

PRODUCT MONOGRAPH

Pr THYROGEN[®]

Thyrotropin alfa for injection

Lyophilized Powder for Reconstitution and Intramuscular Injection
(0.9 mg/mL)

Human Thyroid Stimulating Hormone
ATC code: H01AB01

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PrTHYROGEN®

Thyrotropin alfa for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection in the gluteal muscle	Lyophilized powder/0.9 mg/mL ¹	There are no clinically relevant nonmedicinal ingredients. Nonmedicinal ingredients: Mannitol, Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic heptahydrate, Sodium chloride, Nitrogen, Sterile water for injection

¹THYROGEN® is supplied as a sterile lyophilized powder for reconstitution in a clear 5.0 mL Type I flint tubing vial; gray 20 mm siliconized butyl stopper; 20 mm aluminum 6 bridge seal with a plastic flip off cap dimethicone siliconizing agent

INDICATIONS AND CLINICAL USE

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.

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.
- 2) THYROGEN® testing may be used in patients requiring serum Tg testing and radioiodine imaging, who are unwilling to undergo thyroid hormone withdrawal testing.
- 3) THYROGEN® 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 risk of missing a diagnosis of thyroid cancer or of underestimating the extent of disease. Therefore, thyroid hormone withdrawal Tg testing with radioiodine imaging continues to be the standard diagnostic modality to assess the presence, location and extent of thyroid cancer.
- 2) THYROGEN[®] Tg levels are generally lower than Tg levels after thyroid hormone withdrawal. The extent to which THYROGEN[®] Tg levels correlate with Tg levels after thyroid hormone withdrawal has not been adequately studied.
- 3) 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.
- 4) 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.
- 5) THYROGEN[®] is not recommended to stimulate radioiodine uptake for the purposes of ablative radiotherapy of thyroid cancer.
- 6) The signs and symptoms of hypothyroidism which accompany thyroid hormone withdrawal are avoided with THYROGEN[®] (see *PART II: SCIENTIFIC INFORMATION, CLINICAL TRIALS, Hypothyroid Signs and Symptoms and Quality of life*).

CONTRAINDICATIONS

Patients who are hypersensitive to THYROGEN[®] (thyrotropin alfa for injection) or to any ingredient in the formulation or component of the container. (see **WARNINGS AND PRECAUTIONS: General**). For a complete listing of ingredients in the formulation and components of the container, refer to the table in the **SUMMARY PRODUCT INFORMATION** section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

§ THYROGEN[®] (thyrotropin alfa for injection) should be administered intramuscularly only. It should not be administered intravenously (see **WARNINGS AND PRECAUTIONS, General**).

General

THYROGEN[®] injections should be supervised by a healthcare professional knowledgeable in the management of thyroid cancer. THYROGEN[®] should only be administered intramuscularly in the gluteal muscle. It should not be administered intravenously. One patient enrolled in a clinical trial who received 0.3 mg of THYROGEN[®] as a single IV bolus, experienced severe nausea, vomiting, diaphoresis, hypotension (BP decreased from 115/66 mmHg to 81/44 mmHg) and tachycardia (pulse increased from 75 to 117 bpm) 15 minutes after injection.

Caution should be exercised when THYROGEN[®] is administered to patients who have been previously treated with bovine thyroid stimulating hormone. In particular, patients who have experienced hypersensitivity reactions to bovine or human TSH may be at a greater risk for developing hypersensitivity reactions to THYROGEN[®], and appropriate precautions should be undertaken.

The combination of WBS (Whole Body Scan) and Tg testing after THYROGEN[®] administration improves sensitivity for detection of thyroid remnants of cancer over either alone.

Interpretation of Results

As with other diagnostic modalities, false negative results may occur with THYROGEN[®]. If a high index of suspicion for metastatic disease persists, confirmatory WBS and Tg testing should be considered following thyroid hormone withdrawal.

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.

TSH antibodies have not been reported in patients treated to date. However, exposure has been limited to 27 patients who received THYROGEN[®] in the clinical trials on more than one occasion and remained antibody negative. There have been several reports of hypersensitivity consisting of urticaria, rash, pruritis, flushing and respiratory difficulties requiring treatment (see ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis

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.

Cardiovascular

Caution should be exercised when administering THYROGEN[®] to patients with a known history of heart disease and with significant residual thyroid tissue. THYROGEN[®] is known to stimulate residual thyroid tissue to produce a transient but significant rise in serum thyroid hormone concentration. Elevations in thyroid hormone levels may exacerbate underlying heart disease. When appropriate, physicians should undertake precautionary measures to prevent or mitigate hyperthyroidism, monitor patients for evidence of worsening heart disease, and treat signs and symptoms of hyperthyroidism and worsening heart disease.

Special Populations

Effect on tumor growth:

In patients with thyroid cancer, several cases of stimulated tumor growth have been reported during withdrawal of thyroid hormones for diagnostic procedures due to the subsequent prolonged elevation of thyroid stimulating hormone (TSH) levels.

In clinical trials with thyrotropin alfa, which produces a short-term increase in TSH levels, no case of tumor growth has been reported.

However, due to elevation of TSH levels after THYROGEN[®] administration, thyroid cancer patients with metastatic disease, particularly in confined spaces (for example, brain, spinal cord, orbit or soft tissues of the neck) may be subject to local edema or focal hemorrhage at the site of these metastases. It is recommended that pretreatment with corticosteroids be considered in these patients in whom local tumor expansion may compromise vital anatomic structures prior to the administration of THYROGEN[®].

Pregnant Women: No experience. Animal reproductive studies and studies to evaluate the effects on fertility 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 used in pregnancy only if clearly needed.

Nursing Women: 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.

Pediatrics (< 18 years of age): Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatrics (> 65 years of age): 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.

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

Monitoring and Laboratory Tests

Measurement of serum TSH 72 hours following the second dose of THYROGEN[®] may show levels below the 25 mU/L normally observed in hypothyroid patients. In pharmacokinetic studies, peak serum TSH levels of 116 ± 38 mU/L were reached between 3 and 24 hours following a single dose of THYROGEN[®] (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). THYROGEN[®] has an elimination half-life of 25 ± 10 hours, therefore, several days after the second dose of THYROGEN[®], the serum TSH levels can fall to levels below those normally observed in hypothyroid cancer patients.

