

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020898**

**PHARMACOLOGY REVIEW(S)**

NDA 20-898

8 April 1998

Genzyme Corporation  
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Submission: 12 Dec 97; Received 15 Dec 97

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Original Summary

Thyrogen (thyrotropin alfa)

Recombinant human thyroid stimulating hormone (rhTSH)

Indication: Thyrogen (thyrotropin alfa) is indicated for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy. Thyrogen is indicated for the enhancement of the sensitivity of a serum thyroglobulin test performed in patients on hormone suppression therapy.

Related: IND [redacted]

Dosage and Administration: The recommended dosage regimen is 0.9 mg Thyrogen (thyrotropin alfa) administered by intramuscular injection (to the buttock) every 24 hours for two doses.

Recommendation: Approval [AP]

Convey to Sponsor: Labeling Revision - See p. 11

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• IND = Original Review of IND [redacted]		
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cc: Original NDA 20-898; HFD-510 NDA 20-898; HFD-345;  
Original IND [redacted]; HFD-510 IND [redacted];  
HFD-510 RSteigerwalt, DHertig, SMcCort

[redacted] /S/  
David H. Heftig  
Pharmacologist

CONELL [redacted] /S/  
4/17/98

Formulation: Each vial of Thyrogen is reconstituted with 1.2 ml of water for injection, mannitol, sodium phosphate, sodium chloride, pH 7.0 and thyrotropin alfa at a concentration of 0.9 mg/mL.

Foreign Studies: None

Preclinical Studies: See also IND [redacted]

The unformulated bulk Lot used in toxicology (except for bacterial reverse mutation assay) and pharmacology studies was F0093. Lot F4107 was used for the bacterial reverse mutation assay. This unformulated bulk Lot had a higher level of impurities than Lots used in the clinical studies but was determined by the sponsor to be suitable for the bacterial reverse mutation assay representing a preparation less pure than the product accepted for clinical use.

A minor formulation difference for non-clinical lots was the addition of 1 mg/mL human serum albumin to inhibit non-specific adsorption to the container walls.

The reference dose used by the sponsor in the preclinical pharmacology and toxicology studies was based on the bovine TSH human dose of 10 IU/70 kg which is approximately equal to 10 IU Thyrogen. Ten IU Thyrogen are equivalent to 0.9 mg protein.

Multiples of the human dose used for the IND review (1991) were based on 10 IU/50 kg rather than 10 IU/70 kg. Currently for comparison with preclinical studies, the usual standard used by FDA is a 50 kg individual with multiples of the HTD based on surface area ( $\text{mg}/\text{m}^2$ ).

The following rodent and primate studies were carried out in order to demonstrate the ability of rhTSH to stimulate the expected biological response from the thyroid gland.

Plasma Sample Analysis of Tri-iodothyronine ( $T_3$ ), Thyroxin ( $T_4$ ), and Recombinant Human Thyroid Stimulating Hormone (rhTSH) for "Single Dose Intramuscular Pharmacokinetics Study with r-TSH in Monkeys": 6354-104 dtd. 4 April 97. Analysis by Genzyme Corporation Q.A. - present, dtd 4 Apr 97.

Parent Study, [redacted] 6354-104, was carried out by [redacted] Report dtd. 20 Jun 91; Q.A. - present. [redacted]

Blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours (and stored at  $-20^\circ\text{C}$ ) by [redacted] for the Sponsor to conduct analyses.

Dose: 0.036, 0.143, 0.572 IU/kg rhTSH Single I.M. Dose.  
[ca 0.2, 0.75, 3 times 10 IU human dose (based on 50 kg person)  
or 0.1, 0.2, 1 times on a surface area ( $\text{mg}/\text{m}^2$ ) basis]

No. of Animals: 1/sex/dose Cynomolgus Monkeys (euthyroid)

Results: Plasma levels of  $T_3$  showed a dose-related elevation. By 48 hours postdose,  $T_3$  levels of the two lower dose levels had returned to baseline levels, while 48 hour postdose  $T_3$  levels for the high dose (mean 3.85 ng/ml) remained elevated at near-peak levels (mean 4.31 ng/ml at 24 hrs).

