CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020898

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Division of Metabolic and Endocrine Drug Products

LABEL REVIEW OF DRAFT LABELING

Application Number: 20-898

Name of Drug: Thyrogen® (thyrotropin alfa for injection)

Sponsor: Genzyme

Material Reviewed

Submission Date: November 30, 1998

Receipt Date: November 30, 1998

Background and Summary Description:

The draft labeling submitted with this submission was in response to a November 30, 1998, FAX communication provided by the Division to the October 28, 1998 draft labeling submitted by the Firm.

Review

The November 30, 1998 draft labeling submitted by the firm was compared with the revised draft labeling FAXED to the firm by FDA on November 30, 1998 with minor labeling revisions. All changes agreed upon or requested have been included in the November 30, 1998, draft labeling.

Conclusions

With the concurrence of the reviewing staff the draft labeling dated November 30, 1998 FAXED to the Division is approvable.

/S/ 11-30-98

Steve McCort
Project Manager
Division of Metabolic and
Endocrine Drug Products

/S/ 11/30/98

Florence Houn, M.D.
Deputy Office Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-898
HFD-510/Div. Files
HFD-510/SMcCort
HFD-510/Solomon Sobel, M.D.

APPEARS THIS WAY
ON ORIGINAL

LABEL REVIEW

Division of Metabolic and Endocrine Drug Products

LABEL REVIEW OF DRAFT LABELING

Application Number: 20-898

Name of Drug: Thyrogen® (thyrotropin alfa for injection)

Sponsor: Genzyme

Material Reviewed

Submission Date: November 24, 1998

Receipt Date: November 24, 1998

Background and Summary Description:

The draft labeling submitted with this submission was in response to a November 24, 1998, FAX communication provided by the Division to the October 28, 1998 draft labeling submitted by the Firm.

Review

The November 24, 1998 draft labeling submitted by the firm was compared with the revised draft labeling FAXED to the firm by FDA with labeling revisions. All changes agreed upon or requested have been included in the November 24, 1998, draft labeling.

Division of Metabolic and Endocrine Drug Products

LABEL REVIEW OF DRAFT LABELING

Application Number: 20-898

Name of Drug: Thyrogen® (thyrotropin alfa for injection)

Sponsor: Genzyme

Material Reviewed

Submission Date: November 24, 1998

Receipt Date: November 24, 1998

Background and Summary Description:

The draft labeling submitted with this submission was in response to a November 24, 1998, FAX communication provided by the Division to the October 28, 1998 draft labeling submitted by the Firm.

Review

The November 24, 1998 draft labeling submitted by the firm was compared with the revised draft labeling FAXED to the firm by FDA with labeling revisions. All changes agreed upon or requested have been included in the November 24, 1998, draft labeling.

Conclusions

With the concurrence of the reviewing staff the draft labeling dated ~~October~~ Volume 24 28, 1998 and received November 24, 1998, is approvable.

/S/ 11-25-98
Steve McCort
Project Manager

/S/ 11/25/98
Mike Fossler, Ph.D.
Biopharmaceutics Reviewer

/S/ 11/30/98
Hae Young Ahn, Ph.D.
Biopharmaceutics Team Leader

/S/
Sonia Castillo, Ph.D.
Statistics Reviewer

/S/ 11/25/98
Jean Temeck, M.D.
Medical Reviewer

/S/ 11/30/98
Solomon Sobel, M.D.
Division Director

/S/ 11/25/98
Duu-Gong Wu, Ph.D.
Chemistry Team Leader

/S/ for David Hertig 11/30/98
David Hertig
Pharmacology Reviewer

/S/ 11/30/98
Ron Steigerwalt, Ph.D.
Pharmacology Team Leader

/S/ 11/30/98
Mike Welch, Ph.D.
Statistics Team Leader

/S/ 11/25/98
David Orloff, M.D.
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-898
HFD-510/Div. Files
HFD-510/SMcCort
HFD-510/Solomon Sobel, M.D.

LABEL REVIEW

genzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
FAX 617-252-7600

November 24, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 013

Dr. Solomon Sobel
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Parklawn Bldg., HFD-510, Rm. 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: Thyrogen® NDA: Minor Labeling Amendment

Dear Dr. Sobel:

In accordance with 21 CFR 314.60, the purpose of this correspondence is to provide the final labeling for Thyrogen (thyrotropin alfa for injection) as agreed upon between Genzyme and the Division.

Please find the following documentation to support this amendment:

Attachment 1: Final Thyrogen Package Insert text in manuscript format.

Attachment 2: Color layout of Thyrogen carton and vial labeling.

Should you have any questions or need additional clarification concerning this correspondence, please do not hesitate to call me at 617-374-7425.