In clinical trials, the reference standard for determining whether patients had thyroid remnant or cancer present was a hypothyroid Tg ≥ 2.0 ng/mL and/or a hypothyroid scan (either diagnostic or post-therapy). This analysis evaluated whether Tg testing after THYROGEN[®] administration improved the diagnostic sensitivity of a Tg test in patients with a negative Tg on THST using a cut-off of 2.0 ng/mL. It should be noted that THYROGEN[®] Tg levels are generally lower than hypothyroid Tg levels and thus physicians may need to use a lower Tg cut-off level when using THYROGEN[®] than would be used with a hypothyroid Tg.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reaction data are derived from the two clinical trials in which 381 patients were treated with THYROGEN[®] (thyrotropin alfa for injection), and from post-marketing surveillance.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Prospective Clinical Trials of THYROGEN as an Adjunctive Diagnostic Tool

The percentages in the table below represent adverse reactions experienced by 381 patients who participated in the clinical trials of diagnostic indication for THYROGEN[®]. The most common adverse events (>5%) reported in clinical trials where THYROGEN[®] was used as an adjunctive diagnostic tool were: nausea (10.5%) and headache (7.3%). Events reported in $\geq 1\%$ of patients in the trials are summarized in Table 1:

Table 1: Summary of Adverse Events During Prospective Controlled Clinical Studies Using THYROGEN[®] as an Adjunctive Diagnostic Tool ($\geq 1\%$) (n=381)

System Organ Class	Event Description (MedDRA Preferred Term)	Percentage
Most commonly reported adverse events ($\geq 10\%$)		
Gastrointestinal Disorders:	Nausea	10.5%
Commonly reported adverse events ($\geq 1\%$ and $< 10\%$)		
Nervous System Disorders:	Headache	7.3%
	Dizziness	1.6%
	Paresthesia	1.6%
General Disorders and Administrative Site Conditions:	Asthenia	3.4%
	Pain	1.3%
	Chills	1.0%
	Fever	1.0%
Gastrointestinal Disorders:	Flu Syndrome*	1.0%
	Vomiting	2.1%
	Nausea and Vomiting	1.3%

*See first paragraph below table.

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), chills.

TSH antibodies have not been reported in patients treated with THYROGEN[®] in the clinical trials, although only 27 patients underwent testing for the development of TSH antibodies who received THYROGEN[®] on more than one occasion.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Very rare manifestations of hypersensitivity to THYROGEN[®] reported in clinical trials, post-marketing settings and in special treatment programs involving patients with advanced disease classified by *System Organ Class* include: *Skin and subcutaneous tissue disorder*- urticaria, rash, pruritis, flushing; and *Respiratory, thoracic and mediastinal disorder*- respiratory signs and symptoms.

Post-Market Adverse Drug Reactions

Post-marketing surveillance indicates that the types of events most frequently reported are similar to those seen in the clinical trials (headache, nausea, vomiting and dizziness). Sudden rapid and painful enlargement of locally recurring papillary carcinoma has been reported 12-48 hours after THYROGEN[®] administration. The enlargement was accompanied by dyspnea, stridor or dysphonia. Rapid clinical improvement occurred following glucocorticoid therapy. There have also been several reports of hypersensitivity reactions (including urticaria, rash, pruritus, flushing and respiratory difficulties requiring treatment) reported in the Post-Marketing setting.

A 77 year-old non-thyroidectomized patient with a history of heart disease and spinal metastases who received four 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 (see WARNINGS AND PRECAUTIONS, Interpretation of Results).

DRUG INTERACTIONS

Drug-Drug Interactions

Formal interaction studies between THYROGEN[®] (thyrotropin alfa for injection) 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 T₃ and/or T₄. Data on radioiodine kinetics indicate that the clearance of radioiodine is approximately 50% greater while euthyroid than during the hypothyroid state when renal function is decreased, thus resulting in less radioiodine retention in the body at the time of imaging. This factor should be considered when selecting the activity of radioiodine for use in radioiodine imaging.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

In clinical trials, the reference standard for determining whether patients had thyroid remnant or cancer present was a hypothyroid Tg ≥ 2.0 ng/mL and/or a hypothyroid scan (either diagnostic or post-therapy). This analysis evaluated whether Tg testing after THYROGEN[®] administration improved the diagnostic sensitivity of a Tg test in patients with a negative Tg on thyroid hormone suppression therapy (THST) using a cut-off of 2.0 ng/mL. It should be noted that THYROGEN[®]-Tg levels are generally lower than hypothyroid-Tg levels and thus physicians may need to use a lower Tg cut-off level when using THYROGEN[®] than would be used with a hypothyroid-Tg.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- THYROGEN[®] (thyrotropin alfa for injection) injections should be supervised by a healthcare professional knowledgeable in the management of thyroid cancer.
- THYROGEN[®] should be administered intramuscularly only. It should not be administered intravenously.

Recommended Dose and Dosage Adjustment

After reconstitution with 1.2 mL Sterile Water for injection, USP, 1.0 mL solution (containing 0.9 mg thyrotropin alfa), THYROGEN[®] is administered by intramuscular injection in the gluteal muscle every 24 hours for two doses.

The following parameters were utilized in the second Phase 3 study and these parameters are recommended for radioimaging scanning:

- For radioiodine imaging, radioiodine administration should be given 24 hours following the final THYROGEN[®] injection. Scanning should be performed 48 hours after radioiodine administration (72 hours after the final injection of THYROGEN[®]).
- A diagnostic activity of 4 mCi (148 MBq) ¹³¹I 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 serum Tg testing, the serum sample should be obtained 72 hours after the final injection of THYROGEN[®].

Administration

THYROGEN[®] has to be reconstituted with Sterile Water for Injection. Only one vial of THYROGEN[®] is required per injection.

Instructions for Use (with Aseptic Technique)

Reconstitution:

Add 1.2 mL of Sterile Water for Injection, USP, to the THYROGEN[®] powder in the vial. Swirl the contents of the vial gently until all material is dissolved. Do not shake the solution. When reconstituted as directed, the resulting solution has a concentration of 0.9 mg thyrotropin alfa per mL.

Reconstituted THYROGEN[®] solution should be a clear, colourless solution. Do not use vials

exhibiting foreign particles, cloudiness or discoloration.

Withdraw 1.0 mL of the THYROGEN[®] solution from the product vial. This equals 0.9 mg thyrotropin alfa to be injected.

THYROGEN[®] does not contain preservative.

The THYROGEN[®] solution should be injected within three hours, however the THYROGEN solution will stay chemically stable for up to 24 hours, if kept in a refrigerator (between 2-8°C). It is important to note that the microbiological safety depends on the aseptic conditions during the preparation of the solution.

OVERDOSAGE

Data on exposure above the recommended dose is limited to clinical studies and a special treatment program. Three patients in clinical trials, and one patient in the special treatment program experienced symptoms after receiving THYROGEN[®] (thyrotropin alfa for injection) 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. The third patient experienced nausea, vomiting and hot flashes after 3.6 mg IM dose. In the special treatment program, a 77 year-old non-thyroidectomized patient received 4 doses of THYROGEN[®] 0.9 mg over 6 days, developed atrial fibrillation, cardiac decompensation and terminal myocardial infarction 2 days later.

