CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

October 21, 1998

NDA 21-008
Sandostatin LAR® Depot

General Correspondence - Chemistry

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Sobel:

I refer to the Division telefax dated October 9th with chemistry questions concerning NDA No. 21-008 and specifically to question 10E in which the tradename is stated as Sandostatin LAR® Depot.

Novartis has printed revised packaging with the "new" logo (i.e., tradename).

Attached is a representative sample of the revised packaging for the 10, 20, and 30 mg package containers.

We would be most grateful if you would review these samples by Wednesday, October 28, 1998 so we may begin the process of manufacturing the packaging components.

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 Ms. Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

E. R. McCartney

Elizabeth McCartney
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Section 13: Patent Information

Octreotide acetate (the active ingredient in Sandostatin LAR), pharmaceutical compositions containing octreotide acetate, and the use of octreotide acetate in treating excess GH-secretion and gastro-intestinal disorders are claimed in US Patent No. 4,395,403, which with patent term extension expires November 21, 2002.

The Sandostatin LAR miscrosphere formulation is claimed in US Patent No. 5,538,739, which expires July 23, 2013, and US Patent No. 5,639,480, which expires June 17, 2014. The use of the Sandostatin LAR microsphere formulation in treating acromegaly is covered in US Patent No. 5,688,630, which expires November 18, 2014.

EXCLUSIVITY SUMMARY FOR NDA # 21-008 SUPPL # -

Trade Name SANDOSTATIN LAR Depot Generic Name OCTREOTIDE ACETATE FOR INJECTABLE SUSPENSION

Applicant Name NOVARTIS HFD # 510

Approval Date If Known 11/25/98

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 /✓/ 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 /✓/ 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 /✓/

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 /✓/

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 /✓/

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 /___/

APPEARS THIS WAY
ON ORIGINAL

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

NDA# 19-667 Sandostatin Injection

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 /✓/

(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 /_X_/

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:

SMSC 202-E-ØØ SMSE 351

SMSC 303-E-ØØ

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 SMSC202-E-00 YES /___/ NO /✓/
" #3 SMSE351 /___/ /✓/
Investigation #2 SMSC303-E-00 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 /✓/
" #3 /___/ /✓/
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"):

_____ _____

_____ _____

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: _____

IND /✓/ _____

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? N/A

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: _____

_____

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/16/98
Signature Date
Title: RPM

/S/ 11/25/98
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21008	**Trade Name:**	SANDOSTATIN(OCTREOTIDE ACETATE)LAR DEPOT
Supplement Number:		**Generic Name:**	OCTREOTIDE ACETATE FOR INJECTABLE SUSPENSION
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	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.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

APPEARS THIS WAY
ON ORIGINAL

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
NDA is recommended for APPROVAL; November 25, 1998

APPEARS THIS WAY
ON ORIGINAL

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENA WEBER

/S/ 11/24/98 /S/ 11/24/98

Signature Date

APPEARS THIS WAY
ON ORIGINAL

Sandostatin (octreotide acetate) LAR® Depot Injection

New Drug Application

NOVARTIS CERTIFICATION

IN COMPLIANCE WITH THE

GENERIC DRUG ENFORCEMENT ACT OF 1992

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

May 21, 1998

Date

Eileen A Ryan

Eileen A, Ryan

Associate Director

Drug Regulatory Affairs

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: **Division of** Metabolic and Endocrine Drug Products **HFD**510

Attention: Chien-Hua Niu **Phone:**827-6390

Date: June 9, 1998

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: Sandostatin LAR Depot Injection **NDA/ANDA#** 21-008

Established name, including dosage form: Octreotide acetate Depot Injection Microspheres (Depot form)

APPEARS THIS WAY
ON ORIGINAL

Other trademarks by the same firm for companion products:

Sandostatin Injection

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Indications for Use (may be a summary if proposed statement is lengthy):

Acromegaly, Malignant Carcinoid Tumores, VIPoma

APPEARS THIS WAY
ON ORIGINAL

Initial Comments from the submitter (concerns, observations, etc.):

Sandostatin LAR Depot Injection represents a long acting formulation whereby the active ingredient is allowing patients to receive 1 injection every month instead of the usual 60-120 injections per month (bid to qid regimen) of Sandostatin Injection.

APPEARS THIS WAY
ON ORIGINAL

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

November 3, 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 LAR® Depot (octreotide acetate for Injectable Suspension)

RESPONSE TO FDA REQUEST: Corrected Draft Labeling and 304/308 Gallbladder Response

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29th for Sandostatin LAR® Depot.

On October 27, 1998 a telefax was received from the Division and Novartis responses were telefaxed on October 28th. The responses to questions 1 & 2 included draft labeling for Sandostatin LAR® Depot. I also refer to a telephone discussion with Ms. Jena Weber of the Division on October 30th in which I advised her that a paragraph on gallbladder abnormalities in carcinoid patients was inadvertently left out of the draft labeling provided on October 28th. Per Ms. Weber the corrected labeling was telefaxed to her on October 30th.