Sincerely,

Ilze Ahtons, M.S.
Manager, Regulatory Affairs

Desk Copies: Steve McCort, Project Manager
Division of Metabolism and Endocrine Drug Products

genzyme

October 28, 1998

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
FAX 617-252-7600

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 011

Dr. Solomon Sobel
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Parklawn Bldg., HFD-510, Rm. 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: Thyrogen® NDA: Minor Labeling Amendment

Dear Dr. Sobel:

In accordance with 21 CFR 314.60, the purpose of this correspondence is to provide an updated Package Insert (PI) for Thyrogen based upon the Division's comments provided October 20, 1998 and the teleconference discussions on October 23, 1998 held between Genzyme and the Division. Based upon verbal confirmation of PI text changes following the October 23, 1998 teleconference, it is our understanding that we have come to final agreement on the PI text. Additionally, Dr. Wu has reviewed the chemistry sections of the PI as well as the noninsert labeling and we have reached mutual agreement with these portions of the labeling. As part of this amendment, we are providing color copy of the noninsert labeling that is intended for use initially until a final specific activity is agreed upon with the Agency.

Please find the following documentation in support of this minor labeling amendment:

Attachment 1: Updated Package Insert (PI) incorporating the October 20 and 23, 1998 labeling changes. This version of the PI is in REVISION mode so that you can clearly identify changes that were discussed October 23 and finalized with the reviewers on October 27 and 28, 1998.

Attachment 2: Updated Package Insert (PI) incorporating the October 20 and 23, 1998 labeling changes. This version of the PI is in manuscript format and appears with all revisions incorporated. The text is identical to that in Attachment 1.

Attachment 3: Color copy of the noninsert labeling.

Should you have any questions or need additional clarification concerning this correspondence, please do not hesitate to call me at 617-374-7425.

Sincerely,

Ilze Amons
Manager, Regulatory Affairs

Desk Copies: Dr. Jean Temeck , Dr. David Orloff, Dr. DuGong Wu, Jayne Peterson, DDMAC (*sent under separate cover*), Steve McCort, Regulatory Project Manager

genzyme

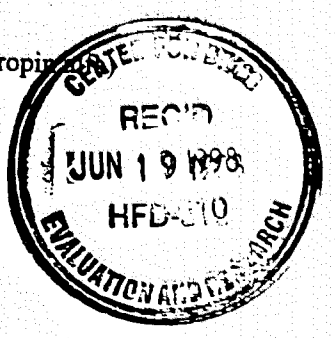
6-1858
<Azel

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
FAX 617-252-7600

June 18, 1998

Mr. Steve McCort
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Parklawn Bldg., HFD-510, Rm. 14-B-30
5600 Fishers Lane
Rockville, MD 20857

Ref. NDA #20-898
Thyrogen® (thyrotropin
Amendment 4



RE: Thyrogen® NDA: Minor Labeling Amendment

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and the facsimile received by Genzyme June 10, 1998 concerning proposed labeling modifications by the Division.

Enclosed please find comments on the latest draft of the Thyrogen Package Insert for discussion during the conference call tomorrow. The changes to the 6/10/98 version Genzyme proposes are itemized in the attached document and the revised labeling follows. In the labeling, underlined text is new and text with strikethrough is to be deleted.

For the 1 pm call tomorrow, please call Genzyme at (617) 252-7757. The attendees from Genzyme are listed below:
Alison Lawton, VP Regulatory Affairs
Richard Moscicki, MD, Chief Medical Officer
David Meeker, MD, VP Medical Affairs
Kevin McEllin, Associate Director, Clinical Affairs
Paul Gelep, Director, Global Marketing, Thyrogen

Should you have any questions or need additional clarification concerning this amendment, please do not hesitate to call Matt Patterson at (617) 252-7676.

Sincerely,

Alison Lawton
Vice President, Regulatory Affairs

Matthew Patterson
for Alison Lawton

Desk Copies: Steve McCort (sent by facsimile)

December 12, 1997

PATENT INFORMATION

Patent Number: U. S. Patent 5,240,832

Date of Expiration: August 31, 2000

Type of Patent: Process of production

Patent Owner: Genzyme Corporation

Original Declaration:

The undersigned declares that Patent No. 5,240,832, issued August 31, 1993, covers a method of producing Thyrogen® (thyrotropin alfa).

Genzyme Corporation

By: William Gosz

William Gosz

Senior Patent Counsel

December 12, 1997

New Drug Application Exclusivity Claim

In accordance with section 505(b)(1)of the Food, Drug and Cosmetic Act and Title 21 CFR 314.108(b)(2), Genzyme hereby claims exclusivity for Thyrogen® (thyrotropin alfa). The active moiety in Thyrogen®, thyrotropin alfa, is a new chemical entity claimed by Genzyme's patent number 5,240,832, approved August 31, 1993.

Genzyme, therefore, requests and claims the 5 years market exclusivity period following approval of this new drug application.

Genzyme Corporation

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT CERTIFICATION

December 12, 1997

Cerification Pursuant to 21 U.S.C. Section 335 a(k)(1)

Genzyme Corporation hereby certifies that it did not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. Section 335 (a) (b)) in connection with this application.

Genzyme Corporation

By: _____

Loan T. Tran, Pharm.D.
Director, Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # __20-898_____ SUPPL #_____

Trade Name _Thyrogen®_____ Generic Name _thyrotropin alfa for injection___

Applicant Name Genzyme Corporation_____ HFD # ___510_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_x__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_x__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_x__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____no_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_x__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !

!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !

!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 11-24-98

Signature Date

Title:_____

/S/ 11/30-98

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac