



NDA 200677

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Sandip Roy, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Roy:

Please refer to your New Drug Application (NDA) dated February 17, 2012, received February 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Signifor (pasireotide) injection, for subcutaneous use, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL.

We acknowledge receipt of your amendments dated March 13, April 3, 12, and 18, May 8, 18, and 30, June 8, 19, 27, and 28, July 24 and 26 (2), August 7, 17, and 24, September 7, 11, and 21, October 5, 12, 16, and 17, and November 6 and 27, 2012. We further acknowledge submission via electronic mail of your revised carton and container labels on December 13, 2012. Finally, we acknowledge submission via electronic mail of the final agreed-upon content of labeling and of your final timetables for the Postmarketing Requirements described in this letter on December 14, 2012.

This new drug application provides for the use of Signifor (pasireotide) injection, for subcutaneous use, for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below and made in the enclosed labeling.

The established name will be corrected from "pasireotide diaspertate" to "pasireotide" throughout the physician labeling, Medication Guide, and Instructions for Use. The established name is already correctly shown on the carton and immediate-container labels.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide, text for the Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted via electronic mail on December 13, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 200677.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Jennifer Johnson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 3114
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of hyperglycemia, QT prolongation, adrenal insufficiency, and atypical infections, or to assess a signal of a serious risk of hepatotoxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1985-1:** A long-term prospective observational cohort study (registry) of patients with Cushing's disease treated with Signifor (pasireotide) to evaluate known and potential serious risks related to the use of Signifor (pasireotide), including serious (requiring treatment in Emergency Department, hospitalization, or death) cases of hyperglycemia, liver-related adverse events, events potentially related to QT prolongation, deaths (including causes of death), atypical infections, and adrenal insufficiency. The registry will continue for three years from the date of last patient enrollment.

The timetable you submitted on December 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2013
Interim Report Submission:	February 2014
	February 2015
	February 2016
	February 2017
	February 2018
	February 2019
	February 2020
	February 2021
	February 2022
	February 2023

February 2024
Study Completion: February 2024
Final Report Submission: November 2024

1985-2: An assessment and analysis of spontaneous reports of serious (resulting in death, hospitalization, life-threatening, or disability) hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing’s disease treated with Signifor (pasireotide) for a period of five years from the date of approval. Specialized follow-up should be obtained on these cases to collect additional information on the events.

The timetable you submitted on December 14, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 2013
Interim Report Submissions: December 2013
December 2014
December 2015
December 2016
Study Completion: December 2017
Final Report Submission: June 2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the management of the known serious risk of Signifor (pasireotide)-induced hyperglycemia.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1985-3: A multi-center, randomized, clinical trial investigating the management of Signifor (pasireotide)-induced hyperglycemia in patients with Cushing’s disease treated with Signifor (pasireotide).

The timetable you submitted on December 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: September 2013
Trial Completion: February 2018
Final Report Submission: June 2018

Submit the protocols to your IND 068635, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment

instructions and program description details at
<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Medication Guide, Instructions for Use, Carton and Container Labels for Signifor (pasireotide) subcutaneous (s.c.) Injection, 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
12/14/2012