In addition in a telefax dated 10/29, Dr. Temeck requested a breakdown of the patients with gallbladder abnormalities in 304 and 308 by the study in which they were originally enrolled. Novartis' response was telefaxed on October 30th.

Also on October 24, 1998 I had a discussion with Dr. Temeck in reference to the 120 Day Safety Update in which she questioned the derivation of "n" and range changes in Tables 21 and 38 respectfully. A response to these questions was telefaxed on November 2,1998.

Attached herein is an official copy of Novartis telefaxes including:

1) Telefax dated October 30, 1998: NDA No. 21-008 Corrected Labeling

2) Telefax dated October 30, 1998: NDA No. 21-008 Studies 304 and 308 GB

3) Telefax dated November 2, 1998: Responses to Dr. Temeck

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

Sincerely,

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

/rah
Attachments
Submitted in duplicate
Desk Copy - letter only: David Orloff M.D. (HFD-510)
Desk Copy - letter only: Mary Parks M.D. (HFD-510)
Desk Copy - letter only: Jean Temeck M.D. (HFD-510)
Desk Copy - letter only: Jena Weber (HFD 510)

981103rh.doc

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

October 30, 1998

ORIG AMENDMENT
3M

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 ~~LAR~~® Depot (octreotide acetate for Injectable Suspension)

RESPONSE TO FDA REQUEST: COPY OF TELEFAXED DATA

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29th for Sandostatin LAR® Depot. I also refer to telefaxes sent to the Division on October 24, 26 and 27, 1998 in response to inquiries by Dr. Temeck.

Included herein is an official copy of the telefaxes for the NDA file. These faxes include:

- October 24, 1998: **NDA No. 21-008 Patient Narratives** for acromegalic and carcinoid patients with changes in thyroid function tests and glycosylated hemoglobin. Also included was a clinical narrative for patient with cellulitis.

- October 26, 1998: **NDA No. 21-008 Patient Narratives: MISSING PAGE** (20A)

- October 24, 1998: **NDA No. 21-008 Carcinoid Gallbladder**

- October 26, 1998: **NDA No. 21-008 Miscellaneous Items**
  1) Acromegaly:
  -TFT and HbA1C listing for every patient in Study 308.

  -120 Safety Update pp32-34: During telephone conversation on Saturday, October 24th, Dr Temeck stated 304 and 308 were not included in the gallstone analyses and yet the "numbers" changed. I wish to inform you that the numbers changed because the 304 and 308 were included in the tables. Attached are copies of these same tables with a clearer legend.

  2) Carcinoid:
  -New presentation of biliary abnormalities for 351.

- October 27,1998: **NDA 21-008 Thyroid Function Tests and HbA1C**

  1) Summary tables for patient narratives on Thyroid Function Test (TFT) and HbA1C for both acromegaly and carcinoid patients.

  2) Narratives on patients with fatty liver and hepatocellular damage and

  3) Narratives for patients with gallbladder polyps.

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

/rah
Attachments
Submitted in duplicate
Desk Copy - letter only: David Orloff M.D. (HFD-510)
Desk Copy - letter only: Mary Parks M.D. (HFD-510)
Desk Copy - letter only: Jean Temeck M.D. (HFD-510)
Desk Copy - letter only: Jena Weber (HFD 510)

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 6325

October 28, 1998

ORIG AMENDMENT
BM

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 LAR® Depot (octreotide acetate for Injectable Suspension)

RESPONSE TO FDA Telefax

Dear Dr. Sobel:

I refer to our New Drug Application submitted May 29th for Sandostatin LAR® Depot. I also refer to a telefax received from Ms. Jena Weber on October 27,1998 with requests from the Division.

In response to that telefax included herein are Novartis' responses.

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

Sincerely,

Eileen A. Ryan
Associate Director
Drug Regulatory Affairs

/rah
Attachments
Submitted in duplicate
Desk Copy -David Orloff M.D., HFD-510
Mary Parks M.D., HFD-510
Jean Temeck M.D., HFD-510

BC

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

October 28, 1998

NDA 21-008
Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)

General Correspondence - Chemistry, Manufacturing and Controls

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Sobel:

Please refer to the Division telefax dated October 9th with chemistry questions concerning NDA No. 21-008 and specifically to question 10E in which the tradename is stated as Sandostatin LAR® Depot. Please also refer to the October 21, 1998 Novartis submission which included packaging with a proposed logo for the 10, 20 and 30mg containers.

Please find enclosed a new version of the proposed logo for the drug product. Please let us know at your earliest convenience if the proposed logo is acceptable.

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 Ms. Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

per clerk for Elizabeth McCartney

Elizabeth McCartney
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachment
Submitted in Duplicate

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIGINAL

October 23, 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 teleconference that Novartis had with the FDA Microbiology Reviewers, Dr. Brenda Uratani and Dr. Peter Cooney, on October 15, 1998.

