HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use THYROGEN safely and effectively. See full prescribing information for THYROGEN.

THYROGEN® (thyrotropin alfa) for injection, for intramuscular use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

THYROGEN® is a thyroid stimulating hormone indicated for:

- Adjunctive Diagnostic Tool for Well-Differentiated Thyroid Cancer:
  Use as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy. (1.1)

Limitations of Use:

• THYROGEN-stimulated Tg levels are generally lower than, and do not correlate with, Tg levels after thyroid hormone withdrawal.
  - Even when THYROGEN-Tg testing is performed in combination with radiodine imaging, there remains a risk of missing a diagnosis of thyroid cancer or underestimating the extent of the disease.
  - Anti-Tg antibodies may confound the Tg assay and render Tg levels uninterpretable.

• Adjunct for Thyroid Remnant Ablation in Well-Differentiated Thyroid Cancer:
  Use as an adjunctive treatment for radiodine 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)

Limitations of Use:

• The effect of THYROGEN on thyroid cancer recurrence greater than 5 years post-remnant ablation has not been evaluated.

2 DOSAGE AND ADMINISTRATION

- THYROGEN should be used by physicians knowledgeable in the management of patients with thyroid cancer. (2.1)
  - A two-injection regimen is recommended: THYROGEN 0.9 mg is administered intramuscularly, followed by a second 0.9 mg intramuscular injection 24 hours later. (2.1)

2.1 Recommended Dosage

For injection: 0.9 mg of thyropinin alfa as a lyophilized powder in a single-dose vial. (3)

2.2 Reconstitution, Preparation, and Administration of THYROGEN

• Reconstitute each 0.9 mg vial of THYROGEN with 1.2 mL of Sterile Water for Injection, USP to yield a single-dose solution containing 0.9 mg/mL of thyrotropin alfa that delivers 1 mL (0.9 mg).

2.3 Timing of Serum Thyroglobulin Testing Following THYROGEN Administration

Limitations of Use:

• THYROGEN-induced hyperthyroidism: Hospitalization for administration of THYROGEN and postadministration observation should be considered for patients at risk. (5.1)
  - Stroke: Stroke in female patients as well as other neurologic events in patients with central nervous system metastases. (5.2, 5.3)
  - Sudden rapid tumor enlargement: Sudden, rapid and painful enlargement in distant metastatic thyroid cancer. (5.3)
  - Risks associated with radioiodine (RAI) combination treatment: If THYROGEN is administered with RAI, the warnings and precautions for RAI also apply to this combination regimen. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (>5%) reported in clinical trials were nausea and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USING SPECIFIC POPULATIONS

• Pregnancy: Concomitant use of THYROGEN and radioiodine (RAI) is contraindicated in pregnancy. (4, 8.1)
  - Lactation: Concomitant use of THYROGEN and therapeutic RAI is contraindicated in lactating women. (4, 8.2)
  - 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: 02/2023
For serum thyroglobulin testing, the serum sample should be obtained 72 hours after the final injection of THYROGEN.

2.3 Timing of Serum Thyroglobulin Testing Following THYROGEN Administration

Oral radiodiode should be given 24 hours after the second injection of THYROGEN in both remnant ablation and diagnostic scanning. The activity of 111I is carefully selected at the discretion of the nuclear medicine physician.

Diagnostic scanning should be performed 48 hours after the radiodiode administration.

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.9 mg per 10-ml vial of THYROGEN.

4 CONTRAINDICATIONS

If THYROGEN is administered with radioiodine, the contraindications to radioiodine also apply to this combination regimen. Refer to the radiodiode prescribing information for a list of contraindications for radioiodine.

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-thyroidectomized 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 postadministration 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 the 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 Ruptured Tumor Enlargement

Sudden, rapid and painful 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. Premtreatment with glucocorticoids should be considered for patients in whom tumor expansion may compromise vital anatomic structures.

5.4 Risks Associated with Radiodiode Treatment

If THYROGEN is administered with radioiodine (RAI), the warnings and precautions for RAI apply to this combination regimen. Refer to the RAI prescribing information for a full list of the warnings and precautions for RAI.

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 a total of 6 clinical trials of THYROGEN: 4 trials for diagnostic use and 2 trials for ablation. In clinical trials, patients had undergone near-total thyroidectomy and had a mean age of 46.1 years. Thyroid cancer diagnosis was as follows: papillary (69.2%), follicular (12.9%), Hurthle cell (2.3%), and medullary (2.3%). The combination regimen. Refer to the radioiodine prescribing information for a list of contraindications for radioiodine.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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/somnia/ailment, headache, and chills.

