Recommended Dosage**
   - 2.2 **Reconstitution, Preparation, and Administration of Thyrogen**
   - 2.3 **Timing of Serum Thyroglobulin Testing Following Thyrogen Administration**
   - 2.4 **Timing for Remnant Ablation and Diagnostic Scanning Following Thyrogen Administration**

3. **Dosage Forms and Strengths**

4. **Contraindications**

5. **Warnings and Precautions**
   - 5.1 **Thyrogen-induced Hyperthyroidism**
   - 5.2 **Stroke**
   - 5.3 **Sudden Rapid Tumor Enlargement**

6. **Adverse Reactions**
   - 6.1 **Clinical Trials Experience**
   - 6.2 **Postmarketing Experience**

8. **Use in Specific Populations**
   - 8.1 **Pregnancy**
   - 8.3 **Nursing Mothers**
   - 8.4 **Pediatric Use**
   - 8.5 **Geriatric Use**
   - 8.6 **Renal Impairment**

10. **Overdosage**

11. **Description**

12. **Clinical Pharmacology**
   - 12.1 **Mechanism of Action**
   - 12.3 **Pharmacokinetics**

13. **Nonclinical Toxicology**
   - 13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
   - 13.2 **Animal Pharmacology and/or Toxicology**

14. **Clinical Studies**
   - 14.1 **Clinical Trials of Thyrogen as an Adjunctive Diagnostic Tool**
   - 14.2 **Clinical Trials of Thyrogen as an Adjunct to Radiiodine Therapy to Achieve Thyroid Remnant Ablation**
   - 14.3 **Quality of Life**

16. **How Supplied/Storage and Handling**

17. **Patient Counseling Information**

“Sections or subsections omitted from the full prescribing information are not listed.”

**Dosage and Administration**

- **Recommended Dosage**
  - **Thyrogen** should be used by physicians knowledgeable in the management of patients with thyroid cancer.
  - **Thyrogen** is indicated as a two-injection regimen. The recommended dosage of **Thyrogen** is a 0.9 mg intramuscular injection to the buttock followed by a second 0.9 mg intramuscular injection 24 hours later. (2.1)

**Dose Forms and Strengths**

- **Thyrogen** is a thyroid stimulating hormone indicated for single use after reconstitution with Sterile Water for Injection. (3)

**Contraindications**

- None

**Warnings and Precautions**

- **Risk of Thyrogen-induced Hyperthyroidism**: Hospitalization for administration of **Thyrogen** and post-administrative observation should be considered for patients at risk. (5.1)
- **Stroke**: In female patients as well as other neurologic events in patients with central nervous system metastases. (5.2) (5.3)
- **Sudden, rapid and painful enlargement in distant metastatic thyroid cancer**: (5.3)

**Adverse Reactions**

- The most common adverse reactions reported in clinical trials were nausea and headache. (6.1)

**Use in Specific Populations**

- **Renal Impairment**: Elimination of **Thyrogen** is significantly slower in dialysis-dependent end stage renal disease patients, resulting in prolonged elevation of TSH levels. (8.6)

**See 17 for Patient Counseling Information**

Revised: 04/2017
• The reconstituted THYROGEN solution must be injected within 3 hours unless refrigerated; if refrigerated, the reconstituted solution may be kept for up to 24 hours.
• Discard unused portions. Do not mix with other substances.

2.3 Timing of Serum Thyroglobulin Testing Following THYROGEN Administration
When given to patients who have substantial thyroid tissue still in situ or functional thyroid cancer metastases, THYROGEN is known to cause a transient (over 7 to 14 days) but significant rise in serum thyroid hormone concentration. There have been reports of death in non-thyrotoxicemic patients and in patients with distant metastatic thyroid cancer in which events leading to death occurred within 24 hours after administration of THYROGEN. Patients with residual thyroid tissue at risk for THYROGEN-induced hyperthyroidism include the elderly and those with a known history of heart disease. Hospitalization for administration of THYROGEN and post-administration observation in patients at risk should be considered.

2.4 Timing for Remnant Ablation and Diagnostic Scanning Following THYROGEN Administration
Oral radioiodine should be given 24 hours after the second injection of THYROGEN in both remnant ablation and diagnostic scanning. The activity of 131I is carefully selected at the discretion of the nuclear medicine physician. Diagnostic scanning should be performed 48 hours after the radiiodine administration.

3 DOSE FORMS AND STRENGTHS
THYROGEN is a lyophilized powder containing 1.1 mg of thyrotropin alfa for single use after reconstitution with Sterile Water for Injection.