A dose response relationship is apparent for  $T_3$ - $C_{max}$  as follows:

rhTSH (IU/kg)	Time 0 avg	Male	$T_3$ ng/ml	Female
Low Dose (.04)	1.69	1.77 at 12 hrs		2.42 at 2 hrs
Mid-Dose (.14)	1.63	2.83 at 24 hrs		3.22 at 8 hrs
High Dose (.57)	1.69	4.12 at 24 hrs		4.49 at 24 hrs

The relationship between  $T_3$  dose and  $T_{max}$  is not straightforward, possibly due to inter-animal variability and low number of animals.

Peak  $T_3$  levels (low to high dose) were increased to an average of 1.2, 1.8 and 2.6 times pre-dose levels, respectively.

Plasma levels of  $T_4$  showed a dose dependent elevation. By 24 hours postdose,  $T_4$  levels for the low and mid-dose were decreasing. By 48 hours postdose,  $T_4$  levels for the two lower doses had returned to near predose levels (i.e. 4.23 vs 3.72  $\mu$ g/dL for the low dose time 0, and 4.03 vs 3.48  $\mu$ g/dL for the mid-dose time 0).  $T_4$  levels for the high dose continued to increase throughout the first 24 hours (mean 16.60  $\mu$ g/dL) postdose and were still substantially elevated at 48 hours (mean 13.15  $\mu$ g/dL).

A dose response relationship is apparent for  $T_4$ - $C_{max}$  as follows:

rhTSH (IU/kg)	Time 0 avg	Male	$T_4$ $\mu$ g/dL	Female
Low Dose (.04)	3.72	6.84 at 8 hrs		5.57 at 8 hrs
Mid-Dose (.14)	3.48	7.71 at 12 hrs		8.80 at 8 hrs
High Dose (.57)	4.07	14.30 at 24 hrs		18.90 at 24 hrs

A relationship between  $T_4$  dose and  $T_{max}$  is apparent. Higher doses of rhTSH result in longer  $T_{max}$  values. [The absence of similar relationships for  $T_3$  leaves the  $T_4$ - $T_{max}$  relationship open to question.]

Peak  $T_4$  levels (low to high dose) were increased to an average of 1.7, 2.4, 4.1 times pre-dose levels, respectively.

Monkey TSH did not appear to interfere with pre-dose measurements of rhTSH which were zero. Plasma levels of rhTSH showed a dose-related response.

Plasma rhTSH levels 24 hours post-dose had declined to 4-9  $\mu$ IU/ml for the low dose and 19-33  $\mu$ IU/ml for the mid-dose. Plasma rhTSH levels for the high dose remained elevated at 132-156  $\mu$ IU/ml at 24 hours post-dose. 48 hour rhTSH plasma levels of the two lower doses had returned to near predose levels. rhTSH levels for high dose animals remained elevated at 11-19  $\mu$ IU/ml at 48 hours.

A dose response relationship is apparent for rhTSH- $C_{max}$  as follows:

rhTSH (IU/kg)	Male	rhTSH $\mu$ IU/ml	Female
Low Dose (.04)	37.7 at 4 hrs		32.5 at 4 hrs
Mid-Dose (.14)	276.6 at 1 hr		142.5 at 2 hrs
High Dose (.57)	653.9 at 8 hrs		733.3 at 4 hrs

$T_{max}$  did not show a dose-dependent relationship with times ranging from 1 to 8 hours.

A nearly linear relationship between input rhTSH dose and rhTSH 48 hour AUC was reported for monkeys of both sexes.

