DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125390/0

BLA APPROVAL

Amylin Pharmaceuticals, LLC
Attn: Kinnari Patel, Pharm.D, M.B.A.
Associate Director, Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) submitted under rolling review with the final major submission dated and received March 27, 2013, submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin), 11.3 mg per vial.

We acknowledge receipt of your amendments dated December 15, 2010, and October 21, 2011, and March 23, April 2, 10, and 13, May 18, and 23, July 12 and 19, August 7, and September 5, 13, 17, and 18, 2012, and February 6, March 4, 5, and 27, April 18 and 29, May 2 and 13, June 17, 18, 19, and 24, July 23 and 24, August 27, September 16, 25, 26 (2), and 27, October 4, 7, 22, 28, 29, and 31, November 5, 7, 8 (2), 11, 13, 14, 19, 21, 26, and 27, December 9 (2), 10, 16, and 27, 2013 and January 16, 17, 21 (2), 24 (2), and February 12 (2), 14, 19 (2), 20, and 21 (2), 2014. We also acknowledge receipt of your emails dated February 23 and 24, 2014, which included your agreement to our minor labeling revisions and your email dated February 24, 2014, which included the final risk evaluation and mitigation strategy (REMS) documents.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1854 to Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb Company), Princeton, NJ, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Myalept (metreleptin). Myalept (metreleptin) is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture metreleptin drug substance (b) (4) and metreleptin final drug product (b) (4) Drug product labeling and packaging will be done (b) (4)
You may label your product with the proprietary name, Myalept, and will market it as a lyophilized product in a presentation of 11.3 mg per vial to deliver metreleptin 5 mg per mL. It is a single dose vial when reconstituted with 2.2 mL of water for injection (WFI) or a multi-dose vial when reconstituted with 2.2 mL of bacteriostatic water for injection (BWFI).

DATING PERIOD

The dating period for Myalept (metreleptin) drug product (11.3 mg per vial) shall be (b) (4) from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date (b) (4) of the formulated drug product. The dating period for your metreleptin (b) (4) shall be (b) (4) The dating period for your metreleptin drug substance shall be (b) (4) from the date of manufacture (b) (4)

Consistent with 21 CFR 601.12, Amylin must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

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 to 60 months under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Myalept (metreleptin) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring 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 Myalept (metreleptin), or in the manufacturing facilities, will require the submission of information to your biologics license application 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, text for the 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, 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 125390/0**." 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.

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(s) 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 Federal Food, Drug, and Cosmetic Act (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 signals of the serious risks of pancreatitis; serious adverse hepatic events; severe hypoglycemia; hypersensitivity reactions; autoimmune disease; adverse pregnancy outcomes; lymphoma and other cancers; and the serious risks resulting from neutralizing antibody formation, including immunodeficiency, which could result in serious infections.

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 these serious risks.

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

1. A long-term prospective observational study (product exposure registry) of patients treated with Myalept (metreleptin), regardless of indication, to evaluate serious risks related to the use of Myalept (metreleptin), by indication, including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, lymphoma, all cancers (excluding non-melanoma skin cancer) by cancer type , exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death). After agreement with FDA on a targeted sample size, the registry will include patients prescribed Myalept (metreleptin) and will continue for 10 years from the date of last patient's enrollment, or September 2029, whichever is later.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2014
Interim Report Submission:	September 2015
	September 2016
	September 2017
	September 2018
	September 2019
	September 2020

September 2021
September 2022
September 2023
September 2024
September 2025
September 2026
September 2027
September 2028
September 2029

Study Completion: September 2029
Final Report Submission: March 2030

2. To develop, validate, and implement a ligand binding assay to supplement the neutralizing bioassay that tests for the presence of neutralizing antibodies in serum samples from patients with generalized lipodystrophy.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

   Final Report Submission: March 2016

3. To test all banked clinical samples from pivotal clinical trials NIH 991265/20010769 and trial FHA101 for the presence of neutralizing antibodies against leptin using the ligand binding assay developed and validated under PMR#2, and to correlate neutralizing antibodies with clinical events.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

   Final Report Submission: August 2016

4. To conduct a study to assess for the immunogenicity of Myalept (metreleptin) in a relevant number of patients receiving metreleptin. The study should include testing for anti-metreleptin and anti-native human leptin binding antibodies at times when antibody responses peak, using a validated assay. The presence of neutralizing antibodies should be assessed using a validated cell-based assay and a validated ligand-binding assay in samples that are confirmed positive for binding antibodies to leptin. All patients with suspected loss of metreleptin efficacy (e.g., worsening glycemic control, increases in triglycerides) or loss of endogenous leptin activity (e.g., severe infections) should be tested for neutralizing activity and followed at least until antibody levels revert to baseline. Antibody titers, neutralizing activity, and associated clinical events should be characterized over time.