Supplied as:
Two vial kit (two vials of lyophilized thyrotropin alfa)

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 THYROGEN-Induced Hyperthyroidism
When given to patients who have substantial thyroid tissue still in situ or functional thyroid cancer metastases, THYROGEN is known to cause a transient (over 7 to 14 days) but significant rise in serum thyroid hormone concentration. There have been reports of death in non-thyrotoxicemic patients and in patients with distant metastatic thyroid cancer in which events leading to death occurred within 24 hours after administration of THYROGEN. Patients with residual thyroid tissue at risk for THYROGEN-induced hyperthyroidism include the elderly and those with a known history of heart disease. Hospitalization for administration of THYROGEN and post-administration observation in patients at risk should be considered.

5.2 Stroke
There are postmarketing reports of radiologically-confirmed stroke and neurological findings suggestive of stroke unconfirmed radiologically (e.g., unilateral weakness) occurring within 72 hours (range 20 minutes to three days) of THYROGEN administration in patients without known central nervous system metastases. The majority of such patients were young women taking oral contraceptives at the time of their event or had other risk factors for stroke, such as smoking or a history of migraine headaches. The relationship between THYROGEN administration and stroke is unknown. Patients should be well-hydrated prior to treatment with THYROGEN.

5.3 Sudden Rapid Tumor Enlargement
Sudden, rapid and painless enlargement of residual thyroid tissue or distant metastases can occur following treatment with THYROGEN. This may lead to acute symptoms, which depend on the anatomical location of the tissue. Such symptoms include acute hemiplegia, hemiparesis, and loss of vision one to three days after THYROGEN administration. Laryngeal edema, pain at the site of distant metastasis, and respiratory distress requiring tracheotomy have also been reported after THYROGEN administration.

Pretreatment with glucocorticoids should be considered for patients in whom tumor expansion may compromise vital anatomical structures.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to THYROGEN in 481 thyroid cancer patients who participated in 248 patients (10 TR) clinical trials. Four trials for diagnostic use and 2 trials for ablation. In clinical trials, patients had undergone near-total thyroidectomy and had a mean age of 46.8 years. Thyroid cancer diagnosis was as follows: papillary (69.2%), follicular (12.9%), Hurthle cell (2.3%) and papillary/follicular (15.6%). Most patients received 2 intramuscular injections of 0.9 mg of THYROGEN 24 hours apart (see Clinical Studies (14.1) (14.2)).

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

Reactions reported in 2-11% of patients in the combined trials are summarized in Table 1. In some studies, an individual patient may have participated in both THYROGEN and thyroid hormone withdrawal [see Clinical Studies (14.1) (14.2)].

Table 1: Summary of Adverse Reactions by THYROGEN and Thyroid Hormone Withdrawal in Pooled Clinical Trials (≥1% of Patients in Any Phase)

<table>
<thead>
<tr>
<th></th>
<th>THYROGEN (N=481)</th>
<th>Thyroid Hormone Withdrawal (N=481)</th>
<th>Preferred Term</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>53 (11)</td>
<td>2 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20 (6)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (2)</td>
<td>2 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (2)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (1)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of THYROGEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Transient (<48 hours) influenza-like symptoms, including fever (<100°F/38°C), chills/shivering, myalgia/arthritis, fatigue/asthenia/malaise, headache, and chills.
• Hypersensitivity including urticaria, rash, pruritus, flushing, and respiratory signs and symptoms.

6 USE IN SPECIFIC POPULATIONS
6.1 Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with THYROGEN.

It is not known whether THYROGEN causes 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.

6.2 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.

6.3 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

6.4 Geriatric Use
In pooled clinical studies of THYROGEN, 60 patients (12%) were 65 years, and 421 (88%) were ≥ 65 years of age. Results from controlled trials do not indicate a difference in the safety and efficacy of THYROGEN between adult patients less than 65 years and those over 65 years of age [see Warnings and Precautions (5.1)].

6.5 Renal Impairment
Elimination of THYROGEN is significantly slower in dialysis-dependent end stage renal disease (ESRD) patients, resulting in prolonged elevation of TSH levels.

6.6 Description
The most common adverse reaction associated with THYROGEN is transient nausea. When THYROGEN is given intravenously, side effects include hypertension, flushing, injection site reactions, including pain, erythema, bruising, and pruritus.

11 DESCRIPTION
The injection strength of THYROGEN contains 1.1 mg thyrotropin alfa, 36 mg Mannitol, 5.1 mg Sodium Phosphate, and 2.4 mg Sodium Chloride.