Effects of Single Bolus IM administration of rhTSH on plasma half-life and 48 hr AUC of euthyroid Cynomolgus Monkeys.

rhTSH Dose (U/kg)	Half-life (hrs)		AUC ( $\mu\text{IU}\cdot\text{hrs}/\text{ml}$ )	
	Male	Female	Male	Female
0.036	8.73	7.83	644	397
0.143	7.98	6.66	2904	1900
0.572	7.81	7.07	12284	12098

For all data, the plasma half-life following single IM administration is  $7.68 \pm 0.73$  hours. For all three dose levels plasma half-life is greater in males than females. [Due to low number of animals, this may only be an approximation.]

Single Dose Intravenous Pharmacokinetics Study with r-TSH in Cynomolgus Monkeys: Study 6354-108 dtd 23 Jun 92. Q.A. - present. Plasma samples sent to Sponsor for analysis. [Clinical Route - Intramuscular]

Dose: 0.572 U/kg i.v. [ca 3 x 10 U human i.m. dose (based on a 50 kg person) or 1 times on a surface area ( $\text{mg}/\text{m}^2$ ) basis]

No. of Animals: 2M;2F [No sacrifice]

Analysis frequency: 0, 0.017, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours postdose.

**Results:**

The single i.v. 0.572 U/kg r-TSH produced no adverse toxic effects.

Pharmacokinetic Analysis: Report dtd 8 Oct 96; Q.A. dtd 17 Oct 96  
Clearance from plasma with a distribution phase half-life of  $34.9 \pm 3.9$  minutes, and an elimination phase half-life of  $9.81 \pm 0.83$  hours. It is reported that there was no apparent sex difference in plasma half-lives since the ranges for both distribution and elimination phase half-lives overlapped between males and females.

APPEARS THIS WAY  
ON ORIGINAL

Plasma Sample Analysis of Triiodothyronine ( $T_3$ ), Thyroxin ( $T_4$ ) and Recombinant Human Thyroid Stimulating Hormone (rhTSH) for "Repeated Dose (3x) Intramuscular Pharmacokinetics Study with r-TSH in Monkeys" Study 6354-105. Lots: C1051, C1052, C1053. Analysis study dtd 4 Apr 97; Q.A. Statement dtd 4 Apr 97.

Parent Study, 6354-105, was carried out by [redacted]  
Report dtd. 24 Jun 91; Q.A. - present. [redacted]

Blood samples were taken immediately prior to the three rhTSH injections (0, 24 and 48 hr. time points). Following the last injection, samples were taken at 0.5, 1, 2, 4, 8, 12, 24 hours and then daily for a total of 5 days. Plasma samples taken by [redacted] were stored at  $-20^\circ\text{C}$  until sample analysis by Genzyme Corporation.

**Dose:** 0.04, 0.14, 0.57 IU/kg r-TSH by IM injection  
 [0.2, 0.75, 3 times the 10 U human dose (based on a 50 kg person)  
 or 0.1, 0.2, 1 times on a surface area (mg/m<sup>2</sup>) basis]

**No. of Animals:** 1/sex/dose Cynomolgus Monkeys

**Results:**

T<sub>3</sub> showed a dose dependent elevation in nadir and post-injection plasma levels for the mid and high rhTSH dose levels. After the third injection, all dose levels of rhTSH showed an unexpected drop in T<sub>3</sub>. [The single dose primate study [redacted] 6354-104) did not show a comparable drop in T<sub>3</sub>.] The sponsor reports that the cause of the systematic drop in T<sub>3</sub> values is not clear, but that, however, it does not affect the overall interpretation of data. T<sub>3</sub> levels of the high dose remained elevated for the longest time after the final injection. T<sub>3</sub> was still elevated above baseline 5 days after the final injection.