The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2014
Study Completion:	December 2021
Final Report Submission:	December 2022

5. An assessment and analysis of spontaneous reports of serious risks related to the use of Myalept (metreleptin) including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death) in patients treated with Myalept (metreleptin) regardless of indication for 10 years from the date of approval.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2014
Interim Report Submission:	March 2015
	September 2015
	March 2016
	September 2016
	March 2017
	September 2017
	March 2018
	March 2019
	March 2020
	March 2021
	March 2022
	March 2023
Study Completion:	May 2024
Final Report Submission:	July 2024

6. To determine the approximate percent of potential impurities derived from the *E. coli* cell line used to manufacture metreleptin that are detected by the ELISA to assess for host cell proteins (HCP) in metreleptin drug substance using a sensitive and discriminating assay such as 2D gel electrophoresis to detect impurities that can lead to increased immunogenicity. If the currently validated assay does not detect a majority of proteins distributed evenly throughout a 2D gel electrophoresis or equivalent method, then a new assay to detect HCP will be developed, validated, and implemented. If the current assay provides adequate HCP detection then a protocol for qualification of new HCP kits will

be developed, validated, and implemented. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: May 2014

7. To confirm the in-use stability of metreleptin drug product (DP) reconstituted in bacteriostatic water for injection containing 0.9% benzyl alcohol (BFWI) with data derived from three additional DP lots, to assess aggregate formation which can impact immunogenicity.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

   Final Report Submission: November 2014

Submit the protocol(s) to your IND 050259, with a cross-reference letter to this BLA. Submit all final report(s) 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:

8. To develop, validate, and implement a suitable assay for the assessment of the genetic stability of metreleptin Working Cell Bank (WCB).

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

   Final Report Submission: April 2015

9. To develop, validate, and implement the quantitative Polymerase Chain Reaction (qPCR) method to detect *E.coli* DNA impurities in drug substance lots. Information demonstrating successful additional validation of the current method may be provided in lieu of developing, validating, and implementing a new method. The revised specification together with the validation information will be submitted to your BLA in accordance with 21 CFR 601.12.

   The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

   Final Report Submission: February 2015

10. To revise Myalept drug product (DP) release and stability specifications acceptance limits for: purity and impurities by reverse phase-high performance liquid chromatography RP-HPLC, metreleptin content by ultra-violet (UV) Spectrophotometry and potency using water for injection (WFI) as diluent and total oligomer content after reconstitution with bacteriostatic WFI containing 0.9% benzyl alcohol (BWFI). Data collected from 20 production scale Myalept DP lots and knowledge about the clinical importance of product quality attributes will be used to justify the revised acceptance criteria. The revised specifications together with supporting information will be submitted to your BLA in accordance with 21 CFR 601.12.

    The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

    Final Report Submission: June 2019

11. To characterize subvisible particles (SVPs) in the (b) (4) size range in metreleptin drug product for release, stability, and under forced or stressed degradation conditions. Results of these studies will be used to assess the risk of SVPs to patients and propose an appropriate strategy for controlling SVP.

The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2017

12. To develop a two-tiered reference material (RM) system comprised of a primary and working RMs that are representative of clinical trial and production material. The working RM will be used for testing of production lots and will be calibrated against the primary reference material.

    The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

    Final Report Submission: March 2015

13. To assess the impact of drug product container closure extractables and leachables on product quality, by (1) determining the extractable substances of both the stopper and vials containing reconstituted drug product (b) (4) and (2) providing detailed data (number of tested vials, method description) on leachable studies to support the summary results in Table 4a-1, submitted on November 7, 2013, as part of your response to the FDA information requests (IR) sent on October 8, 2013. The drug product should be reconstituted in the presence and absence of benzyl alcohol to conduct these studies.