One additional patient enrolled in a clinical trial who received 0.3 mg THYROGEN[®] as a single IV bolus, 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) 15 minutes after injection.

When necessary, symptomatic treatment should be considered for potential cardiac symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

THYROGEN[®] (thyrotropin alfa for injection) is a heterodimeric glycoprotein produced by recombinant DNA technology. It has comparable biochemical properties to human pituitary thyroid stimulating hormone (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).

THYROGEN[®] offers an alternative to thyroid hormone withdrawal for the follow-up of patients with a history of well-differentiated thyroid cancer permitting the treating physician to perform TSH stimulated Tg testing with or without radioiodine imaging while the patient remains euthyroid on THST (thyroid hormone suppressive therapy).

Pharmacodynamics

THYROGEN[®] has comparable biochemical properties to 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 Tg, T₃ and T₄.

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

Pharmacokinetics

The pharmacokinetics of THYROGEN[®] were studied in 16 patients with well-differentiated thyroid cancer given a single 0.9 mg IM dose. After injection, mean peak concentrations of 116 ± 38 mU/L were reached between 3 and 24 hours after administration (median 10 hours). The mean apparent elimination half-life was found to be 25 ± 10 hours. TSH clearance in man has not been fully elucidated, but studies with pituitary-derived TSH suggest that the liver and kidney are involved.

Absorption: Following a single intramuscular injection of 0.9 mg of thyrotropin alfa (0.9 mg/mL formulation), the mean ± SD peak plasma level (C_{max}) was 116±38mU/L which occurred approximately at 22±8.5 hours (T_{max}). The AUC_{0→∞} was 5088±1728 mU·hr/L.

Distribution: As with endogenous TSH, rTSH binds to the TSH receptors on thyroid epithelial cells. The volume of distribution (V_d) is 68.7±32.05L.

Metabolism: Since THYROGEN[®] is a highly purified, recombinant form of the naturally occurring endogenous TSH, it is reasonable to assume that the metabolic pathway of rhTSH will be common to that of the endogenous TSH (i.e. broken down in the body to its component amino acids).

Excretion: The major elimination route of TSH is believed to be renal and to a lesser extent hepatic. In contrast, pre-clinical data on endogenous human pituitary derived TSH (phTSH) show that the kidney and liver appear to be the major organs of clearance for phTSH (Szkudlinski et al., 1995). The carbohydrate composition of rhTSH differs from phTSH in both the presence of terminal sialic acid residues and the absence of sulphated GalNAc. These differences may both contribute to the reduced clearance of rhTSH by the liver and enhanced clearance by the kidney (Szkudlinski et al., 1995). Based on these data, the kidney appears to be the major organ of clearance of rhTSH from the plasma, with a smaller additional clearance contributed by the liver. Serum clearance rate in humans was calculated as 36.3±11.6 mL/min.

STORAGE AND STABILITY

THYROEGN[®] (thyrotropin alfa for injection) should be stored at 2-8°C (36-46°F). Each vial, after reconstitution with 1.2 mL 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.

DO NOT USE THYROGEN[®] after the expiration date on the vial. Protect from light.

The reconstituted solution must be used immediately. Although not recommended, the reconstituted solution may be stored for up to 24 hours at a temperature between 2°C and 8°C, while avoiding microbial contamination.

DOSAGE FORMS, COMPOSITION AND PACKAGING

THYROGEN[®] (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic lyophilized product. It is available as a kit containing two 1.1 mg vials (4-12 IU/mg) THYROGEN.

Composition:

The quantitative composition of the lyophilized drug per vial is:

Thyrotropin alfa	1.1 mg
Mannitol	36 mg
Sodium Phosphate	
Monobasic, monohydrate	1.4 mg
Dibasic, heptahydrate	3.7 mg
Sodium Chloride	2.4 mg
Nitrogen	qs

THYROGEN[®] is preservative free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Thyrotropin alfa for injection

Chemical name: Recombinant Human Thyroid Stimulating Hormone (rhTSH).

Molecular formula and molecular mass:

Overall Molecular Formula: $C_{1039}H_{1602}N_{274}O_{307}S_{27}$

Molecular Weight: The molecular weight of TSH has been determined by amino acid sequence analysis to be approximately 10,205 for the alpha subunit and 13,503 for the beta subunit. Due to the differences in the observed type of glycosylation in rhTSH from that of phTSH and the fact that the glycosylation is variable and heterogeneous, the molecular formula and weight provided here represent the theoretical protein backbone only.

Structural formula:

Amino acid sequence of the alpha subunit of thyrotropin alfa.

The amino acid sequence contains 92 residues with the two N-linked glycosylation sites at asparagine (Asn) residues 52 and 78 shown in bold print.

1				5					10					15					20
Ala	Pro	Asp	Val	Gln	Asp	Cys	Pro	Glu	Cys	Thr	Leu	Gln	Glu	Asn	Pro	Phe	Phe	Ser	Gln
21				25					30					35					40
Pro	Gly	Ala	Pro	Ile	Leu	Gln	Cys	Met	Gly	Cys	Cys	Phe	Ser	Arg	Ala	Tyr	Pro	Thr	Pro
41				45					50					55					60
Leu	Arg	Ser	Lys	Lys	Thr	Met	Leu	Val	Gln	Lys	Asn	Val	Thr	Ser	Glu	Ser	Thr	Cys	Cys
61				65					70					75					80
Val	Ala	Lys	Ser	Tyr	Asn	Arg	Val	Thr	Val	Met	Gly	Gly	Phe	Lys	Val	Glu	Asn	His	Thr
81				85					90										
Ala	Cys	His	Cys	Ser	Thr	Cys	Tyr	Tyr	His	Lys	Ser								

Amino acid sequence of the beta subunit of thyrotropin alfa.

The beta subunit is comprised of 118 residues with the single N-linked glycosylation site shown in bold print at asparagine (Asn) residue 23.