T<sub>4</sub> levels also showed a dose-related elevation in nadir plasma levels for mid and high doses of rhTSH. All three dose levels of rhTSH showed a dose-related elevation in T<sub>4</sub> plasma levels 0.5 to 24 hrs. after injection. Mid and high dose groups showed a dose-related additive T<sub>4</sub> response to the second and third injections of rhTSH. This is consistent with the single dose primate study [redacted] 6354-104) in which 24 hour T<sub>4</sub> levels remained substantially above baseline for the mid and high dose groups.

Plasma rhTSH levels showed greater variability between males and females than for either T<sub>3</sub> or T<sub>4</sub>. All three dose groups showed a dose-related elevation in nadir and post injection levels of plasma rhTSH.

Following the last injection C<sub>max</sub> was as follows:

rhTSH (IU/kg)	Male	rhTSH $\mu$ IU/ml	Female
Low Dose (.04)	52.94	at 50 hrs	34.98 at 52 hrs
Mid-Dose (.14)	274.6	at 49 hrs	97.40 at 52 hrs
High Dose (.57)	782.5	at 50 hrs	488.2 at 52 hrs

Plasma Sample Analysis of Thyroxin (T<sub>4</sub>) for Single Dose Acute Intramuscular and Intravenous Toxicity Study with r-TSH in Crl:CD BR Rats. [redacted] 6354-100).  
 Analysis portion of Study by Genzyme Corp. dtd 7/31/97. rhTSH Lot Nos. C1021, C1022, C1023, C1024.

QA (Analysis Portion) dtd 8/1/97. [Reported: Although GLP regulations, as set forth in the U.S. Code of Federal Regulations Title 21, Part 58 were not strictly followed, we believe the data to be accurate and complete. Additionally, the report has been audited by R&D Quality Assurance (Parent Study Q.A. dtd 12 Jun 91).]

Parent Study, 6354-100, was carried out by [redacted]  
 Report dtd. 12 Jun 91; Q.A. - present. [IND [redacted]]

**Dose:** 0, 0.143, 1.43, 7.14 U/kg rhTSH Single i.m. or i.v. dose.  
 [ca 1, 7, 35 times the 10 U human dose (based on a 50 kg person)  
 or 0.1, 1.3, 6.3 times on a surface area (mg/m<sup>2</sup>) basis]

**No. of Animals:** 5M;5F per i.m. and i.v. group for blood sample analysis.

Sample times (Study 6354-100): Blood samples were collected by [redacted] from the baseline [5/sex] and treated animals [all during Week 3] at the clinical pathology sample collection. Samples were frozen and shipped to the Sponsor to conduct  $T_4$  analysis. Samples were stored at  $-20^{\circ}\text{C}$  until sample analysis.

**Results:**

Plasma  $T_4$  levels (mean  $\pm$  s.d.) were statistically significantly elevated ( $p < 0.05$ ) in the male mid- ( $6.32 \pm 0.91$ ) and high ( $5.66 \pm 0.53$ ) dose i.m. groups vs control ( $4.75 \pm 0.48$ ). No significant increase in plasma  $T_4$  was reported for any other dose groups including the i.v. groups.

[No elevation in plasma  $T_4$  was seen in study [redacted] 6354-101 (below) in which male rats were given 5 daily doses of 1.43 U/kg rhTSH. Plasma  $T_4$  levels were evaluated at 1 (Day 6) and 14 (Day 20) days after completion of dosing.]

Plasma Sample Analysis of Thyroxin ( $T_4$ ) for Acute Repeated Dose (5 daily doses) Intramuscular Toxicity Study with r-TSH in Crl:CD BR Rats":

6354-101). Analyses portion of Study by Genzyme Corp. dtd 7/31/97. rhTSH Lot Nos. C1017, C1018, C1019, C1020 and

QA dtd 8/1/97. [Reported: Although GLP regulations, as set forth in the U.S. Code of Federal Regulations Title 21, Part 58 were not strictly followed, we believe the data to be accurate and complete. Additionally, the report has been audited by R&D Quality Assurance.]

