Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIGINAL SU

ORIG AMENDMENT

October 16, 1998

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin LAR® Depot (octreotide acetate for Injectable Suspension)

120-Day Safety Update Report

Dear Dr. Sobel:

Reference is made to Novartis Pharmaceuticals Corporation's New Drug Application for Sandostatin LAR® Depot indicated for long term maintenance therapy in patients who have been shown to respond to and can tolerate Sandostatin® (octreotide acetate) Injection. Specifically, Sandostatin LAR® is indicated for the reduction of growth hormone and IGF-1 in acromegaly, the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome and for the treatment of the profuse watery diarrhea associated with VIPoma (vasoactive intestinal peptide tumor). The NDA was submitted May 29, 1998.

In accordance with 21 CFR §314.50, included herein is the "120-Day Safety Update Report" from ongoing clinical studies with Sandostatin LAR®. Relative to this report, I refer to a telephone conversation with Dr. Temeck and the undersigned on September 14, 1998, in which we discussed additional data on biliary abnormalities to be included in the 120-Day Safety Update. Because of these additional analyses Dr. Temeck agreed the 120-Day Safety Update could be submitted by mid October.

The 120-Day Safety Update includes data from three additional acromegaly studies:

Study SMSC 304-E-00

An open-labeled study to extend the available information on the tolerability and safety of the long-term treatment with Sandostatin® LAR in patients who completed one of the phase-II studies, either SMSC 201 or SMSC 202

REVIEWS COMPLETED

CSO ACTION:

Study SMSC 308-E-00

An open-labeled study to extend the available information on the tolerability and safety of the long-term treatment with Sandostatin® LAR® in acromegalic patients who completed one of the phase II or phase III studies with Sandostatin® LAR®

Study SMSC 309-E-00

An open-labeled, multicentre switch study in acromegalic patients to assess the pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety of Sandostatin® LAR® manufactured at the new site of production

The safety summary for acromegaly includes an integration of safety data of patients from the original NDA Studies 201, 202, and 303 with the safety data from Studies 304 and 308. In addition safety data from the ongoing study SMSC 309 are also included but not integrated as the trial is ongoing. Also provided is a survey of the published literature on octreotide from July 1997 through June 1998 and a survey of spontaneous reports for octreotide between January 1997 and June 1998.

For the indication of Metastatic Carcinoid Syndrome no new safety data have emerged. Included in this 120-Day Safety Update is the Final Study Report for Study 451 for which 6 months of data were presented in the original NDA.

If you have any questions or comments, please contact me at (973) 781-7661.

Sincerely,

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/lat
Attachments
Submitted in duplicate

DUPLICATE

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

BM

NOVARTIS

October 9, 1998

ORIG AMENDMENT

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

IND
Sandostatin (octreotide acetate) LAR®-Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

Cross Reference: NDA No. 19-667 and NDA No.21-008

Serial No. 206

Dear Dr. Sobel:

I refer to a meeting on June 17, 1998 in which we discussed with the Division a proposed clinical trial of Sandostatin LAR® vs transphenoidal surgery in newly diagnosed or previously untreated pituitary macroadenoma patients in whom surgery was not considered a necessity. This trial was proposed to support a change in the **Indications** section of the Sandostatin® package insert and the draft Sandostatin LAR® package insert.

Although the Division felt that the proposed study was reasonable, Dr. Orloff questioned the necessity of doing the trial. Dr. Orloff suggested the sponsor review the existing data to support Sandostatin as first line treatment in appropriate patients with pituitary macroadenomas and request a meeting with the Division to discuss our findings.

Included within this submission are:

1) Introduction to the proposed changes for the **Indications** section of Sandostatin® and Sandostatin LAR® package inserts.

2) **Indications** section of Sandostatin® Injection and Sandostatin LAR® Depot package insert(s)

3) Appendices ~~A to F~~ containing references

Because the NDA for Sandostatin LAR® (NDA No. 21-008) is under review, we would appreciate the opportunity to discuss our proposal with the Division prior to finalizing the LAR labeling. We are most willing to discuss this proposal either in a face to face meeting or a telephone or video conference at your earliest convenience.

If you have any questions or comments, please contact me at (973) 781-7661.