1				5					10					15					20
Phe	Cys	Ile	Pro	Thr	Glu	Tyr	Thr	Met	His	Ile	Glu	Arg	Arg	Glu	Cys	Ala	Tyr	Cys	Leu
21				25					30					35					40
Thr	Ile	Asn	Thr	Thr	Ile	Cys	Ala	Gly	Tyr	Cys	Met	Thr	Arg	Asp	Ile	Asn	Gly	Lys	Leu
41				45					50					55					60
Phe	Leu	Pro	Lys	Tyr	Ala	Leu	Ser	Gln	Asp	Val	Cys	Thr	Tyr	Arg	Asp	Phe	Ile	Tyr	Arg
61				65					70					75					80
Thr	Val	Glu	Ile	Pro	Gly	Cys	Pro	Leu	His	Val	Ala	Pro	Tyr	Phe	Ser	Tyr	Pro	Val	Ala
81				85					90					95					100
Leu	Ser	Cys	Lys	Cys	Gly	Lys	Cys	Asn	Thr	Asp	Tyr	Ser	Asp	Cys	Ile	His	Glu	Ala	Ile
101				105					110					115				118	
Lys	Thr	Asn	Tyr	Cys	Thr	Lys	Pro	Gln	Lys	Ser	Tyr	Leu	Val	Gly	Phe	Ser	Val		

Physicochemical properties: Thyrotropin alfa (active ingredient) is human hormone produced by recombinant DNA technology. (See Product Characteristics section below)

Product Characteristics

Thyrotropin alfa (recombinant human thyroid stimulating hormone, rhTSH), the active ingredient in THYROGEN[®] is synthesized in a genetically modified Chinese hamster ovary cell line. It 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 the human pituitary thyroid stimulating hormone.

Thyrotropin alfa is a mixture of glycosylation variants differing from human TSH by absence of sulfated GalNAc and a higher percentage more highly branched carbohydrate structures; in addition, the two alpha subunit glycosylation sites contain a mixture of bi- and triantennary complex oligosaccharides with core fucosylation. The oligosaccharides found on rhTSH are typical of CHO-expressed therapeutic proteins.

The specific activity of thyrotropin alfa is calibrated against the World Health Organization (WHO) human pituitary derived TSH reference standard, NIBSC 84/703. The biological activity of thyrotropin alfa has been determined to be no less than 4-12 IU/mg by the cell-based bioassay.

CLINICAL TRIALS

Study demographics and trial design

Two Phase 3 clinical trials were conducted in 358 evaluable patients with well-differentiated thyroid cancer to compare 48-hour radioiodine (^{131}I) whole body scans obtained after THYROGEN[®] (thyrotropin alfa for injection) administration to the whole body scans after thyroid hormone withdrawal. One of these trials also compared thyroglobulin (Tg) levels after THYROGEN[®] administration 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 2.0 ng/mL. Only successfully ablated patients [defined as patients who have undergone total or near total thyroidectomy (removal of both the lobes and most of the isthmus of the thyroid gland) 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 Tg value was obtained 72 hours after the final THYROGEN[®] injection, and this value was used in the analysis (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Study results

Radioiodine Whole Body Scan Results

Whole Body Scanning Alone

In one trial (TSH 95-0101), the effectiveness of THYROGEN[®] in detecting thyroid remnants and thyroid cancer using radioiodine whole body scanning (WBS) was compared to the standard thyroid hormone withdrawal (W/D) in 220 Intent-to-Treat (ITT) patients with evaluable scans. The results of the comparison are presented below in Tables 2 and 3.

THYROGEN[®] WBS for the overall population and subgroups were statistically comparable but not identical to WBS following thyroid hormone withdrawal. As shown in Tables 2 and 3, in some patients receiving THYROGEN[®] the WBS was more sensitive. In the majority of discordant scans however, the WBS following thyroid hormone withdrawal was more sensitive. Although numerically different, the difference in discordant scans was not statistically significant.

Table 2
Summary of Whole Body Scan (WBS) Data*
0.9 mg THYROGEN[®] q 24 hr x 2 doses

Patient Category	Overall (n=113)	POSITIVE WBS (n = 48)	Metastatic Patients** (n = 19)
THYROGEN [®] Scan ≥ Hypothyroid Scan [95% C.I.]	104/113 (92.0%) [85-96%]	39/48 (81.3%) [66.9-90.6%]	15/19 (78.9%) [53.9-93.0%]
Hypothyroid Scan ≥ THYROGEN [®] Scan [95% C.I.]	110/113 (97.3%) [91.9-99.3%]	45/48 (93.8%) [81.8-98.4%]	18/19 (94.7%) [71.9-99.7%]
Concordance	101 (89.4%)	36 (75.0%)	14 (73.7%)
Discordance Favoring THYROGEN [®] Phase Favoring Hypothyroid Phase p- value	12 (10.7%) 3 (2.7%) 9 (8.0%) 0.146	12 (25.0%) 3 (6.3%) 9 (18.8%) 0.146	5 (26.3%) 1 (5.3%) 4 (21.1%) 0.375

≥: equivalent or more sensitive than

CI: Confidence Interval

* All scans were performed using 4 mCi (148 MBq) of ¹³¹I

**THYROGEN[®] WBS in combination with Tg using a threshold value of ≥ 2ng/mL detected all patients with metastatic disease.

Table 3
Summary of Whole Body Scan (WBS) Data*
0.9 mg THYROGEN[®] q 72 hr x 3 doses

Patient Category	Overall (n = 107)	Positive WBS (n = 60)	Metastatic Patients (n= 30)**
THYROGEN [®] Scan ≥ Hypothyroid Scan [95% C.I.]	99/107 (92.5%) [85.4-96.5%]	99/107 (92.5%) [85.4-96.5%]	26/30 (86.7%) [68.4-95.6%]
Hypothyroid Scan ≥ THYROGEN [®] Scan [95% C.I.]	102/107 (95.3%) [88.9-98.3%]	102/107 (95.3%) [88.9-98.3%]	29/30 (96.7%) [80.9-99.8%]
Concordance	94 (87.9%)	94 (87.9%)	25 (83.3%)
Discordance	13 (12.2%)	13 (12.2%)	5 (16.7%)
Favoring THYROGEN [®] Phase	5 (4.7%)	5 (4.7%)	1 (3.3%)
Favoring Hypothyroid Phase	8 (7.5%)	8 (7.5%)	4 (13.3%)
p-value	0.581	0.581	0.375

≥: equivalent or more sensitive than

CI: Confidence Interval

* All scans were performed using 4 mCi (148 MBq) of ¹³¹I

**THYROGEN[®] WBS in combination with Tg using a threshold value of ≥ 2ng/mL detected all patients with metastatic disease.

Combination of a WBS and Tg Test

Clinically, WBS is performed in combination with Tg testing. In one trial, the effectiveness of THYROGEN[®] to detect thyroid remnant or cancer by the combination of WBS and Tg testing was evaluated in 163 successfully ablated Tg antibody-negative patients (two-dose regimen n=78; three- dose regimen n=85). In this study, 125/163 patients had thyroid remnant or cancer present as defined by a hypothyroid Tg ≥ 2 ng/mL or a positive hypothyroid diagnostic scan or post-therapy scan.