THYROGEN (thyrotropin alfa for injection) contains recombinant human thyroid stimulating hormone (TSH). THYROGEN is synthesized in a genetically modified Chinese hamster ovary cell line. THYROGEN contains 1.1 mg thyrotropin alfa. 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 TSH.

6.7 Precautions
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 CLINICAL PHARMACOLOGY
7.1 Mechanism of Action
THYROGEN (TSH) is a pituitary hormone that stimulates the thyroid gland to produce thyroid hormone. 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 thyroid hormones.

Clinical Studies (14.1) (14.2).

The effect of thyroid stimulating hormone activation of thyroid cells is to increase uptake of radioiodine to allow scan detection or radioiodine killing of thyroid cells. TSH activation also leads to the release of thyroglobulin by thyroid cells. Thyroglobulin functions as a tumor marker which is detected in blood specimens.

7.2 Pharmacokinetics
The pharmacokinetics of THYROGEN were studied in 16 patients with well-differentiated thyroid cancer to compare 131I uptake in patients who received THYROGEN. The majority of patients were young women taking oral contraceptives at the time of their event or had other risk factors for stroke, such as smoking or a history of migraine headaches. The relationship between THYROGEN administration and stroke is unknown. Patients should be well-hydrated prior to treatment with THYROGEN.

The pharmacokinetics of THYROGEN were studied in 16 patients with well-differentiated thyroid cancer to compare 131I uptake in patients who received THYROGEN. The majority of patients were young women taking oral contraceptives at the time of their event or had other risk factors for stroke, such as smoking or a history of migraine headaches. The relationship between THYROGEN administration and stroke is unknown. Patients should be well-hydrated prior to treatment with THYROGEN.
then scanned after thyroid hormone withdrawal. In both studies, the primary endpoint was the rate of concordant scans (scan findings in agreement in a given patient using each preparation method).

**Study 1** (n=127) compared the diagnostic scanning following a THYROGEN regimen of 0.9 mg IM daily on two consecutive days to thyroid hormone withdrawal. In addition to body scans, Study 2 (n=229) also compared thyroglobulin (Tg) levels obtained after THYROGEN to those at baseline 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. Patients who were included in the Tg analysis were those who had undergone total or near-total thyroidectomy with or without 131I ablation, had <1% uptake in the thyroid bed on a scan after thyroid hormone withdrawal, and did not have detectable anti-Tg antibodies. The maximum THYROGEN Tg value was obtained 72 hours after the final THYROGEN injection, and this value was used in the analysis.

### Diagnostic Radioiodine Whole Body Scan Results

Study 1 enrolled 127 patients, 71% were female and 29% male, and mean age was 44 years. The study included the following forms of differentiated thyroid cancer: papillary cancer (88%), follicular cancer (9%), and Hurthle cell (2%). Study results are displayed in Table 2.

In Study 2, patients with differentiated thyroid cancer who had been thyroidectomized (n = 229) were randomized into one of two THYROGEN treatment regimens: THYROGEN 0.9 mg IM daily on two consecutive days (n = 117), and THYROGEN 0.9 mg IM daily on days 1, 4, and 7 (n = 112). Each patient was scanned first using THYROGEN, then scanned using thyroid hormone withdrawal. The group receiving the THYROGEN 0.9 mg IM × 2 regimen was 63% female/27% male, had a mean age of 44 years, and generally had low-stage papillary or follicular cancer (AJCC/TNM Stage I/II, Stage II/III, Stage III/IV). The group receiving the THYROGEN 0.9 mg IM × 3 regimen was 86% female/14% male, had a mean age of 50 years, and generally had low-stage papillary or follicular cancer (AJCC/TNM Stage I, II, Stage III, IV, V). The amount of radioiodine used for scanning was 4 mCi ± 10%, and scanning times were lengthened in some patients to capture cancer (AJCC/TNM Stage I 50%, Stage II 20%, Stage III 20%, Stage IV 9%). The amount of radioiodine used for scanning was 4 mCi ± 10%, and scanning times were lengthened in some patients to capture cancer (AJCC/TNM Stage I 50%, Stage II 20%, Stage III 20%, Stage IV 9%). The maximum THYROGEN Tg value was obtained 72 hours after the final THYROGEN injection, and this value was used in the analysis.