Sincerely,

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/cs
Submitted in triplicate
Desk Copy: Jean Temeck, MD, HFD-510
David Orloff, MD, HFD-510

INDPRAMD.DOT
981007cs.doc

ORIGINAL BI

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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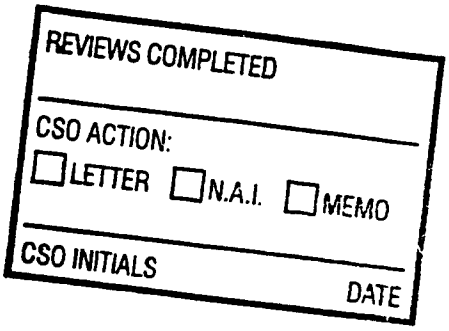
ORIG AMENDMENT

October 9, 1998

NDA 21-008
Sandostatin (octreotide acetate) LAR® Depot Injection

Response to FDA Request for Information:
Chemistry/Microbiology



Center for Drug Evaluation and Research (HFD-510)
Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

Attn: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products

Dear Dr. Sobel:

Please refer to the above cited NDA that was submitted on May 29, 1998. Please also refer to telephone discussions that took place between Dr. Brenda Uratani, the Microbiology Reviewer, and the undersigned on September 30, 1998 and October 5, 1998 during which Dr. Uratani requested additional information regarding the

This submission contains the information requested by Dr. Uratani. The information enclosed is presented as a point-by-point response to each of her requests.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-8391. If there are any general or Clinical related issues please contact Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

E. R. McCartney

APPEARS THIS WAY
ON ORIGINAL

Elizabeth R. McCartney
CMC Project Manager
Drug Regulatory Affairs

submitted in duplicate

Desk copy: Dr. Brenda Uratani, Microbiology Reviewer, Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD/160)

APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

September 28, 1998

NDA 21-008
Sandostatin (octreotide acetate) LAR® Depot Injection

Response to FDA Request for Information:
Chemistry/Microbiology

Center for Drug Evaluation and Research (HFD-510)
Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

Attn: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products

Dear Dr. Sobel:

Please refer to the above cited NDA that was submitted on May 29, 1998. Please also refer to a telefax Novartis received on August 13, 1998 from the Microbiology Reviewer, Dr. Brenda Uratani, requesting additional information regarding the sterile validation of the manufacture of the diluent and the drug product.

On September 11, 1998 Novartis provided to the Division the information requested by Dr. Uratani concerning the manufacture of the diluent. This submission contains the information requested by Dr. Uratani concerning the sterile validation of the drug product. The information enclosed is presented as a point-by-point response to the items listed in the FDA telefax.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-8391. If there are any general or Clinical related issues please contact Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

E. R. McCartney

Elizabeth R. McCartney
CMC Project Manager
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

submitted in duplicate

Desk copy: Dr. Brenda Uratani, Microbiology Reviewer (HFD/160)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BI

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

FDA Telefax

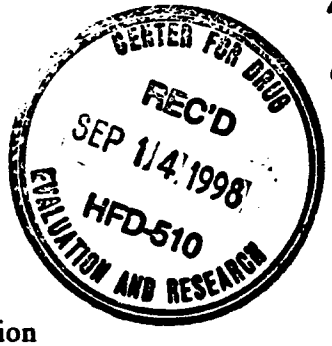
Novartis Responses

Attachment 1.b.

Attachment 1.c.

Attachment 2

Mailed
9/17/98



September 11, 1998

NDA 21-008
Sandostatin (octreotide acetate) LAR® Depot Injection

FDA Request for Information:
Chemistry/Microbiology

Center for Drug Evaluation and Research (HFD-510)
Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

Attn: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products

Dear Dr. Sobel:

Please refer to the above cited NDA that was submitted on May 29, 1998. Please also refer to a telefax Novartis received on August 13, 1998 from the Microbiology Reviewer, Dr. Brenda Uratani, requesting additional information regarding the sterile validation of the manufacture of the diluent and the drug product.