Parent Study, 6354-101, was carried out by [redacted] Report dtd. 20 Jun 91; Q.A. - present. [IND [redacted]]

Dose: 0, 0.143, 0.714, 1.43 U/kg I.M for 5 daily doses  
[ca 1, 3.5, 7 times the 10 U human dose (based on a 50 kg person)  
or 0.1, 0.6, 1.3 times on a surface area ( $\text{mg}/\text{m}^2$ ) basis]

No. of Animals: 5/sex/group

Thyroxin Analyses: Blood samples were collected (and stored at  $-20^{\circ}\text{C}$ ) by [redacted] for the Sponsor to conduct  $T_4$  analyses. Approximately 0.5 ml of blood was collected from baseline and treated animals at clinical pathology sample collection.

Results: The female 0.714 U/kg (3.5 x dose) group showed a statistically significant decrease ( $p < 0.05$ ) in plasma  $T_4$  levels (mean  $\pm$  s.d.  $2.38 \pm 0.63$  vs  $3.16 \pm 0.46$  for controls) on day 6 (1 day after the final dose). No statistically significant changes in plasma  $T_4$  levels were seen in other groups, including the high dose group.

APPEARS THIS WAY  
ON ORIGINAL

**Mutagenicity Study:**

**Bacterial Reverse Mutation Assay: Thyrogen (Recombinant Human Thyroid Stimulating Hormone).** Study G96CD61.502  
 dtd. 26 Jan 97. Genzyme Corporation Project TH-96-001. Q.A. - present.  
 Lot F4107-BFD

- Thyrogen was tested in the bacterial reverse mutation assay using *S. typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *E. coli* tester strain WP2 *uvrA* in the presence and absence of Aroclor 1254-induced rat liver S9. Solvent - Phosphate-mannitol buffer. Five to 7 dose levels plus vehicle and positive control were plated. The maximum dose was 5000 µg per plate. Plating was in triplicate. Positive controls consisted of: 2-aminoanthracene, 2-nitrofluorene, sodium azide, 9-aminoacridine, and methyl methanesulfonate.

- Due to confluent bacterial growth, tester strain WP2 *uvrA* in the absence of S9 activation was not evaluated during the first testing, but was retested.

A 3.4-fold, non-dose responsive increase was observed with tester strain TA1537 [at 33 µg per plate] in the absence of S9 activation. To clarify this response, tester strain TA1537 in the absence of S9 activation was retested.

In a second experiment, no positive responses were observed with tester strains TA1537 and WP2 *uvrA* in the absence of S9 activation.

No positive response was observed with the test substance with any of the tester strains (TA1537 upon retest) in the presence and absence of Aroclor-induced rat liver S9. Under study conditions, Thyrogen was concluded by the sponsor to be negative in the Bacterial Reverse Mutation Assay.

**Reprints:**

A number of reprints have been submitted, the majority of which are clinical and have to do with the actions of thyroid hormone and effects of hyper- or hypothyroidism on various biochemical parameters. Topics included allergic reactions and/or the development of TSH antibodies due to the administration of bovine TSH; thyroid hormone and T<sub>3</sub> effects on the heart (thyroid hormone has effects on both the peripheral circulation and the myocardium). Of interest were papers by Braverman, et al, and Szkudlinski, et al, - see comments section below.

**Labeling (as submitted by the sponsor):** [See recommendations under Comments and Conclusions.]

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**DRAFT LABELING**

**Pregnancy Category C**

**DRAFT LABELING**

Nursing Mothers

**DRAFT LABELING**Comments and Conclusions:

NOTE: In order to summarize findings with this drug some of the information found in the Pharmacology review of IND \_\_\_\_\_ has been repeated in this section. [See Attached, as well as, body of reviews for further information.]