- Hypersensitivity including urticaria, rash, pruritus, flushing, and respiratory symptoms and symptoms.

- Injection site reactions, including pain, erythema, bruising, and pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no available data on the presence of thyrotropin alfa in human milk, the effects on the nursing mother, or the effects on the breastfed infant in this animal study. The effects on human fertility are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

The concomitant use of THYROGEN and therapeutic radioiodine (RAI) is contraindicated in lactating women because RAI concentrates in the breast tissue and increases the risk of radiation breast toxicity (refer to the therapeutic RAI Prescribing Information).

If THYROGEN is administered with RAI for diagnostic use, discontinue breastfeeding after RAI administration because of the potential for severe adverse reactions from RAI in the breastfed infant (refer to the diagnostic RAI Prescribing Information).

If THYROGEN is not administered with RAI, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for THYROGEN and any potential adverse effects on the breastfed child from THYROGEN or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

THYROGEN may be used in combination with radioiodine (RAI). If THYROGEN is administered with RAI, the combination regimen is contraindicated in pregnant women because fetal exposure to RAI can lead to neonatal hyperthyroidism, which in some cases is severe and irreversible. Refer to the RAI prescribing information for more information on use during pregnancy.

Available data from case reports and postmarketing experience with THYROGEN use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with THYROGEN.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.6 Renal Impairment

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

10 OVERDOSAGE

In clinical trials of THYROGEN, three patients experienced symptoms after receiving THYROGEN dosages either higher than those recommended. Two patients had nausea after a 2.7 mg IM dose (3 times the recommended 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 (4 times the recommended dose). There is no specific therapy for THYROGEN overdose. Supportive care is recommended.

11 DESCRIPTION

Thyrotropin alfa, a recombinant human thyroid stimulating hormone, is a heterodimeric glycoprotein comprised of 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. Thyrotropin alfa is synthesized in a genetically modified Chinese hamster ovary cell line. Both thyrotropin alfa and naturally occurring human pituitary TSH are synthesized as a mixture of glycoprotein 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 thyrotropin alfa activity by measuring light output. The specific activity of thyrotropin alfa is determined relative to an internal Genzyme reference standard that was calibrated against the World Health Organization (WHO) human TSH reference standard.

THYROGEN (thyrotropin alfa) for injection is a sterile, white to off-white lyophilized powder in a single-dose vial for intramuscular use after reconstitution.

Table 1: Summary of Adverse Reactions by THYROGEN and Thyroid Hormone Withdrawal in Pooled Clinical Trials (<1% of Patients in any Phase) (continued)
Each single-dose vial provides 0.9 mg of thyrotropin alfa, and contains mannitol (36 mg); sodium chloride (2.4 mg); sodium phosphate dibasic, heptahydrate (3.7 mg); and sodium phosphate monobasic, monohydrate (1.4 mg). After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the concentration is 0.9 mg/mL with a deliverable volume of 1 mL (0.9 mg) and a pH of approximately 6.5 to 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Thyrotropin (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 thyroglobulin (Tg), triiodothyronine (T3) and thyroxine (T4). The effect of thyroid stimulating hormone activation of thyroid cells is to increase uptake of radiodine to allow scan detection or radiiodine 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.

12.2 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 serum TSH concentration 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Clinical Trials of THYROGEN as an Adjunctive Diagnostic Tool for Well-Differentiated Thyroid Cancer
Two prospective, randomized phase 3 clinical trials were conducted in patients with well-differentiated thyroid cancer given a single 0.9 mg IM dose. Mean peak serum TSH 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.

Table 2: Concordance of Positive Thyroid Scans Following THYROGEN Treatment with Scans Following Thyroid Hormone Withdrawal (continued)

<table>
<thead>
<tr>
<th>Concordance of scan pairs between THYROGEN scan and thyroid hormone withdrawal scan</th>
<th>Concordance of scan pairs by disease category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for metastatic Disease</td>
<td>9</td>
</tr>
<tr>
<td>Positive thyroid hormone withdrawal scan</td>
<td>67%</td>
</tr>
<tr>
<td>Total positive withdrawal scans</td>
<td>44</td>
</tr>
<tr>
<td>Positive for metastatic Disease</td>
<td>82%</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.
†In the two clinical studies radioactive 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 ng/mL or a positive scan [after thyroid hormone withdrawal or after radioactive therapy]), the THYROGEN Tg was positive (>2.5 ng/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% (49/58) 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 ng/mL) in all 35 patients, while Tg on thyroid hormone suppressive therapy was positive (>2.5 ng/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 radiodiode imaging has not been studied.