Enclosed is the sterile validation information requested by Dr. Uratani for the manufacture of the diluent. The information enclosed is presented as a point-by-point response to the items listed in the FDA telefax. The sterile validation information Dr. Uratani requested regarding the manufacture of the drug product will be provided within the next two weeks.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue, please contact me directly at (973) 781-8391. If there are any general or Clinical related issues, please contact Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

E. R. McCartney

Elizabeth R. McCartney
CMC Project Manager
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

submitted in duplicate

Desk copy: Dr. Brenda Uratani, Microbiology Reviewer (HFD/160)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

N-000 BM

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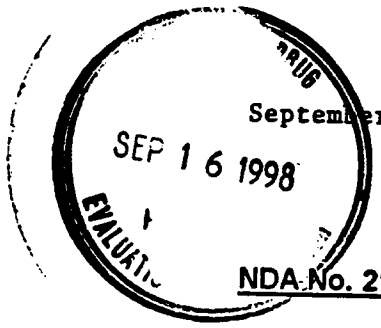
NOVARTIS



September 10, 1998

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin (octreotide acetate)
LAR® Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

I refer to telephone conversations between Dr. Jean Temeck of the Division and Mr. Robert Miranda and Steve Nettler of Novartis.

During these conversations Dr. Temeck requested some additional tables for presentation of Growth Hormone and IGF-1 data.

These tables were telefaxed on August 28, 1998 to Dr. Temeck. Included herein is an official copy for the files of the facsimiles.

If you have any questions, please contact me at (973) 781-7661.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/rah
Attachments
Submitted in duplicate
Desk Copies: Jean Temeck, MD HFD-510 (letter only)

980904rh.doc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐

CSO INITIALS DATE

BB

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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NOVARTIS

ORIGINAL

ORIG AMENDMENT

September 9, 1998

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin (octreotide acetate) LAR® Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Sobel:

I refer to a telefax dated August 14, 1998 from Dr. Robert Shore, Biopharmaceutics reviewer, in which he identified a list of studies for which he would like electronic study synopsis.

Included herein are the electronic versions of the synopsis for the following studies:

Study	Diskette #
SMSW 352 SMSW 353 SMSW 354	1. SMS FDA1.Doc
SMSE 351 SMSL 101 SMSL 102 SMSE 101	2. E351 L101 L102 E101
SMSC 201-E-00 SMSC 201-E-01/02 SMSC 202-E-00/01	3. 201-E-00 201-E-01/02 202-E-00/01
SMSC 201-E-01/02/03/04 and SMSC 202-E-~~00~~01/02/03	4. Int Pk.Doc

If you have any questions, please contact me at (973) 781-7661.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/rah
Attachments
Submitted in duplicate
Desk Copy: Robert Shore PhD, HFD-870

0908rh.doc

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS

FDA Telefax 8/14/98

Diskette #1

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

August 17, 1998

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin (octreotide acetate) LAR® Depot Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29, 1998. I also refer to a telephone conversation with Dr. Jean Temeck on August 4th in which we discussed descriptions of tables included in the ISE for acromegaly. As agreed to during the conversation we telefaxed on August 7th expanded descriptions for specific tables in the ISE which were discussed on August 4th.

Included herein is a copy of the telefax.

If you have any questions, please contact me at (973) 781-7661.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/cs
Attachments
Submitted in duplicate
Desk Copies: Jean Temeck, MD HFD-510 (letter only)

APPEARS THIS WAY

ORIGINAL

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

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Fax 973 781 6325

NOVARTIS

NDA SUPPL AMEND

July 31, 1998

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin (octreotide acetate) LAR® Depot Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29th for Sandostatin LAR® Depot Injection and to the telefax received on July 9th (Attachment 1) containing three requests from the Division of Biopharmaceutics.

I also refer to our submission dated July 16th which contained our responses to questions 1 and 2 and a partial response to question 3.

Included herein is Novartis' additional response to question 3.

Response to FDA Question 3 of July 9,1998

- **FDA Question 3:** *Only limited assay validation data (octreotide, GH, and IGF-1) are available for studies SMSC 201 and 202 (e.g., Volume 106, page 12-15). Please submit details for the assays QC's for these studies with summary evaluation of intra- and inter-day accuracy and precision.*

Novartis Response: *Please see Attachment 3 for our additional response.*

Also, for your convenience, included in Attachment 2 is a copy of our initial response to question 3 provided as part of the letter for the July 16th submission.