### 14.2 Clinical Trials of THYROGEN as an Adjunct to Radioiodine Therapy to Achieve Thyroid Remnant Ablation

A randomized, prospective clinical trial compared the rates of thyroid remnant ablation achieved after preparation of patients with thyroid hormone withdrawal or THYROGEN. Patients (n = 63) with low-risk, well-differentiated thyroid cancer who underwent near-total thyroidectomy were made euthyroid after surgery by receiving thyroid hormone replacement and were subsequently randomized to a thyroid hormone withdrawal or THYROGEN. Patients in the THYROGEN group received THYROGEN 0.9 mg IM daily on 2 consecutive days and radioiodine 24 hours after the second dose of THYROGEN. Patients in the thyroid hormone withdrawal group had the thyroid replacement withheld until they became hypothyroid. Patients in both groups received 100 mCi 131I ± 10% with the intent to ablate any thyroid remnant tissue. The primary endpoint of the study was the rate of successful ablation, and 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 3 summarizes the results of this evaluation.

### Table 2: Concordance of Positive Thyroid Scans Following THYROGEN Treatment with Scans Following Thyroid Hormone Withdrawal

<table>
<thead>
<tr>
<th>Number of Scan Pairs by Disease Category</th>
<th>Concordance of scan pairs between THYROGEN scan and thyroid hormone withdrawal scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (0.9 mg IM qd ×2)</td>
<td></td>
</tr>
<tr>
<td>Positive for remnant or cancer in thyroid bed</td>
<td>48</td>
</tr>
<tr>
<td>Positive for metastatic disease</td>
<td>15</td>
</tr>
<tr>
<td>Total positive withdrawal scans</td>
<td>63</td>
</tr>
<tr>
<td>Study 2 (0.9 mg IM qd × 2)</td>
<td></td>
</tr>
<tr>
<td>Positive for remnant or cancer in thyroid bed</td>
<td>35</td>
</tr>
<tr>
<td>Positive for metastatic Disease</td>
<td>9</td>
</tr>
<tr>
<td>Total positive withdrawal scans</td>
<td>44</td>
</tr>
</tbody>
</table>

*Across both 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.

†The two clinical studies radionuclide scan results using thyroid hormone withdrawal were taken as the true clinical status of each patient and as the comparator for THYROGEN scans. Thyroid hormone withdrawal trace-positive scans were scored conservatively as positive with no allowance for false positives.

Across the two clinical studies, and scoring all false positives in favor of thyroid hormone withdrawal, the majority of positive scans using THYROGEN and thyroid hormone withdrawal were concordant. The THYROGEN scan failed to detect remnant and/or cancer localized to the thyroid bed in 17% (14/83) 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 29% (7/24) 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 anti-Tg antibody negative patients with a thyroid remnant or cancer (as defined by a withdrawal Tg ≥ 2.5 mg/mL or a positive scan [after thyroid hormone withdrawal or after radioiodine therapy]), the THYROGEN Tg was positive (≥ 2.5 mg/mL) in 69% (40/58) of patients after 2 doses of THYROGEN. In these same patients, adding the whole body scan increased the detection rate of thyroid remnant or cancer to 84% (48/58) of patients after 2 doses of THYROGEN.

Among patients with metastatic disease confirmed by a post-treatment scan or by lymph node biopsy (35 patients), THYROGEN Tg was positive (≥ 2.5 mg/mL) in all 35 patients, while Tg on thyroid hormone suppressive therapy was positive (≥ 2.5 mg/mL) in 79% of these patients.

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

### Hypothyroid Signs and Symptoms

THYROGEN administration was not associated with the signs and symptoms of hypothyroidism that accompanied thyroid hormone withdrawal as measured by the Billwicz scale. Statistically significant worsening in all signs and symptoms were observed during the hypothyroid phase (p<0.01) (Figure 1).

### Table 3: Remnant Ablation in Clinical Trial of Patients with Well-Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (Yr)</th>
<th>Gender (F:M)</th>
<th>Cancer Type (Pap:Fol)</th>
<th>Ablation Criterion (Measure at 8 Months)</th>
<th>Thyroid Bed Activity</th>
<th>No Visible Thyroid Bed Activity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>THYROGEN Withdrawal (N=28)</td>
<td>43</td>
<td>24:6</td>
<td>29:1</td>
<td>28/28 (100%)</td>
<td>&lt;0.1%</td>
<td>24/28 (86%)</td>
</tr>
<tr>
<td>THYROGEN (N=32)</td>
<td>44</td>
<td>26:7</td>
<td>30:3</td>
<td>32/32 (100%)</td>
<td>24/32 (75%)</td>
<td>†</td>
</tr>
</tbody>
</table>

Abbreviations: fol = follicular, pap = papillary

*60 per protocol patients with interpretable scan data.