14.2 Clinical Trials of THYROGEN as an Adjunct for Thyroid Remnant Ablation in Well-Differentiated Thyroid Cancer
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=83) with low-risk, well-differentiated thyroid cancer who underwent near-total thyroidectomy were 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 radioactive 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 on 10% ± 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 radiodiode 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.
success was defined as radioiodine uptake of <0.1%. All patients from both original treatment groups who had scanning were found to be successfully ablated if there was no visible thyroid bed uptake on the scan, or if visible, uptake was less than 0.1%. Patients were still considered to have been thyroidectomized. In both studies, patients were randomized to 1 of 4 treatment groups: THYROGEN + 30 mCi 131I, THYROGEN + 100 mCi 131I, thyroid hormone withdrawal + 30 mCi 131I, or thyroid hormone withdrawal + 100 mCi 131I. Patients were assessed for efficacy (ablation success rates) at approximately 8 months. The second study (Study B) randomized 752 patients (tumor stages T1–T3, Nx, ND and N1, M0). Ablation success was defined as radioiodine uptake of <0.1% in the thyroid bed and stimulated thyroglobulin levels of <2 ng/mL. Results are summarized below (Table 4). For Study B, 726 (97%) of the original 752 patients were followed up for disease recurrence. The median follow-up was 5.4 years (0.5 to 9.2 years). Five-year follow-up data of THYROGEN for remnant ablation with two different RAI doses in Study A and Study B observed similar rates of thyroid cancer recurrence as thyroid hormone withdrawal. 14.3 Quality of Life Quality of Life (QOL) was measured during both the diagnostic study (see Clinical Studies (14.1)) and the ablation of thyroid remnant study (see Clinical Studies (14.2)) 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 2). 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). Figure 2: SF-36 Health Survey Results Quality of Life Domains Diagnostic indication

### 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</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>Thyroid Hormone Withdrawal</td>
<td>43</td>
<td>24:6</td>
<td>29:1</td>
<td></td>
<td>100%</td>
<td>86%</td>
</tr>
<tr>
<td>THYROGEN</td>
<td>44</td>
<td>26:7</td>
<td>30:3</td>
<td></td>
<td>100%</td>
<td>75%</td>
</tr>
</tbody>
</table>

| Abbreviations: fol = follicular, pap = papillary | 16 | HOW SUPPLIED/STORAGE AND HANDLING | THYROGEN (thyrotropin alfa) for injection is as a sterile white to off-white lyophilized powder in a single-dose vial. Each carton (NDC 59468-0030-2) contains two 0.9 mg single-dose vials of THYROGEN (NDC 59468-0030-1). Store THYROGEN refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. | 17 | PATIENT COUNSELING INFORMATION | Prior to THYROGEN administration, counsel patients to seek care immediately for any neurologic symptoms occurring after administration of the drug. | Inform patients for whom THYROGEN induced hypothyroidism could have serious consequences, hospitalization for administration of THYROGEN and postadministration observation should be considered. | Dosing and Administration | Inform patients that if serum Tg testing is performed, blood will be drawn 72 hours or later after the second injection of THYROGEN. | Inform patients the treatment regimen is two doses of THYROGEN administered at a 24 hour interval. | Encourage patients to remain hydrated prior to treatment with THYROGEN. | Schedule of Procedures | Inform patients that if diagnostic scanning will be performed, radiodine will be given 24 hours after the second injection of THYROGEN, and patients should return for the scan 48 hours after radiodine administration. | Inform patients that if serum Tg testing is performed, blood will be drawn 72 hours or later after the second injection of THYROGEN. | Inform patients that if remnant ablation is performed radiodine will be administered 24 hours after the second injection of THYROGEN. | Pregnancy and Lactation Risks Associated with Radiodine Treatment | When THYROGEN is administered in combination with radiodine (RAI), refer to the RAI prescribing information for patient counseling information. Inform patients to notify their healthcare provider immediately in the event of a pregnancy (see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)). | Manufactured by: Genzyme Corporation Cambridge, MA 02141 A SANOFI COMPANY THYROGEN is a registered trademark of Genzyme Corporation. | THR-FPLR-SL-FEB23 Rx Only |