If you have any questions or comments, please contact me at (973) 781-7661.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/lej
Attachments
Submitted in duplicate
Desk Copies: Dr. Robert Shore HFD-870
Dr. Hae-Young Ahn HFD-870 (letter only)

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

NDA SUPPL AMENDMENT 38

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

July 16, 1998

ORIGINAL

Solomon Sobel, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-008

Sandostatin (octreotide acetate)
LAR® Depot Injection

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29th for Sandostatin LAR® Depot Injection and to the telefax received on July 9th containing the requests from the Division of Biopharmaceutics.

cluded herein are Novartis' responses to the three requests.

Response to FDA Questions of July 9,1998

- ***FDA Question 1:*** *You indicated that Origin® software was used to evaluate the PK/PD relationship. Please submit background information on this software.*

Novartis Response: On July 13th the undersigned contacted Dr. Hae-Young Ahn in the absence of Dr. Robert Shore. Dr. Ahn agreed introductory information be provided to Dr. Shore and if he needs additional information he'll contact the undersigned.

For the individual PK/PD analyses and plots was used. The software was developed and is distributed by Information regarding can be obtained on the The software is designed for data analysis and technical graphics. It operates with Windows® 95 and NT™. A professional version with enhanced graphics and analysis tools is available.

- **FDA Question 2:** *Volumes 106, 107, and 108 contain pages full of tables. Please provide a list of table titles and pages.*

Novartis Response: In the attachment is provided an Excel file listing of the tables in volumes 106, 107, and 108.

- **FDA Question 3:** *Only limited assay validation data (octreotide, GH, and IGF-1) are available for studies SMSC 201 and 202 (e.g., Volume 106, page 12-15). Please submit details for the assays QC's for these studies with summary evaluation of intra- and inter-day accuracy and precision.*

Novartis Response: Below please find summary data for the analysis of QC samples for octreotide assays conducted for studies SMSC 201-E-01 and SMSC 201-E-02, and 115 assays in studies SMS C 202-E-00 and SMSC 202-E-01. QC data for growth hormone and IGF-1 will be provided during the week of July 20th.

If you have any questions or comments, please contact me at (973) 781-7661.

Sincerely,

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/cjw
Attachments
Submitted in duplicate
Desk Copies: Dr. Robert Shore HFD-870
Dr. Hae-Young Ahn HFD-870 (letter only)

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

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
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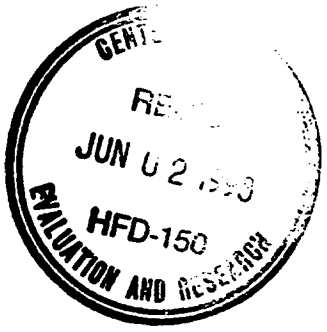
NOVARTIS



May 29, 1998

NDA No. 21-088
Sandostatin (octreotide acetate) LAR® Depot Injection
Original New Drug Application

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Dear Sir or Madam:

In accordance with 21 CFR 314.50, Novartis Pharmaceuticals Corporation herewith submits an original New Drug Application for Sandostatin (octreotide acetate) LAR® Depot Injection.

Sandostatin LAR® is indicated for long term maintenance therapy in patients who have been shown to respond to and can tolerate Sandostatin® (octreotide acetate) Injection. Specifically, Sandostatin LAR® is indicated for the reduction of growth hormone and IGF-1 in acromegaly, the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome and for the treatment of the profuse watery diarrhea associated with VIPoma (vasoactive intestinal peptide tumor). Sandostatin LAR® was studied under IND and IND

Sandostatin LAR® represents a product line extension for Sandostatin® Injection approved for malignant carcinoid tumors and VIPoma on October 21, 1988 and for acromegaly on May 3, 1994. The active ingredient, octreotide acetate, is contained in both formulations. However, Sandostatin LAR® Depot Injection represents a long acting formulation whereby the active ingredient is microencapsulated allowing patients to receive 1 injection every month instead of the usual 60-120 injections per month (bid to qid regimen) of Sandostatin® Injection.

The safety and efficacy of Sandostatin LAR® in the treatment of acromegaly is supported by five controlled and eight uncontrolled clinical trials encompassing a total of 270 patients.