In the THYROGEN[®] two-dose regimen, the prevalence of patients with thyroid remnant or cancer was 57/78 (73 %). The combination of a THYROGEN[®] scan and a THYROGEN[®] Tg test correctly identified 50 (88%) of the 57 patients. The combination correctly identified all 9 patients with metastatic disease as confirmed by a post-therapy scan. In the three-dose regimen the number of patients with thyroid remnant or cancer was 68/85 (80 %). The combination of a THYROGEN[®] scan and a THYROGEN[®]-stimulated Tg test correctly identified 63/68 (92.6 %) patients and all 23 patients with metastatic disease.

In summary, the combination identified all 32 patients with confirmed metastatic disease. This data along with the presence of discordant scans highlights the importance of concomitant WBS and Tg testing.

Table 4
Clinical Utility of the Combination of THYROGEN[®] WBS and Tg Test in Detecting Thyroid Remnant or Cancer

Dosing Regimen	Thyroid Cancer or Remnant	Patients treated with radioiodine	Metastatic Patients
0.9 mg THYROGEN [®] q 24 hr x 2 doses	50/57 (88%)	27/28 (96%)	9/9 (100%)
0.9 mg THYROGEN [®] q 72 hr x 3 doses	63/68 (93%)	45/46 (98%)	23/23 (100%)

Tg Testing Alone

Frequently, in the follow up of thyroid cancer patients, Tg levels are monitored while the patient remains on THST so that the potentially debilitating effects of hypothyroidism can be avoided. In the second Phase 3 study, THYROGEN[®]-stimulated Tg levels were compared to baseline levels (i.e., while the patient was on THST).

Detection of Thyroid Remnant or Cancer

In the two- dose Regimen of the second Phase 3 study, there were 58 patients with thyroid remnant or cancer; however, one patient in this group did not have a THYROGEN[®]-stimulated

Tg value and was, therefore, not included. The THYROGEN[®]-stimulated Tg levels correctly identified 41/57 (72%) patients, including: all 9 patients with confirmed metastatic cancer, 10 patients with thyroid bed uptake, 19 patients with elevated Tg levels ≥ 10 ng/mL, and 3 patients with elevated Tg levels < 10 ng/mL. Without THYROGEN[®] stimulation, Tg on THST correctly identified 21/58 (36%) patients.

In the three-dose Regimen of the second Phase 3 study, there were 68 patients with thyroid remnant or cancer; however, four patients in this group did not have a Tg value on THST and were, therefore, not included in Table 4. The THYROGEN[®]-stimulated Tg levels correctly identified 52/68 (77%) patients, including: all 23 patients with confirmed metastatic cancer, 16 patients with thyroid bed uptake, all 7 patients with elevated Tg levels ≥ 10 ng/mL, and 6 patients with elevated Tg levels < 10 ng/mL. Without THYROGEN[®] stimulation, Tg on THST correctly identified 31/64 (48%) patients.

Table 5
Detection of Thyroid Remnant or Cancer by THYROGEN[®]-Stimulated Tg and on THST

Category	2 dose		3 dose	
	THYROGEN ^{**}	THST	THYROGEN	THST ^{***}
Metastatic	9/9	5/9	23/23	18/21
Thyroid Bed Only	10/20	5/21	16/29	5/27
Elevated Tg Only (≥ 10 ng/mL) [*]	19/20	11/20 [*]	7/7	6/7
Slightly Elevated Tg Only (2 ng/mL - 10 ng/mL)	3/8	0/8	6/9	2/9
TOTAL	41/57 (72%)	21/58 (36%)	52/68 (77%)	31/64 (48%)

^{*} includes one patient with indeterminate scan classification

^{**} One patient did not have a THYROGEN[®] Tg value.

^{***} Four patients did not have THST Tg values and were therefore excluded.

Of note, 4 out of 9 patients (two-dose regimen) and 3 out of 21 patients (three-dose regimen) with metastatic disease, no thyroid remnants were detected while on THST. Data from these patients are presented below in Table 6.

Table 6
Metastatic Patients detected by THYROGEN[®]-Stimulated Tg Levels
but Missed by Tg on THST

Dose	Patient No.	TNM stage	THYROGEN [®] Scan classification*	Hypothyroid Scan classification*	Tg THST(ng/mL)	THYROGEN [®] Tg -72 hr.(ng/mL)	Hypothyroid Tg(ng/mL)	Post-therapy Scan classification*
2 dose	201	3	1	2B	1.5	16.5	9.0	2B
	202	1	1	1	0.9	5.2	22.0	2B
	310	1	4A	4A	0.5	6.9	11.8	4A
	1426	1	0	0	0.5	5.4	25.3	2B
3 dose	207	1	1	1	1.5	22.2	32.8	3B
	311	1	1	1	0.5	2.0	16.5	2B
	1713	3	0	3A	1.6	8.7	45.4	3A

* American Joint Committee on Cancer, 1992

These results clearly demonstrate that THYROGEN[®]-stimulated Tg testing improved the sensitivity of Tg testing while patients were maintained on THST for the detection of thyroid remnant and cancer. THYROGEN[®] increased the sensitivity of Tg testing by an average of 26% across the three cut-off values. Therefore, THYROGEN[®] may be used to increase the sensitivity of Tg testing on THST in the long-term follow-up of patients.

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 Billewicz Scale (Figure 1). Statistically significant worsening in all signs and symptoms were observed during the hypothyroid phase (p<0.01).