Thyrogen (thyrotropin alfa, referred to as rhTSH), a recombinant form of the naturally occurring human glycoprotein, thyroid stimulating hormone (TSH), is produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary). Thyrogen is supplied as a sterile, non-pyrogenic, lyophilized product, intended for i.m. administration (buttock only) after reconstitution with Sterile Water for Injection, USP. The recommended dosage regimen is 0.9 mg (10 IU) Thyrogen administered i.m. every 24 hours for two doses.

The primary amino acid sequence of Thyrogen is identical to that of the natural type protein. However, rhTSH is highly sialylated in contrast to pituitary (pTSH) which is predominately sulfated.

Thyrogen binding to TSH receptors on thyroid epithelial cells stimulates iodine uptake and organification, and synthesis and secretion of thyroglobulin (Tg), the endogenous protein from which triiodothyronine (T<sub>3</sub>), and thyroxin (T<sub>4</sub>) are derived.

In general the properties of Thyrogen are reported to be comparable to those of the natural human thyroid stimulating hormone (TSH). However, some differences in pharmacokinetics and pharmacodynamics have been observed between rhTSH and pTSH (pituitary human TSH) which may be attributable to differences in the carbohydrate moiety. It is reported that Szkudlinski et al. [Endocrinology, 136, No.8, 3325-3330, 1995] have shown that the bioavailability of highly sialylated rhTSH exceeds that of predominately sulfated pTSH. In addition rhTSH is eliminated primarily by the kidney whereas pTSH is cleared by the liver. These authors concluded that the native protein is removed in the liver by a specific receptor-mediated clearance mechanism which recognizes sulfated oligosaccharides. The absence of sulfated oligosaccharides in rhTSH presumably leads to a loss of receptor binding activity in the liver and subsequent renal clearance.

Thyrogen is indicated for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy. Following a near total or total thyroidectomy, patients with thyroid cancer 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. Thyrogen provides the TSH stimulation necessary for the diagnostic procedures [radioiodine (<sup>131</sup>I) imaging and serum thyroglobulin (Tg) testing] while patients are maintained euthyroid on thyroid hormone suppression therapy thus, avoiding the effects of hypothyroidism associated with withdrawal of thyroid hormone suppression therapy. [It is reported that to date clinical studies have not demonstrated any antibody formation to Thyrogen. Bovine

TSH (bTSH) formerly used to stimulate radioiodine uptake prior to whole body scanning was associated with an unacceptable incidence of adverse immunological reactions and has been withdrawn from the market. Bovine TSH differs from human TSH at 26 of 92 amino acids in the  $\alpha$ -chain and at 12 of 118 amino acids in the  $\beta$ -chain.]

Acute toxicity studies in rats with single i.m. and i.v. doses up to 7.14 U/kg [ca 6.3 times the HTD for a 50 kg person on a surface area ( $\text{mg}/\text{m}^2$ ) basis] showed no apparent drug-related effects. Repeated administration of rTSH up to 1.43 U/kg i.m. [ca 1.3 times the HTD for a 50 kg person on a surface area ( $\text{mg}/\text{m}^2$ ) basis] for 5 days had no effects on mortality, clinical signs, body weight/food consumption, clinical chemistry or histopathology.

A rTSH-stimulated radioiodine uptake study in Rhesus monkeys demonstrated that repeated administration of 10 U rTSH i.m. as a single dose for 2 days doubles radioiodine uptake in these monkeys. The effects of a single 10 U dose of rTSH are equivocal since radioiodine uptake was increased in 1 monkey and unchanged in another. Administration of rTSH, 0.3 U/kg, [0.5 times the HTD for a 50 kg person on a surface area ( $\text{mg}/\text{m}^2$ ) basis] was not associated with any ill effects in this study.

Cynomolgus monkeys (1/sex/dose) were given a single dose of 0.036, 0.143, and 0.572 U/kg rhTSH i.m. [0.1, 0.2, 1 times the HTD for a 50 kg person on a surface area ( $\text{mg}/\text{m}^2$ ) basis]. Blood samples were collected pre-dose and at 0.5, 1, 2, 4, 8, 12, 24 and 48 hours post-dose for thyroid parameter analyses.