    The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

    Final Report Submission: May 2018

14. To perform studies to determine the minimum leak size detectable by the dye and microbial ingress container closure integrity test methods. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

    The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

    Final Report Submission: December 2014

15. To verify the reliability of the LAL endotoxin assay by conducting endotoxin spiking studies with three undiluted drug product lots. The drug product lots will be spiked with endotoxin levels close to the specification acceptance criterion, and held for up to 8 days

before being assayed. The final report will be submitted to the BLA in accordance with 21 CFR 601.12.

The timetable you submitted on February 14, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2014

Submit clinical protocols to your IND 050259 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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Myalept (metreleptin) to ensure the benefits of the drug outweigh the risks of developing anti-metreleptin antibodies with neutralizing activity and the risk of lymphoma.

Pursuant to 505-1(f)(1), we have also determined that Myalept (metreleptin) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks, which are listed in the labeling. The elements to assure safe use will help ensure that the benefits of the drug outweigh the risks by educating prescribers about the development of anti-metreleptin antibodies with neutralizing activity, the serious adverse sequelae that may result from these antibodies, and the risk for lymphoma associated with Myalept (metreleptin), and by limiting the population exposed to Myalept (metreleptin) by requiring that healthcare providers who prescribe Myalept (metreleptin) are specially certified, pharmacies that dispense Myalept (metreleptin) are specially certified, and prescribers attest that each patient has a diagnosis consistent with the approved indication.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted via email on February 24, 2014, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Myalept (metreleptin) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

For all categories, provide data for the reporting period and cumulatively.

1. REMS Program Outreach
    a. Number of Introductory Information Sheets *(Myalept REMS Program: An Introduction)* provided to prescribers and stratified by method of distribution.
    b. Number of unique visits to the Myalept REMS website.
2. REMS Program Utilization Statistics
    a. Prescriber Utilization
        i. Number and specialties of certified prescribers, type of practice setting, and method of enrollment
        ii. Volume of prescriptions stratified by prescriber and specialty
        iii. Summary and analysis of neutralizing antibody testing requested by prescribers
    b. Pharmacy Utilization
        i. Number of certified pharmacies
        ii. Total number of prescriptions dispensed by each certified pharmacy
    c. Patient Utilization
        i. Number of patients who have received at least one prescription for Myalept
        ii. Number of patients with a completed Prescription Authorization Form who have not received a dispensed prescription for Myalept
        iii. Time between receipt of Prescription Authorization Form and prescription dispensing (mean, median, range) and an analysis summarizing any reasons for delays that are related to the Myalept REMS Program requirements.
        iv. For i and ii, provide demographics of patients including age and gender

v. Duration of Myalept therapy for patients (mean, median, range)

vi. Number of patients who discontinued you treatment and duration of treatment (mean, median, range)

3. Program Infrastructure and Performance

a. Summary of call center Frequently Asked Questions

b. Summary of program problems reported

c. Number of prescriptions written by non-certified prescribers

d. Number of prescriptions dispensed by non-certified pharmacies

e. Number of prescriptions dispensed to patients without a completed Prescription Authorization Form.

f. Number of prescribers inactivated for noncompliance with the Myalept REMS Program requirements. Include summary of reasons for inactivation

g. Number of pharmacies inactivated for noncompliance with the Myalept REMS Program requirements. Include summary of reasons for inactivation

h. A summary report of serious or critical deviations found, and corrective actions taken for any certified pharmacy audits conducted during the reporting period.

4. Assessment of Prescribers and Pharmacists understanding of the following:

BMS will conduct healthcare provider surveys at 1 and 2 years after initial approval of the REMS. The surveys will evaluate understanding of:

a. The risks of metreleptin

i. Serious adverse events resulting from the development anti-drug antibodies with neutralizing activity

ii. Lymphoma

b. The appropriate use of metreleptin

c. The metreleptin REMS program requirements

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125390 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125390 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125390
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125390
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions

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 Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation Research

Enclosures:

- Content of Labeling
  - Package Insert
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling
  - Vial Label
  - Vial Carton Label
- REMS
  - Myalept REMS
  - Prescriber Enrollment Form
  - Prescription Authorization Form
  - Prescriber Training Module
  - Myalept REMS Program: An Introduction
  - Myalept REMS website screen shot

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

/s/

MARY H PARKS
02/24/2014