**HYPOTHYROID SYMPTOM ASSESSMENT
BILLEWICZ SCALE**

0.9 mg Thyrogen q24 x 2 doses

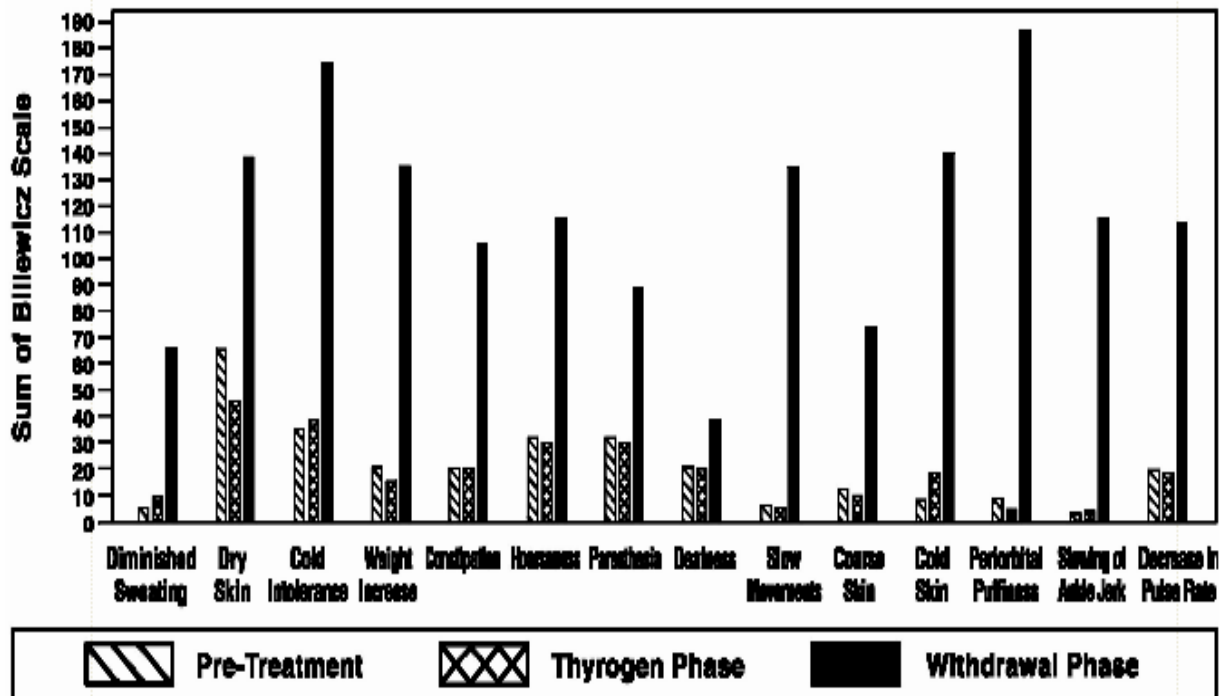
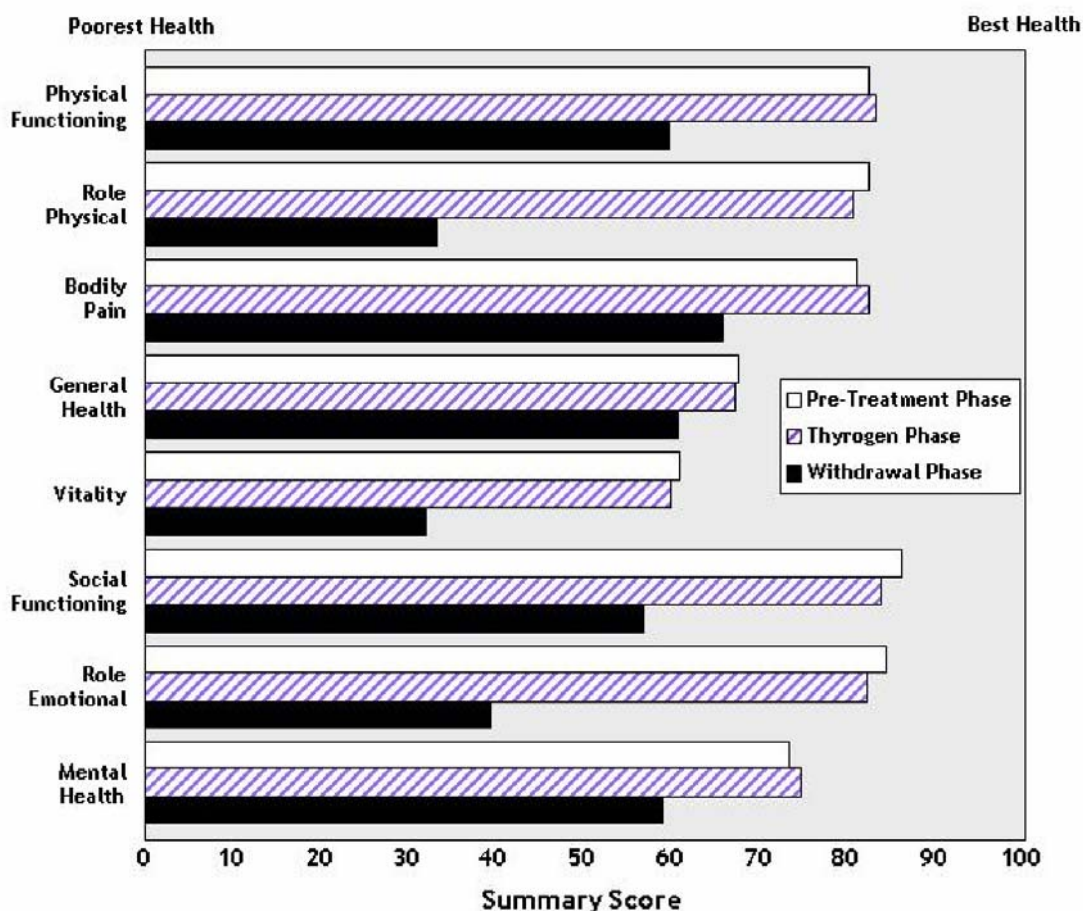


Figure 1

Quality of Life

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

FIGURE 2 – SF-36 HEALTH SURVEY RESULTS
QUALITY OF LIFE DOMAINS



DETAILED PHARMACOLOGY

Summary of Pharmacodynamic Studies

The pharmacodynamic effects of THYROGEN[®] (thyrotropin alfa for injection)/rhTSH have been assessed by measurement of radioiodine uptake and assessment of thyroid function (serum T₃, T₄ thyroglobulin, TSH levels) following single and repeated dose intramuscular administration to rhesus monkeys; measurement of plasma T₄ levels following intraperitoneal administration to mice and measurement of c-AMP production in a bovine microsomal preparation *in vitro*.

In rhesus monkeys, radioiodine uptake increased approximately 2-fold following multiple

administration (2 units (approximately 0.3 units/Kg) on 3 consecutive days) in both animals but the results were equivocal following a single administration (2 units) since only one animal demonstrated increased uptake. In all cases uptake was higher at 20 hours post radioiodine administration than at 6 hours. In mice, stimulation of T₄ levels were sufficiently consistent to allow the use of this model as a bioassay. THYROGEN[®] was also shown to modulate cAMP production in a bovine microsomal preparation, again in a manner which was consistent across several lots, to allow this method to be used to measure Lot to Lot variation.

In rhesus monkeys, 2 to 3 fold increases in T₄ and T₃ levels were seen 6 hours after a single injection of rhTSH but Tg levels were unaffected. Plasma concentration of TSH declined from over 500 µIU/mL at the end of the 26 hour post-dose period. In the corresponding multiple dose study, a similar T₃ elevation was detected. Interestingly the plasma TSH levels over the 24 hour period following the final dose declined from 100 to 10 µIU/mL. These data imply that, in a multiple dose setting, a plasma concentration of TSH in the range 10-100µIU/mL was effective in raising T₃, T₄ and Tg levels in contrast to the less marked response seen after a single dose which was associated with a higher peak plasma level. This clearly suggests that a sustained plasma concentration is more effective in triggering the release of thyroid hormones than a higher peak of shorter duration. The reason for the difference in TSH plasma levels following single and multiple administrations of the same dose is not clear at this time.