Enclosed is information concerning the validation and sterile manufacture of Sandostatin LAR® Depot requested by Dr.'s Uratani and Cooney during the teleconference.

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

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

submitted in duplicate

Telefax: Dr. Brenda Uratani, Microbiology Reviewer, Division of Medical Imaging and Radiopharmaceutical Drug Products, sent on 23-Oct-98

SUBMISSIONS

ORIGINAL

NOVARTIS

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

Tel 973 781 7500
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ORIG AMENDMENT
EC

October 22, 1998

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

Response to FDA Request for Information:
Chemistry/Microbiology

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

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 October 9, 1998 from Dr. Stephen Moore, the Chemistry Team Leader, which contained a list of chemistry deficiencies and comments pertaining to NDA 21-008.

Enclosed is a point-by-point response to each of the chemistry deficiencies and comments listed in the FDA telefax. To help facilitate the review of this response, desk copies of this submission have been provided to Dr. Stephen Moore and Dr. Chien Hua Niu.

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 Ms. 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

Attachments
Submitted in Duplicate

Telefax: Dr. Robert Shore, Biopharmaceutics Reviewer, on 19-Oct-98

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 6325

ORIG AMENDMENT

Noted
Review completed BL
(See Chem. Rev. #2
for NDA 21-008)

/S/
11/5/98

October 21, 1998

NDA 21-008
Sandostatin LAR® Depot

General Correspondence - Chemistry

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
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Rockville, Maryland 20857

Attention: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Sobel:

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Attached is a representative sample of the revised packaging for the 10, 20, and 30 mg package containers.

We would be most grateful if you would review these samples by Wednesday, October 28, 1998 so we may begin the process of manufacturing the packaging components.

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 Ms. Eileen Ryan, Associate Director of Drug Regulatory Affairs at (973) 781-7661.

Sincerely,

E. R. McCartney

Elizabeth McCartney
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

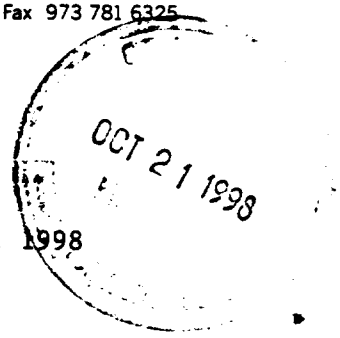
DUPLICATE

BM

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 6325



October 20, 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 our New Drug Application for Sandostatin LAR Depot submitted to the Division on May 29, 1998. During September there were discussions with Dr. Jean Temeck relative to Growth Hormone and IGF-1 control in acromegalic patients.

In response to these discussions included in this submission are:

1. A justification for presenting normalization of GH based on a basal GH level of ≤ 2.5 mg/L. This justification is supported in the published literature included herein.

2. Also included are tables for the NDA studies SMSC 201, 202 and 303 with GH < 5.0, < 2.5 and < 1.0 mg/L. For each of the studies there are two tables:

   - Using total N as the denominator to calculate percentage of GH control.

   - Using the corresponding GH denominator to calculate the percentage of patients having normalized IGF-1 with a specific reduction in GH.

Based upon the information provided in #2 above, we hope you will consider our proposal for normalization of Growth Hormone to be < 2.5 mg/L rather then < 2.0 mg/L.

In addition, as requested by Dr. Temeck for NDA studies SMSC 201, 202 and 303, we have also provided tables for GH at < 5.0, < 2.0 and < 1.0 mg/L.

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

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

981009rh.doc

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIG AMENDMENT
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October 19, 1998

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

FDA Request for Information:
Chemistry/Microbiology

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, MD, Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Sobel:

Please refer to the above cited NDA which was submitted to the Division on May 29, 1998. I also refer you to a telephone conversation between Dr. Robert Shore, the Biopharmaceutics Reviewer, Ms. Eileen Ryan, Associate Director of Novartis Drug Regulatory Affairs, and the undersigned on October 9, 1998 in which the dissolution method and proposed provisional specifications were discussed. At that time Dr. Shore requested that Novartis submit additional dissolution data for review.

Enclosed are the additional dissolution data that Dr. Shore requested: 7 batches of release data, and 6 batches of stability data.

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

cc: Ms. Jena Weber, Project Manager, Division of Metabolic and Endocrine Drug Products (HFD-510)

Desk copy: Dr. Stephen Moore, Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products (HFD-510)
Dr. Chien Hua Niu, Chemistry Reviewer, Division of Metabolic and Endocrine Drug Products (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

NOVARTIS

Novartis Pharmaceuticals Corporation
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Tel 973 781 7500
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October 19, 1998

ORIG AMENDMENT
BI

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 manufacture of the diluent, and to the point-by-point response submitted by Novartis on September 11, 1998.

Enclosed is information concerning the qualification of the autoclave used to sterilize the diluent that was requested by Dr. Uratani, but not available at the time Novartis submitted the September 11, 1998 response.

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

submitted in duplicate

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