In support of registration for malignant carcinoid tumors, there is one controlled clinical trial where patients were treated for 6 months duration. This was determined adequate for registration during telephone conversations with the Division of Metabolic and Endocrine Drug Products.

Although no actual trials were conducted in patients with VIPoma, the sponsor feels that appropriate dosage recommendations can be provided for VIPoma patients and the explanation is further described within this application.

During a meeting with the Division of Metabolic and Endocrine Drug Products, Dr. Sobel stated that Sandostatin LAR® represented a major contribution to the medical field and therefore would be given a priority review. Likewise, it was noted that this NDA would predominantly be a PK/PD document for review.

During a telephone conversation with Dr. Robert Shore, Biopharmaceutics reviewer, we agreed to provide an electronic submission which includes:

- Section 6 summary and all attachments
- SAS Data Sets for Clinical Pharmacology studies used to determine PK/PD characteristics of Sandostatin LAR®

Also, a paper copy of all FDA meeting minutes are provided in NDA Volume No. 116 as requested by Dr. HaeYoung Ahn, Division of Biopharmaceutics.
In addition, a diskette of the proposed package insert (PI) with annotations is provided for all reviewers.

A certified copy of Section 3 of this New Drug Application is being provided to our district office in compliance with the pre-approved inspection (PAI) requirements.

Therefore, foreign inspections, in addition to a local PAI, may be necessary.

The FDA User Fee for this application was submitted on May 8, 1998.
Also, I wish to bring to your attention that we submitted on May 21, 1998, requests for Orphan Drug designations for Sandostatin LAR® for acromegaly and malignant carcinoid syndrome and VIPoma.

Novartis considers the information contained in this application as confidential, and its contents are not to be disclosed without express written consent.

If there are any questions or comments related to Chemisty, please contact Elizabeth McCartney at 973-781-8391. All other questions or comments on this application should be directed to the undersigned at 973-781-7661.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

Submitted in duplicate

Desk Copy (Section 3)

Ms. Regina Brown, FDA NJ District PAI Coordinator
Attila T. Kadar, MD (HFC-134)
Peter H. Cooney, PhD (HFD-160)

APPEARS THIS WAY
ON ORIGINAL

NDA: 21,008
Drug: Sandostatin LAR
Sponsor: Novartis
Date: 10/27/98

APPEARS THIS WAY
ON ORIGINAL

Jena,

Please request the sponsor to submit the following information ASAP:

1. We have not yet received a revised draft PI, which reflects the discussions you have had with Dr. Temeck, the last being, Wednesday, October 21, based on the efficacy and safety data collected in studies 201, 202 and 303. Please submit this as soon as possible.

2. The draft PI should then be updated from #1 to reflect the safety information from the additional studies submitted on October 16, 1998: studies 304, 308, 309 and 451.

3. The newly occurring/worsening gallbladder abnormalities for acromegaly studies 304, 308 and 309 should be presented by individual study and analyzed as was previously done for studies 201, 202 and 303. These abnormalities should be categorized as follows: gallstones/microlithiasis (+/- also with sediment, sludge, dilatation/wall thickening); sediment/sludge without stones (+/- also with dilatation/wall thickening); dilatation/wall thickening only; separating patients taking bile-acid dissolution agents from those not on bile acid dissolution agents. Also note the number of patients in whom gallbladder polyps developed during LAR treatment.

4. Volume 20, page9-29, section 3.9, specify the ECG abnormalities in the patients referred to, and using relevant clinical information, assess the clinical significance of these findings.

5. Provide narratives on the patients in 303-E-00 who developed fatty liver and hepatocellular damage.

6. Provide narratives on the 2 patients in 201-E-04, #'s 3001 and 3004, who developed cholesterol-rich polyps as an adverse event.

7. We are awaiting clarification regarding the difference between your analysis and Dr. Temeck's regarding the median % change from baseline to study endpoint for 24 hour urinary 5-HIAA in patients enrolled in study 351.

