

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125499Orig1s000

Trade Name: Plegridy prefilled syringe and Plegridy Pen prefilled pen

Generic Name: Peginterferon beta-1a

Sponsor: Biogen Idec, Inc.

Approval Date: August 15, 2014

Indications: Plegridy and Plegridy Pen are indicated for the treatment of patients with relapsing forms of multiple sclerosis.

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APPROVAL LETTER



BLA 125499/0

BLA APPROVAL

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your Biologics License Application (BLA) dated May 15, 2013, received May 16, 2013, submitted under section 351(a) of the Public Health Service Act for Plegridy (peginterferon beta-1a) prefilled syringe and Plegridy Pen (peginterferon beta-1a) prefilled pen.

We acknowledge receipt of your amendments dated:

June 11, 2013	October 2, 2013 (2)	January 27, 2014
June 14, 2013	October 4, 2013	January 31, 2014 (2)
July 8, 2013	October 9, 2013	February 7, 2014 (2)
July 17, 2013	October 28, 2013	February 14, 2014 (2)
July 24, 2013 (2)	October 29, 2013	February 19, 2014
August 1, 2013	October 31, 2013	February 20, 2014
August 2, 2013 (2)	November 8, 2013	February 28, 2014
August 5, 2013	November 15, 2013	March 7, 2014
August 8, 2013	November 26, 2013	March 14, 2014 (2)
August 12, 2013	November 27, 2013	March 31, 2014
August 20, 2013	December 2, 2013	April 2, 2014
August 22, 2013	December 13, 2013 (2)	April 10, 2014
August 26, 2013	December 17, 2013 (2)	April 30, 2014 (2)
August 27, 2013	December 30, 2013	May 2, 2014
August 29, 2013	January 10, 2014	May 8, 2014
August 30, 2013	January 13, 2014	May 15, 2014
September 5, 2013	January 14, 2014	June 6, 2014
September 10, 2013	January 15, 2014	June 11, 2014
September 17, 2013	January 17, 2014	June 12, 2014
September 23, 2013	January 23, 2014	June 25, 2014
September 30, 2013	January 24, 2014	July 22, 2014

LICENSING

We have approved your BLA for Plegridy and Plegridy Pen (peginterferon beta-1a) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Plegridy and Plegridy Pen under your existing Department of Health and Human Services U.S. License No. 1697. Plegridy and Plegridy Pen are indicated for the treatment of patients with relapsing forms of multiple sclerosis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture peginterferon beta-1a drug substance at Biogen Idec, Inc., in Cambridge, Massachusetts. The final formulated product in prefilled syringe dosage form will be manufactured, filled, labeled, and packaged at (b) (4). The prefilled pen will be assembled at Biogen Idec in Hillerod, Denmark. You may label your product in the prefilled syringe and pen with the proprietary names Plegridy and Plegridy Pen, respectively, and market it in 0.5ml of solution containing 63, 94, or 125 micrograms of peginterferon beta-1a in a prefilled syringe or prefilled pen.

DATING PERIOD

The dating period for Plegridy and Plegridy Pen shall be 36 months from the date of manufacture when stored at 5 ± 3 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C. Results of ongoing stability studies should be submitted throughout the dating period as they become available. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Plegridy/Plegridy Pen to the Center for Drug Evaluation and Research (CDER) for release by the CDER Director under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, which requires completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Plegridy and Plegridy Pen, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

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 enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, 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, Medication Guide, and Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” 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 container labels that are identical to the carton and immediate container labels submitted on June 25, 2014, 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 titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” 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 “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125499/0.**” Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for Plegridy and Plegridy Pen was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with relapsing forms of multiple sclerosis.

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.

We are waiving the pediatric study requirement for patients from birth to 9 years of age because necessary studies are impossible or highly impracticable due to the small number of patients in this age group with multiple sclerosis.

Additionally, we are deferring submission of your pediatric study for patients from ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2760-1 A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Plegridy (peginterferon beta-1a) compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Final Protocol Submission: 08/31/2015
Study Completion: 08/31/2018
Final Report Submission: 11/30/2019

Submit the protocol to your IND 100110, with a cross-reference letter to this BLA.

Submit the draft protocol at least 3 months prior to the final protocol submission date to allow for review and agreement on the protocol design.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 an unexpected serious risk of teratogenicity in humans.

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:

- 2760-2 A prospective, observational, exposure cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Plegridy (peginterferon beta-1a) during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to Plegridy in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

The timetable you submitted on May 1, 2014, and June 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/31/2015
1st interim report:	08/31/2015
2nd interim report:	08/31/2016
3rd interim report:	08/31/2017
4th interim report:	08/31/2018
5th interim report:	08/31/2019
6 th interim report:	08/31/2020
7 th interim report:	08/31/2021
8 th interim report:	08/31/2022
9 th interim report:	08/31/2023
Study Completion:	12/31/2023
Final Report Submission:	05/31/2024

Submit the draft protocol at least 4 months prior to the final protocol submission date to allow for review and agreement on the protocol design.

Submit the protocol to your IND 100110, with a cross-reference letter to this BLA. Upon submission of the final protocol, submit a supplement to BLA 125499 to update the product labeling to provide pregnancy registry information. Submit the final report to your BLA. 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 601.70 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 601.70 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 601.70. 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2760-3 Re-evaluate the acceptance criteria release and stability specifications for Plegridy (peginterferon beta-1a) drug substance (DS) and reevaluate Plegridy (peginterferon beta-1a) drug product (DP) release and stability specification acceptance limits for: cytopathic effect potency (CPE) assay, (b) (4) high molecular weight impurities as measured by size exclusion chromatography, and (b) (4) and purity as measured by reverse phase HPLC for drug product. Justify revised acceptance data using data collected from production scale Plegridy (peginterferon beta-1a) DS and DP manufactured using 30 distinct DS batches and knowledge about the clinical importance of product quality attributes. The re-evaluation will be submitted as a prior approval supplement after data is analyzed from the DP and DS batches or within three years, whichever is sooner.

The timetable you submitted on May 1, 2014, states that you will conduct this study according to the following schedule:

Submission due date: 09/30/2017

- 2760-4 Extend the Plegridy (peginterferon beta-1a) prefilled syringe leachables study from 24 months to 36 months, the intended shelf life of the product.

The timetable you submitted on May 1, 2014, states that you will conduct this study according to the following schedule:

Submission due date: 11/30/2014

- 2760-5 Reevaluate the sub-visible particulate level in Plegriidy (peginterferon beta-1a) drug product pre-filled syringe by using an orthogonal method or methods to support the results submitted in the BLA.

The timetable you submitted on May 1, 2014, states that you will conduct this study according to the following schedule:

Submission due date: 11/30/2014

Submit clinical protocols to your IND 100110 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

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 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. 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

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-approval 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc., (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (“the Program”). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ELLIS F UNGER
08/15/2014