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genzyme

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

February 26, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence

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

RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to the facsimile received by Genzyme February 19, 1998.

Enclosed please find responses to the following requests for information:
1) Point 3b of the February 19, 1998 fax to Genzyme.
2) Diagnostic Utility analyses based on 48 hour Thyroglobulin data, as requested in the February 24, 1998 conference call between Genzyme and FDA.
3) Information on TSH95-0101 patients 1315 and 1210, as requested in the February 24, 1998 conference call.
4) Explanation of Data Listing 3.1.0 of TSH95-0101, from Volume 40, pg. 66-78 of the NDA.

Each response is found after the appropriate tab in this volume and includes relevant summary tables and data listings as necessary. This is the information Genzyme committed to providing by February 27, 1998.

Please note that points 2, 3a, and 5 of the February 19, 1998 fax to Genzyme will not be addressed per FDA request in the conference call February 24, 1998.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson
Principal Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

AMENDMENT ORIGINA

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GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562 U.S.A
617-252-7500
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February 23, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence

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

RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to the facsimile received by Genzyme February 11, 1998.

Enclosed please find the information on Microbiology requested in the February 11 fax to Genzyme. The submission consists of the following:

- Volume 1/3: The information requested in points 1 and 2, specifically Thyrogen NDA Part IIB volume 3, Pages 58-121 (Viral Safety Information/Viral Clearance Validation) and Part II B, volume 3, pages 122-166 (Stability Data).
- Volumes 2/3 and 3/3: The information requested in point 3, specifically Thyrogen NDA Appendices IIB/8-3 through 8/23.

Finally, in response to request number 4, Genzyme would like to provide the following information:

The sterile Water for Injection (WFI) to be provided with each vial of Thyrogen is manufactured. A letter authorizing Genzyme's cross-reference of this application is included in Volume 1 of the Thyrogen NDA.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson
Principal Regulatory Affairs Associate

REVIEWS COMPLETED
CSO ACTION:
/S/ N.A.I. ☒ MEMO
CSO INITIALS 2-24-98 DATE

Archive

~~AMENDMENT~~ ORIGINAL
NEW CORRESP

genzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
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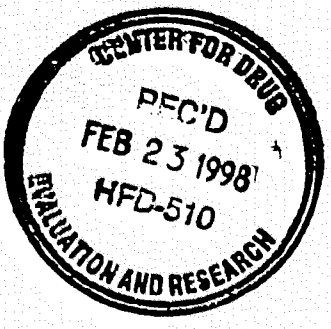
February 20, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence



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

RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997.

Enclosed please find the following items:

1) Copies of the cover letters for four recent submissions to Dr. H.W. Ju in the Division of Scientific Investigation. This information was sent to Dr. Ju at his request for the purpose of auditing Thyrogen investigational sites and is being provided to you for your reference.

2) A copy of two tables to assist the NDA review of Mike Fossler, Ph.D. These are updated versions of the same tables included in response to the Biopharmaceutics question in the 2/13/98 submission. Genzyme committed to providing these updates in the original response.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson
Principal Regulatory Affairs Associate

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Will review my copy.
/S/ 2/25/98

Noted
/S/ 2/25/98
3/17/98
Noted
/S/

Noted
/S/ 3/18/98

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GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
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February 19, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence

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

RE: **Thyrogen® NDA: Requested information**

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to recent communications between Genzyme and FDA.

Enclosed please find responses to points 1A-1C as outlined in the facsimile received by Genzyme today (attached). Each response is found after the appropriate tab in this volume and includes relevant summary tables and data listings as necessary. This is the information Genzyme committed to providing by February 20, 1998.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson
Principal Regulatory Affairs Associate

NDA20-898: GenCorr011

AMENDMENT; ORIGINA

B2

enzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562 U.S.A.
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February 13, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence
Serial #009

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

RE: Thyrogen® NDA 20-898
Response to Requested Information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA No. 20-898 submitted to FDA December 12, 1997, the facsimiles received from FDA February 5th, 6th, and 11th and the conference calls held between FDA and Genzyme February 10th and 11th 1998.