No treatment-related effects on survival, clinical signs, body weight/food consumption or vital signs were noted. At 24-48 hours after rhTSH administration, serum cholesterol levels for the low, mid- and high dose levels declined by 23, 13 and 26%. It is suggested that a maximal decline in cholesterol levels may have been elicited by the low dose. [An association between thyroid status and serum cholesterol levels in humans is reported to be documented in the literature (Walton et al., Clin Sci 29, 199-215, 1965; Valdemarsson et al., Scan J Clin Lab Invest, 44, 183-189, 1984; and others).]

There were dose-related plasma level responses of both  $T_3$  and  $T_4$  for all three dose levels of rhTSH. At 48 hours, plasma  $T_3$  levels for the low and mid dose levels had returned to baseline while the high dose remained elevated close to peak values.  $T_4$  plasma levels showed a somewhat similar pattern.

Monkey TSH did not appear to interfere with pre-dose measurements of rhTSH which were zero. After a rhTSH  $C_{\text{max}}$  for the low dose of 37.7/32.5 (M/F)  $\mu\text{IU}/\text{ml}$  at 4 hours, plasma rhTSH levels declined to 4-9  $\mu\text{IU}/\text{ml}$  at 24 hours. The mid-dose  $C_{\text{max}}$  values of 276.6/142.5 at 1 and 2 hours declined to 19-33  $\mu\text{IU}/\text{ml}$  at 24 hours. Plasma rhTSH levels for the high dose ( $C_{\text{max}}$  653.9/733.3  $\mu\text{IU}/\text{ml}$  at 8/4 hours) were 132-156  $\mu\text{IU}/\text{ml}$  at 24 hours post-dose. By 48 hours rhTSH plasma levels of the two lower doses had returned to near pre-dose levels while the high dose showed values of 11-19  $\mu\text{IU}/\text{ml}$ .

Studies in Cynomolgus monkeys with rhTSH were reportedly designed primarily for the purpose of obtaining pharmacokinetic and pharmacodynamic data. There was no sacrifice.

Cynomolgus monkeys (1/sex/gp) also received 3 daily i.m. injections of rhTSH at dose levels of 0.036, 0.143 and 0.572 IU/kg [0.1, 0.2, 1 times the HTD for a 50 kg person on a surface area ( $\text{mg}/\text{m}^2$ ) basis]. Blood samples for thyroid analyses were collected from all monkeys on day -4; pre-dose on days 1, 2 and 3; 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96 and 120 hours after the third dose. Hematology and clinical chemistry were evaluated at day -4 and 24 hours after the final dose. Vital signs and cardiovascular parameters were studied on day 8 (too long after dosing to be meaningful considering  $T_{\text{max}}$  is measured in hours).

No treatment-related effects on survival, body weight or vital signs were noted.

Cholesterol decreases for the three rhTSH levels averaged ca 25%. Triglyceride decreases showed a more variable decrease with an average of ca 27%. [It is reported that changes in triglycerides have also been noted with changes in thyroid hormone levels (Abrams et al, J Lipid Res, 22, 323-338 1981; Nikkila et al, J Clin Invest, 51, 2103-2114, 1972; Tulloch et al, Lancet 24 (Feb), 391-394, 1973).] It appears that a sustained elevation in  $T_3$  and  $T_4$  levels are required to induce an effect on triglycerides.

Following administration of rhTSH, there was a drug-related elevation in plasma levels of  $T_3$ . Plasma  $T_3$  levels of all dose groups showed an unexpected drop after the third injection. This drop is unexplainable. A similar drop in  $T_3$  was not seen in the single dose monkey study.

Plasma  $T_4$  levels were elevated in a dose-related manner. Although declining, levels remained elevated 48 hours after dosing.