These studies show that THYROGEN[®]/rhTSH can modulate a number of physiologically relevant and important processes in a predictable and consistent manner. The range of plasma concentrations seen in the single and repeated dose studies were broadly similar to the C_{max} concentrations seen in the pharmacokinetic studies which provides assurance that the observed pharmacodynamic responses occurred over a physiologically relevant range of plasma concentrations.

It is also notable that the doses used were close to the low and intermediate doses used in the primate repeated dose toxicity study and were identical with those used in the single dose study. As doses which produced a physiologically relevant pharmacodynamic response did not lead to any adverse events in toxicity studies, the doses selected in these preclinical studies would support an acceptable safety margin.

Human pharmacodynamics studies were not specifically performed as stand alone investigations. Extensive pharmacodynamics data were collected within the context of the safety and efficacy studies.

Summary of Pharmacokinetic Studies

The pharmacokinetics of THYROGEN[®] have been evaluated in a series of studies in cynomolgus monkeys following a single intravenous administration and single and repeated intramuscular administrations.

After a single intravenous administration of rhTSH, clearance from plasma was found to be a biphasic process. There was a rapid-phase elimination half-life of about 35 minutes and a post-distribution phase of about 10 hours. The rapid-phase elimination was similar to values obtained from studies in euthyroid humans with purified human pituitary-derived TSH which gave values of between 54 and 100 minutes. These data indicate that the proposed clinical regime, in which patients could be screened twice per year for up to 10 years would not result in any accumulation of THYROGEN[®].

The relationship between rhTSH dose and C_{max} was linear following single and multiple intramuscular administrations but there was no consistent relationship for T_{max}. C_{max} values were consistent between the single and multiple dose regimes ranging from about 32.5 to 780 μIU/mL at doses of 0.36 and 0.572 IU/kg respectively. These results are consistent with those obtained in the pharmacodynamic studies.

Comparison of single dose toxicokinetic and pharmacokinetic data in monkeys and humans given comparable doses show that, although similar peak plasma levels were achieved, the time to achieve peak concentration was longer in man than in monkey. Similarly the plasma half-life in man was longer than in monkey which is the expected result of the allometric scaling effect of body weight on plasma clearance rate. The similarity in C_{max} values lead to the conclusion that organ exposure in the primate would be similar to that obtained in man given an equivalent dose. In humans, it is generally accepted that the desired dynamic response is achieved when TSH levels > 25 mU/L are achieved.

Plasma concentrations of T₃ and T₄ were elevated in a dose-related manner after both single and repeated administrations. After both regimes, T₄ values remained elevated 24 hours after dosing although rhTSH were greatly reduced by this time and returned to near baseline levels by approximately 48 hours following a single administration and 144 hours following repeated administration.

Decreases in serum cholesterol, which are associated with increases in levels of thyroid hormone, were similar at all levels and were not related to the number of administrations. The absence of a dose-response suggested that a maximal effect was achieved with the lowest dose. A decrease in serum triglycerides was seen following repeated, but not single, dose administrations suggesting that sustained elevation in T₃ and/or T₄ levels are required to induce an effect on triglycerides.

A preliminary pharmacokinetic evaluation was conducted in the Phase I/II study, although the number of patients treated with the various doses was too small to make any definitive conclusions. A more complete human study of the pharmacokinetic profiles of THYROGEN[®] was conducted (TSH94-0301) and was designed as a two-arm, randomized, two-way crossover study to determine the pharmacokinetic profiles of THYROGEN[®], including absorption, distribution, and elimination, and to compare the bioavailability of two product formulations.

The study enrolled 20 patients with well-differentiated thyroid cancer, of whom sixteen were included in the pharmacokinetic analysis.

Patients in Arm I participated in a cross-over design that compared single 0.9 mg intramuscular doses of two formulations of THYROGEN, to compare their bioavailability. Patients in Arm II were to receive 0.3 mg dose of THYROGEN in a cross over design comparing intramuscular (IM) and intravenous (IV) administration. However, Arm II was discontinued after the first patient who received an IV injection of THYROGEN[®] experienced severe nausea, vomiting and diaphoresis within 15 minutes of receiving the injection.

Study results indicated that the 2 different formulations administered during the Phase III clinical trials exhibited a comparable bioavailability. Study results of the 0.9 mg/mL formulation indicated that the mean maximum serum TSH concentration (C_{max}) was 116 ± 38 mU/L, with a mean time to maximum serum concentration (T_{max}) of 13 ± 8 hours. The analysis indicated a mean elimination half-life (T_{1/2}) of 22 ± 8 hours and mean clearance rate (Cl) of 36 ± 12 mL/min.

TOXICOLOGY

Seven preclinical studies were conducted to evaluate the toxicologic potential of THYROGEN[®] (thyrotropin alfa for injection). The in vivo studies included single dose and repeat dose studies conducted in primates and rodents. A bacterial reverse mutation assay (Ames Test) was performed to evaluate mutagenic potential. Overall, the studies demonstrated that:

- No dose-related toxic effects of rhTSH were observed in either the single or repeat dose rodent studies at levels up to 50X the expected human dose.
- No dose-related toxic effects were observed in either the single or repeat dose primate studies at levels up to 10X the expected human dose.
- THYROGEN had no mutagenic potential, as determined by the bacterial reverse mutation assay.

Long-term toxicity studies in animals to evaluate the carcinogenic potential of THYROGEN[®] have not been performed. The lack of mutagenicity of THYROGEN[®] in the bacterial reverse mutation assay and the impurity profile do not suggest the existence of any such material hazard. Administration of THYROGEN[®] to rodents in a dosage regime similar to that intended for use in man produced none of the well characterized structural changes which can indicate potential oncogenicity after protracted exposure. A tabular summary of the preclinical studies is presented below in Table 7.

Table 7
Summary of Preclinical Studies

Study Number	HWI 6354-100	HWI 6354-101	HWI 6354-104	HWI 6354-105	HWI 6354-108	N/A	MA G96CD61.502
Study Title	Acute Intramuscular and Intravenous Toxicity Study with rhTSH in Rats	Acute Repeat Dose Intramuscular Toxicity Study with rhTSH in Rats	Single Dose Intramuscular Pharmacokinetics Study with rhTSH in Monkeys	Repeated Dose Intramuscular Pharmacokinetics Study with rhTSH in Monkeys	Single Dose Intravenous Pharmacokinetic Study in Monkeys	Iodine Uptake Study in Monkeys	Evaluation of THYROGEN in the Bacterial Reverse Mutation Assay
Study Type	Toxicity	Toxicity	Pharmacology/Toxicity	Pharmacology/Toxicity	Pharmacokinetic	Pharmacodynamics	Mutagenicity
Study Duration	14 days	20 days	18 days	22 days	18 days	10 days	N/A
Animal Species	Crl:CDBR rats	Crl:CDBR rats	Cynomolgus monkeys	Cynomolgus monkey	Cynomolgus monkey	Rhesus monkey	Salmonella typhimurium TA98, TA100TA1535, TA1537 Escherichia coli WB2 uvrA
Number of Animals	45 females 45 males	45 females 45 males	3 females 3 males	3 females 3 male	2 females 2 males	4 females	N/A
Dosages	0, 0.14, 1.4, and 7.1 IU/kg x 1	0, 0.14, 0.71, and 1.4 IU/kg X 5 days	0.04, 0.14, and 0.57 IU/kg x 1 day	0.04, 0.14, and 0.57 IU/kg X 3 days	0.57 IU/kg x 1 day	2 IU X 1 and 2 IU X 3 days	Up to 5000 µg/plate for all strains
Route of Administration	IM and IV injection	IM injection	IM injection	IM injection	IV injection	IM injection	in vitro
Findings	No dose related AEs	No dose related AEs	Well-tolerated, Mild decrease in cholesterol levels Demonstrated T ₃ and T ₄ release	Well-tolerated, Mild decrease in cholesterol levels Demonstrated T ₃ and T ₄ release	Rapid clearance half-life of 35 minutes; Post-distribution half life 9.8 hours	Increased ¹³¹ I uptake; demonstrated in vivo potency; demonstrated T ₃ and T ₄ release	non-mutagenic

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PART III: CONSUMER INFORMATION

PrTHYROGEN®
(Thyrotropin alfa for injection)

This leaflet is part III of a three-part "Product Monograph" published when THYROGEN® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about THYROGEN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

If you have had surgery to remove your thyroid gland because of thyroid cancer it's important to get regular checkups to make sure that you remain cancer free. Your doctor will want to test you to see if the cancer has come back or spread to other parts of your body. Usually two types of tests are used, one is a blood test called thyroglobulin or Tg test and the other is a scan called a Whole Body Scan (WBS).

THYROGEN® allows you to be tested accurately without having to stop taking your thyroid medication.

THYROGEN® may be used for testing in patients who are:

- Unwilling to undergo thyroid hormone withdrawal/ hypothyroid testing
- Unable to tolerate withdrawal/ hypothyroidism (medically contraindicated)
- Unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal

Your treatment should be supervised by a healthcare professional knowledgeable in the management of thyroid cancer.

What it does:

THYROGEN® is recombinant human thyroid stimulating hormone (rhTSH) manufactured in a laboratory. Because it's just like the TSH that the body normally produces it causes thyroid cells to do two things on a short-term basis:

- Make thyroglobulin and release it into your blood stream, and
- Absorb radioactive iodine.

Only thyroid cells or well-differentiated thyroid cancer cells that have spread to other parts of your body can do these two things.

When it should not be used:

You should tell your doctor, if you have ever had an allergic reaction (for example, rash, or itchiness) to bovine or human thyroid stimulating hormone (TSH) or any ingredient in this medicine, before you take this medicine.

What the medicinal ingredient is:

It is called thyrotropin alfa (recombinant human thyroid

stimulating hormone)

What the important nonmedicinal ingredients are:

Mannitol, Sodium Chloride, Sodium phosphate monobasic, monohydrate, Sodium phosphate dibasic, heptahydrate.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

THYROGEN® is supplied as a sterile powder that when mixed with sterile water forms a solution for intramuscular injection in the gluteal muscle (buttocks).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
THYROGEN® should only be injected into a muscle; it should not be infused into a vein.

BEFORE you use THYROGEN® talk to your doctor or pharmacist if:

- Your doctor decides that you belong to a specific group of patients for which pre-treatment with corticosteroids is to be considered (for example, patients with intracerebral or spinal cord metastases).
- You are pregnant or plan to become pregnant or are breast-feeding.
- You have any allergies to this drug or its ingredients or components of the container.
- You have a history of heart disease.
- You are taking any other medicines or treatments, including any products you buy, such as over-the-counter medicines and herbal or home remedies.

THYROGEN® injections should be supervised by a healthcare professional knowledgeable in the management of thyroid cancer.

INTERACTIONS WITH THIS MEDICATION

There are no known drug interactions with the thyroid hormones you may be taking.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of THYROGEN® is two doses of 0.9 mg thyrotropin alfa administered intramuscularly at 24 hour intervals. Your doctor or nurse will inject 1.0 ml of the THYROGEN® solution (0.9 mg thyrotropin alfa).

THYROGEN® should only be administered into the gluteal muscle (buttocks). THYROGEN® solution should never be injected into a vein.

When you undergo radioiodine imaging, your doctor will give you radioiodine 24 hours after your final THYROGEN[®] injection. Diagnostic scanning should be performed 48 to 72 hours after the radioiodine administration (72 to 96 hours after the final injection of THYROGEN).

Day 1	Day 2	Day 3	Day 4	Day 5
THYROGEN [®]	THYROGEN [®]	Radioiodine		WBS +/- Tg testing
Monday	Tuesday	Wednesday	Thursday	Friday

For serum thyroglobulin (Tg) testing, your doctor or nurse will take a blood sample 72 hours after the final injection of THYROGEN[®].

Day 1	Day 2	Day 3	Day 4	Day 5
THYROGEN [®]	THYROGEN [®]			Serum Tg testing
Monday	Tuesday	Wednesday	Thursday	Friday

Overdose:

In case of overdose, contact your doctor or poison control center

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, THYROGEN[®] can have side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist
Most common (≥10%)	Nausea	T
Common (≥1% and ≤10%)	Headache, weakness, vomiting, dizziness, tingling sensation, pain (including pain at site of metastases), chills, fever, flu symptoms	T
Uncommon (≤1%)	Hypersensitivity (allergic reactions): urticaria, rash, pruritis, flushing, respiratory signs & symptoms	T

This is not a complete list of side effects. For any unexpected effects while taking THYROGEN[®], contact your doctor or

immediately.

Missed Dose:

If you have missed a THYROGEN[®] injection, please contact your doctor.

HOW TO STORE IT

Keep out of reach and sight of children.

Store at 2 to 8°C (in a refrigerator). Although not recommended, the reconstituted solution can be stored for up to 24 hours at a temperature between 2 to 8°C, while avoiding microbial contamination.

Keep the vial in the outer carton in order to protect from light.

Do not use after expiry date on the label.

MORE INFORMATION

pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax 866-678-6789
 By email: cadrmpp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

This document plus the full product monograph, prepared for

health professionals can be found at:
<http://www.genzyme.ca>
or by contacting the sponsor, Genzyme Canada Inc.,
at: 1-877-220-8918

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