Enclosed please find responses to FDA requests and questions as outlined in the faxes sent to Genzyme February 5th, 6th and 11th concerning the Thyrogen NDA. This submission consists of two volumes, as described below:

Volume 1 of 2
- Cover Letter
- Copies of faxes sent to Genzyme
- Tabs 1-11: Responses to each of the medical questions outlined in the three faxes sent to Genzyme. Each tab contains the FDA request in bolded type followed by the response to each issue, along with any relevant new or updated tables.
- Tab 12 "Biopharmaceutics": Response to FDA request for information related to Part VI of the Thyrogen NDA, Human Pharmacokinetics and Bioavailability.

Volume 2 of 2

- Cover Letter (copy)
- Updated index for Part IV Clinical section of the Thyrogen NDA, in response to Request 1 and 2 of the February 5 fax and Request 2 of the February 11 fax.

  The new index includes a general Overall Table of Contents (TOC) for the Clinical Section, as well as new detailed tables of contents for each volume (volume 26-45; tabbed with the corresponding number). As discussed and agreed to in our conference calls on February 10 and 11, 1998, Genzyme has reviewed the index for clarity the titles and content of all tables and figures in the reports of the Clinical Section. For those table and figure titles that were confusing we have added italicized "Notes" just after these titles in the revised TOCs for each volume and group tables according to the types of topics for ease of reference. We have not changed the actual existing tables/figures since this would require re-running various tables/figures, study reports revision, and thus re-submission of the entire Clinical Section. We trust that you will find these "Notes" and table grouping helpful in clarifying the content of the tables/figures.

  Please note also that during this review, we found several tables incorrectly referenced and have noted them in the volume index. Where required, any tables missing are included immediately following the index of that particular volume.

- "Abbreviations" Tab: This is the result of part (d) of Request 1 of the February 5 fax, which requested clarification of abbreviations used in tables and figures in the Clinical Section.

Confirmation of timelines for the submission of additional information requested by FDA is included in the responses to the faxes in Volume 1 of this submission. These are the timelines agreed to with FDA during the conference call of February 11th.

In addition, Genzyme commits to providing the new table described in the fax to FDA February 10th. It was agreed during the conference call February 11th that this table would be provided for the data using the reference cut-offs of 3 ng/mL and 10 ng/mL for Thyrogen and withdrawal, respectively.

Finally , Genzyme commits to providing the information requested in the February 11th fax concerning Microbiology within two weeks.

We trust that all your requests have been satisfactorily addressed and look forward to an interactive NDA review process with the Division. Should you have any questions about this submission, please do not hesitate to contact Matthew Patterson at (617) 252-7676 or myself at (617) 761-8924.

Sincerely,

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

ORIG AMENDMENT

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GENZYME CORPORATION
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January 30, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence
Serial #005

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

RE: Thyrogen® NDA: Requested BioPharm information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted to FDA December 12, 1997 and the facsimile received from FDA January 16, 1998.

Enclosed please find the information requested by Biopharm reviewer Mike Fossler, Ph.D. in your recent facsimile. Please note the following points:

3) The final study reports for TSH91-0601 and TSH94-0301 have been provided as Word 7.0 files. The individual data for each of these studies is provided as an Excel 6.0 file. Please refer to the "Read Me" file on the disk, which explains that the 1.1 mg doses listed on the Excel table for TSH94-0301 correspond to the proposed 0.9 mg dose.

Please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
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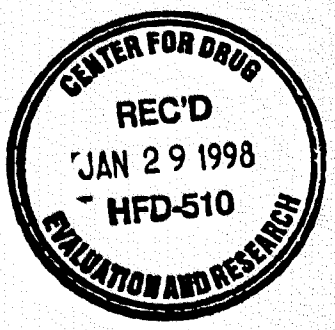

GENZYME CORPORATION
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617-252-7500
FAX 617-252-7600

January 28, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence
Serial #004

Dr. Jean Temeck
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

RE: Thyrogen® NDA: Information Request

Dear Dr. Temeck:

Reference is made to our recent telephone conversations and your request for information related to the Thyrogen® NDA.

Enclosed please find the following information:

Distribution of Patients with Eligible Scan Table (TSH95-0101): UPDATED

1) This is an updated version of the table you received recently in NDA general correspondence serial #003. As discussed January 20, the original table did not identify those patients who were Tg-antibody positive. These patients are now clearly identified in the table. (Appendix 1)

2) Enclosed is a separate table that contains all available 72 hour scan data from TSH95-0101. If you recall this was not available at the time of my previous submission (serial #003). (Appendix 2)

3) As requested January 26, Table 25 has been updated and now provides information on number and distribution of lesions for all patients, not just concordant patients. In addition, the "TSH Classification" category for this table now provides the actual scan rating by each independent reviewer rather than just the consensus rating as it did before. Patients are listed in this table in the same order as on the main data table for TSH95-0101. (Appendix 3)

Distribution of Patients with Eligible Scan Table (TSH92-0601)

4) The same table that was developed for TSH95-0101 has been developed for TSH92-0601. As we discussed previously, the data available for this table is more limited than for the TSH95-0101 table. (Appendix 4)

5) A table entitled "Data Listing, Intent to Treat Population" is included, which contains the same type of information as provided on Table 25 for TSH95-0101. However, please note that because the data was collected in a different manner for TSH92-0601, the available information is slightly different. Specifically, independent reviewers provided written descriptions only for discordant scan pairs and not all patients.

I hope this information is helpful for your review. Thank you and please call me at (617) 252-7676 if you have further questions.

Sincerely,

Matthew R. Patterson
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

[redacted] [redacted] [redacted]

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GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
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January 16, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence
Serial #003

Dr. Jean Temeck
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

RE: Thyrogen® NDA: Information Request

Dear Dr. Temeck:

Reference is made to our recent telephone conversations and your request for information related to the Thyrogen® NDA.

Enclosed are the data tables you requested. Please note the following important points and answers to your questions from our conversation Wednesday:

Distribution of Eligible Patients Table (TSH95-0101) (Appendix 1)

- The enclosed table contains the data you requested for patients from TSH95-0101 only. As I mentioned on the phone, I will follow-up with the available information for the TSH92-0601 patients as soon as possible. As you know, more data is available for the TSH95-0101 patients than the TSH92-0601 patients. Thus, the corresponding table for TSH92-0601 patients will be somewhat more limited. In addition, I was unable to incorporate the 72 hour scan data for TSH95-0101 patients into this table. I will prepare a separate table with these data and will send this to you along with the table for TSH92-0601 as soon as possible.

- The table has been altered from the draft version which was faxed to you on Wednesday to list patients according to concordant (first) and discordant (second) scan pairs, as requested.

- Please note that in the table category of "Ablation Status" a "Y" designation means a patient was successfully ablated. Related to this subject, please note that the available criteria for confirmation of successful ablation were expanded slightly for data analysis in the TSH95-0101 study. The minor addition to these criteria is explained in section 3.3.4 of the final study report, which can be found on page 35 of Volume 36/68 of the Thyrogen NDA. In summary, in the protocol successful ablation was defined as confirmation prior to enrollment of less than 1% uptake in the thyroid bed, or, if these data were not available, a negative scan of the thyroid bed was acceptable. This definition was expanded to include certain patients for whom confirmation of successful ablation was not available at the time of enrollment; however, a negative diagnostic scan during the conduct of the study after Withdrawal was determined to be confirmation of successful ablation. These additional patients were included in the Thyroglobulin data analysis.