Males and females showed a considerable variation in the circulating levels of rhTSH, however, there was a dose-response relationship with the exogenous dose.  $C_{max}$  showed a clear drug-related relationship after the third dose. However,  $T_{max}$  did not show a clear drug-related relationship. [It is stated that constraints on the size and frequency of blood samples immediately after the first and second doses prevented accurate calculation of total AUCs.]

A single intravenous dose of 0.572 U/kg administered to 2 male and 2 female cynomolgus monkeys produced an average rapid phase half-life of ca 35 minutes and a post-distribution clearance half-life of ca 9.8 hours. [These data differ somewhat from that reported by Braverman et al, (JCE&M, Vol. 74, No. 5, 1135-1139; 1992) in rhesus monkeys of 63 vs 35 min and 5.4 vs 9.8 hours. Differences in rhTSH clearance may be species specific. The half-life of pituitary derived TSH in euthyroid humans has been estimated to be 54-100 minutes.

A bacterial reverse mutation assay (Ames test) was carried out with Thyrogen. A 3.4-fold, non-dose responsive increase was seen with tester strain TA1537 in the absence of S9 activation. No positive response was observed with the test substance with any of the other test strains, nor with TA1537 upon retest, in the presence or absence of Aroclor-induced rat liver S9.

Some preclinical studies were carried out by a contract laboratory in 1991. Plasma samples were stored at  $-20^{\circ}\text{C}$  and shipped to the sponsor for analysis of rhTSH,  $T_3$ , and  $T_4$ . Analysis Reports and Quality Assurance Statements are dated in 1997. I called Matthew R. Patterson, Senior Regulatory Associate, Genzyme to find out when the samples were analyzed. Mr. Patterson checked into the matter and informed me that the samples were sent to Genzyme in 1991 and analyzed immediately. He stated that the reports were not formalized in the technical format until preparation of the NDA and thus the final copies were dated 1997.

It is reported that there were minor differences between formulations used in preclinical studies and the final clinical formulation. The main difference was the addition of 1 mg/ml of human serum added to the preclinical lots to inhibit non-specific absorption to the container. This difference would not be expected to affect assessment of clinical safety.

Due to the short term diagnostic use of this recombinant human TSH, only limited preclinical studies were carried out. No carcinogenicity, reproduction, or embryo-fetal toxicity studies were conducted. Cautions with regard to these areas are contained in the labeling.

Local tolerance studies have not been performed. Thyrogen is reportedly formulated to provide normal osmolarity and neutral pH to reduce the risk of irritation on injection. Local tolerance (although not specifically looked for!) did not appear to be a problem in preclinical studies. It is reported that in clinical trials there were no serious adverse reactions related to local irritation.

Both rodent and primate studies have demonstrated the ability of rhTSH to stimulate the expected biological response from the thyroid gland of euthyroid animals.

The properties of TSH are known and the recommended dosage regimen of 0.9 mg Thyrogen administered intramuscularly every 24 hours for two doses would not be expected to pose a problem of toxicity. It was stated in the pharmacology review of 1991 that with the available toxicology data only short term use of this agent for a cancer indication was acceptable. This submission provided only pharmacodynamic data, no additional toxicologic information was provided. Therefore, the recommendation set forth in the 1991 pharmacology review still holds.

Thus, from the standpoint of Pharmacology, Approval is recommended for the indicated (short term) use of Thyrogen: As an adjunct to radiiodine imaging and/or serum thyroglobulin testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

Convey to the Sponsor:

Labeling needs revision:

Labeling should be rewritten per 21 CFR 201.57 to read as follows:

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

[Redacted]

**Pregnancy Category C**

[Redacted]

**Nursing Mothers**

[Redacted]

cc: Original NDA 20-898; HFD-510 NDA 20-898; HFD-545  
Original IND [Redacted] HFD-510 IND [Redacted]  
HFD 510 RSteigerwalt, DHertig, SMCcort

[Signature] / S /  
David H. Hertig  
Pharmacologist