/S/

Jean Temeck, M.D. 10/27/98

cc. NDA Arch21-008
HFD-510: Dr. Orloff, Dr. Parks and Ms. Weber
HFD-510 Div. file

APPEARS THIS WAY
ON ORIGINAL

TELECON

Russ Hume, Regulatory Liaison, **Novartis** (301-468-5604)
and
Jean Temeck, Medical Officer, DMEDP
Jena Weber, Project Manager, DMEDP
Enid Galliers, CPMS, DMEDP

23 October 1998

NDA 21-008 Sandostatin LAR (octreotide acetate depot injection)

This NDA is a PRIORITY application with a user fee goal date of November 29, 1998, and the firm submitted the complete response to the CMC deficiencies today and the Medical Officer just got the safety update (SU) that was received earlier in the week. We were unable to reach the firm's regulatory contact, Eileen Ryan; so we called Russ Hume to discuss the problems with the huge SU that almost certainly will cause a delay in the action on this NDA.

We told Mr. Hume that the 120-day SU (stamp date: Oct. 19, 1998) contained 22 volumes including four new studies, and all the safety information for the new and old studies were presented using the old (unacceptable) method of data analysis. The firm had been told approx. 6-8 weeks ago about the way in which the data had to be reanalyzed. Furthermore, the FDA was unaware that such a huge amount of new material would be submitted (SU was four weeks late).

Dr. Temeck said that the new submission had to be reanalyzed using the same method requested previously by her. The GH and IGF-1 data were only presented at baseline and end of study. She had asked for the intervening data, and they were submitted for the original NDA, but not for the SU. Other data analyses were required also.

We asked why is there no updated PI to reflect an increased incidence of adverse events. It is inconceivable that there would be no change when new studies were added to the database. Jean Temeck said that she and Eileen Ryan have done extensive re-working of the label based on the *reanalyzed* data from the original NDA.

Russ understands the problems that will cause us to run out of time (to meet the 6-month goal). In fact, he asked if the expression "shooting oneself in the foot" sounded familiar. He will try to reach Eileen Ryan today and have her contact Jean Temeck at work or at home. He will communicate the problems to her. We said that FDA wants to do everything to make this happen as quickly as possible.

Mr. Hume was disappointed to learn of this problem because he had thought that the delivery of the complete chemistry response today would keep the NDA on track, but he was very grateful for our prompt response and efforts to inform the firm quickly of the problem.

Cc: Orig. NDA
HFD-510/division file
HFD-510/JTemeck/DOrloff/SSobel/JWeber

/S/

Enid Galliers

MEMORANDUM OF T-CON

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: Friday October 30, 1998

Location: Weber's office

Between: Robert Shore, Pharm.D., Jena Weber from FDA and, Eileen Ryan from Novartis

Ref. NDA 21-008, Sandostatin LAR; 120-day Safety Update

Novartis submitted a 120-day safety update (22 volumes) which included PK/PD data. Eileen was contacted to clarify the source of this data. She indicated that the could not supply sufficient amounts of Sandostatin LAR (LAR) When the supply ran out, patients in study 308 were switched to LAR produced in the first batch (study 309). However, there were some clinical indications that patients were not responding to this product as well as the product. This was investigated. The sponsor found that the batch was not suspending properly upon reconstitution and so they added wetting agent to the formulation; this became batch 2. In order to collect clinical data on this second batch (Eileen indicated that this would be the to-be-marketed formulation), study 309 was extended. Therefore, the PK and PD data that was submitted was from patients who were stable on product and were switched to batch 1 then batch 2 from

(In a follow-up phone conversation between Dr. Shore and Eileen, Eileen stated that the data were not intended for a bioequivalence analysis. She indicated that study W354 is the only bioequivalence study of the (batch 2) products.)

/S/ 11/03/98
Robert Shore, Pharm.D.

/S/
Jena Weber, RHPM 11/3/98

APPEARS THIS WAY
ON ORIGINAL

NDA 21-008
HFD-510/RShore/JWei/HYAhn/JTemeck/MParks/CHNIU
HFD-511/JWeber

APPEARS THIS WAY
ON ORIGINAL

NOV - 3 1998

MEMORANDUM OF T-CON

Meeting Date: Monday October 26, 1998

Time: noon

Location: Weber's office

Between: Jean Temeck, M.D., Jena Weber from FDA and,
Eileen Ryan and Marion Finkel, M.D. (Consultant), Novartis

Ref. NDA 21-008, Sandostatin LAR; 120-day Safety Update - data included for 2 main indications of acromegaly and malignant carcinoid syndrome.