In preparing the expanded data table you requested, we realized that the data column for the ablation status of metastatic patients Table 17.0.0 of the final study report, as submitted on pages 309-312 of Volume 37/68 of the NDA, needed to be updated to reflect the revised definition of successful ablation. In addition, as a result of reviewing this information in support of your recent request, one other minor error was noted on Table 17.0.0. The THST TSH values listed in this table were incorrect and have been corrected. Table 17.0.0 has been updated and is enclosed (Appendix 6). Please replace the original Table 17.0.0 with this revised version. Sorry for this inconvenience.

• In reference to your question about the categorization of patients as low-risk or high-risk, please note that in our study analyses we designated patients with a TNM stage of 1 or 2 as low-risk and patients with stage 3 and 4 are high-risk. This risk stratification approach was recommended by our study investigators and is consistent with the published literature when discussing low and high risk well-differentiated thyroid carcinoma. We have included two citations from the literature which provide an example of the utilization of this approach (Appendix 5).

• As we discussed, the data on the number and distribution of lesions will not fit into the enclosed table format. As you recall, with the use of the classification system for TSH95-0101, clinically relevant differences in the number and distribution of lesions were incorporated into the classification system. In addition, a lesion numbering system was employed where the reviewer would designate "multiple" lesions only when he could not determine the exact number of discrete multiple lesions (for your quick reference see Appendix 2). Therefore, the classification assigned to the scans by the reviewers included this evaluation (e.g. a patient scan classified as 4B (multiple skeletal lesions) was more sensitive than a corresponding patient scan classified as 4A (single skeletal lesion).

To ensure that clinically relevant differences between scans rated with the same classification were not incorrectly designated as "concordant", the reviewers answered the question "Within the same classification, could a difference in the number and distribution of lesions between the scans potentially change or alter the clinical management of the patient?" If a consensus of the reviewers answered yes to this question, the patient scan pair was sent to panel reviewer for mediation to determine whether or not the scans should be determined to be discordant.

The results of this evaluation are described in section 5.4.10.1 of the final study report (Appendix 3). The data from these assessments for patients with metastatic disease and scans rated with the same classification are presented in Table 25.1.0 of the TSH95-0101 final report. As noted in the table, the scan pair for patient 801 was sent to panel for this reason. The panel concluded that the scans for this patient were indeed concordant.

Table 25.1.0 Concordant Scan Pairs for TSH Classification (Appendix 4)

• In Table 25.1.0 two scan pairs are listed for each patient. In reviewing this table it was determined that the order of scan data for each patient (i.e. Thyrogen then Withdrawal) was not consistent throughout the table. This has been changed and a new column ("Scan Type") has been added for clarity. As you can see, for each patient the first scan number is the always the Thyrogen scan and the second is always the Withdrawal scan. Unfortunately, this now means that the original Table 25.1.0 from the final study report is now outdated. Please replace the old Table 25.1.0 from TSH95-0101 with this updated version. Table 25.1.0

can be found on pages 342 to 346 of Volume 37/68 of the Thyrogen NDA. Sorry for this inconvenience.

• In Table 25.1.0 some patients only have a classification listed from one or two independent reviewers rather than all three. There are two reasons for this. First, if a reviewer felt that the scan was inadequate for interpretation he ended his review at that time and did not make a rating. Second, the independent reviewers had the option of not rating a scan and instead sending it to panel if they either could not determine a rating or felt that they would need additional input from the other reviewers to make a definitive rating.

• As you pointed out during our recent discussion, in Table 25.1.0 the reviewers did not always fill out the written description to be inclusive of every site of uptake observed on the scan (i.e. the description for patient 607 by CLI seems like a 3C but the rating was a 3D). In such cases the reviewers saw uptake in addition to what was written in the description, which made the classification a 3D. It is important to note that the scan pair in question was rated a 3D by all three reviewers for both the Thyrogen and W/D scans. This unanimous consensus strongly indicates that there was evidence of additional intra-thoracic disease beyond what reviewer CLI described as diffuse uptake.

• Footnotes have been added to the table you requested to explain all the abbreviations used by the independent reviewers.

I hope this information is helpful for your review. Thank you and please call me at (617) 252-7676 if you have further questions.

Sincerely,

Matthew R. Patterson
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
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