†95% CI for difference in ablation rates THYROGEN minus Thyroid Hormone Withdrawal, = 7% to 27%.

Interpretation by 2 of 3 reviewers.

The mean radiation dose to blood was 0.26±0.061 mGy/MBq in the THYROGEN group and 0.39±0.135 mGy/MBq in the thyroid hormone withdrawal group. Radioiodine residence time in remnant tissue was 0.9±1.3 hours in the THYROGEN group and 1.4±1.5 hours in the thyroid hormone withdrawal group. It is not known whether this difference in radiation exposure would convey a clinical benefit.

Patients who completed were followed up for a median duration of 3.7 years (range 3.4 to 4.4 years) following radioiodine ablation. Tg testing was also performed. The main objective of the follow-up study was to evaluate the status of thyroid remnant ablation by using THYROGEN-stimulated neck imaging. Of the fifty-one patients enrolled, forty eight patients received THYROGEN for remnant neck/whole body imaging and/or thyroglobulin testing. Only 43 patients had imaging. 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%. 1% of patients had a definitive cancer recurrence during the 3.7 years of follow-up. Overall, 48 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.
Two large prospective multi-center randomized studies compared THYROGEN to thyroid hormone withdrawal using two different doses of radioactive iodine in patients with differentiated thyroid cancer who had been thyroidectomized. In both studies, patients were randomized to 1 of 4 treatment groups: THYROGEN + 30 mCi \( ^{131}I \), THYROGEN + 100 mCi \( ^{131}I \), thyroid hormone withdrawal + 30 mCi \( ^{131}I \), or thyroid hormone withdrawal + 100 mCi \( ^{131}I \). Patients were assessed for efficacy (ablation success rates) at approximately 8 months.

The first study (Study A) randomized 438 patients (tumor stages T1–T3, Nx, N0 and N1, M0). Ablation success was defined as radioiodine uptake of <0.1% in the thyroid bed and stimulated thyroglobulin levels of <1.0 ng/mL. It is available as a two-vial kit, containing 1.1 mg of THYROGEN.

The second study (Study B) randomized 752 patients with low-risk thyroid cancer (tumor stages pt1 < 1 cm and N1 or Nx, pt1 >1-2 cm and any N stage, or ptT2 N0, all patients M0). Ablation success was defined by neck ultrasound and stimulated thyroglobulin of <1.0 ng/mL. Results for both trials are summarized below.

### Table 4: Successful Remnant Ablation Rates in Study A

<table>
<thead>
<tr>
<th></th>
<th>THYROGEN</th>
<th>Thyroid Hormone Withdrawal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose radioiodine</td>
<td>91/108 (84.3%)</td>
<td>91/106 (85.8%)</td>
<td>182/214 (85.0%)</td>
</tr>
<tr>
<td>High-dose Radioiodine</td>
<td>92/102 (90.2%)</td>
<td>92/105 (87.6%)</td>
<td>184/207 (88.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>183/210 (87.1%)</td>
<td>183/211 (86.7%)</td>
<td>366/421 (86.9%)</td>
</tr>
</tbody>
</table>

95% CI of difference in ablation rate (low-dose minus high dose): -10.2% to 2.6%
95% CI of difference in ablation rate (THYROGEN - Thyroid Hormone Withdrawal): -6.0% to 6.8%

### Table 5: Successful Remnant Ablation Rates in Study B

<table>
<thead>
<tr>
<th></th>
<th>THYROGEN</th>
<th>Thyroid Hormone Withdrawal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose radioiodine</td>
<td>160/177 (90.4%)</td>
<td>156/170 (91.8%)</td>
<td>316/347 (91.1%)</td>
</tr>
<tr>
<td>High-dose Radioiodine</td>
<td>159/171 (93.0%)</td>
<td>156/166 (94.0%)</td>
<td>315/337 (93.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>319/348 (91.6%)</td>
<td>312/336 (92.9%)</td>
<td>631/684 (92.3%)</td>
</tr>
</tbody>
</table>

95% CI of difference in ablation rate (low-dose minus high dose): -5.8% to 0.3%
95% CI of difference in ablation rate (THYROGEN minus Thyroid Hormone Withdrawal): -4.5% to 2.2%

#### 14.3 Quality of Life

Quality of Life (QOL) was measured during both the diagnostic study (see Clinical Studies [14.1]) and the ablative study (see Clinical Studies [14.1]) 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 (physical functioning, role physical, vitality, social functioning and mental health).

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

THYROGEN (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available as a two-vial kit, containing 1.1 mg of THYROGEN.