Novartis: (see Novartis correspondence dated October 27, 1998). Acromegaly section of 120-day update was integrated data from ORIGINAL NDA studies 201, 202 and 203, with data from studies 304 and 308. Studies 304 and 308 represent extensions of the original NDA studies. They were assigned new study numbers to distinguish them from the original NDA trials. No new safety data was generated from the extension trials. The only significant change in the safety parameters occurred with regard to the occurrence of gallstones and sludge due to additional exposure to the drug; this will be specified in a revised PI.

Dr. Finkel: study 304 & 308 furnished from other studies, only in 308 was thyroid function measured. There is no baseline value because study 308, like 304, was an extension study of the thyroid function and HbA1c and glucose abnormalities.

FDA: We would like to see the summary in table and or paragraph form.

FDA: Also, in evaluating the thyroid function, data in acromegaly patients, it is important to distinguish between those who had pituitary surgery/irridation, and those patients who had neither.

FDA: Although studies 304 and 308 are small in number, Novartis should indicate the incidence of newly occurring patients or worsening abnormalities with respect to thyroid function and glucose control. This is a clinical issue, not a statistical issue. We would like interim results and study synopsis.

FDA: Note, the table of gallbladder abnormalities submitted by Novartis on October 7, 1998, doesn't match with ISE on page 60 (see baseline and endpoint). This should be corrected.

FDA: For gallbladder abnormalities, a similar table should be provided, and a summary thereof.

Novartis: Eileen Ryan will provide written responses to our comments for the file.

/S/
11/3/98

/S/
11/3/98

NDA 21-008
HFD-510/RShore/JWei/HYAhn/JTemeck/MParks
HFD-511/JWeber

APPEARS THIS WAY
ON ORIGINAL

NDA: 21,008
Drug: Sandostatin
Sponsor: Novartis
Date: 10/28/98

Jena,

Please convey the following to the firm:

APPEARS THIS WAY
ON ORIGINAL

Regarding point #3 in our 10/27/98 fax, please provide a breakdown of the gallbladder abnormalities which occurred in studies 304 and 308 by the study (201, 202 or 303) in which the patients were initially enrolled. For example, patients enrolled in study 304 were initially enrolled in 201 or 202. For those who were initially enrolled in 201 and entered 304, the incidence of newly occurring/worsening gallbladder abnormalities was.... (follow format suggested in point 3, 10/27 fax).

/S/

Jean Temeck, M.D. 10/28/98

cc. NDA Arch 21,008
HFD-510: Dr. Orloff, Dr. Parks and Ms. Weber
HFD-510 Div. file

APPEARS THIS WAY
ON ORIGINAL

-21-008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 24, 1998

Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

APPEARS THIS WAY
ON ORIGINAL

Attention: Eileen A. Ryan
Associate Director, Drug Regulatory Affairs

Dear Ms. Ryan:

Reference is made to the orphan product application of May 21, 1998 submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (FFDCA) for the designation of Sandostatin LAR (octreotide) as an orphan product

We have completed the review of this application and have determined that Sandostatin LAR qualifies for orphan designation for the treatment of acromegaly.

Please be advised that if Sandostatin LAR were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of Sandostatin LAR as designated. Also an annual progress report must be submitted within 14 months

after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact John J. McCormick, M.D. at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan product designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-008

Novartis Pharmaceuticals Corporation
Attention: Eileen A. Ryan
Associate Director
59 Route 10
East Hanover, NJ 07936

JUN - 9 1998

Dear Ms. Ryan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sandostatin LAR (octreotide acetate)Depot Injection, 10,20,30 mg
Therapeutic Classification:	Priority
Date of Application:	May 29, 1998
Date of Receipt:	May 29, 1998
Our Reference Number:	NDA 21-008

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 28, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Jena Weber, Project Manager, at (301) 827-6422.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 6/3/98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 21-008
HFD-510/Div. Files
HFD-510/CSO/J. Weber
HFD-510/JTemeck/DOrloff/SMoore/CNiu/RSteigerwalt
DISTRICT OFFICE

Drafted by: emg/June 3, 1998/ \21008ack.nda
Final:

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL