DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203568/S-009

SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION

PPD, Inc.
Agent for Kastle Therapeutics
Attention: George Hemsworth, Ph.D.
Senior Director, Clinical Regulatory Consulting
2400 Research Blvd.-Suite 200
Rockville, MD 20850

Dear Dr. Hemsworth:

Please refer to your supplemental New Drug Application (sNDA) dated and received July 8, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kynamro (mipomersen) injection, 200 mg/mL.

This Prior Approval sNDA was submitted in response to and proposes modifications described in our Safety Labeling Change Notification/REMS Modification Notification letter dated March 11, 2016. The labeling changes to comply with this notification were approved in supplement-008 on May 23, 2016.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Kynamro (mipomersen) was originally approved on January 29, 2013, and the most recent modification was approved on July 28, 2015. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to ensure that the benefits of Kynamro (mipomersen) outweigh its risks, we determined that you were required to make the REMS modifications outlined in our Safety Labeling Change Notification/REMS Modification Notification letter issued on March 11, 2016, which included modifications to the REMS document, changes to the existing REMS materials, and the following new REMS materials: Patient Guide and Patient-Prescriber Acknowledgement Form.

Your proposed modified REMS, submitted on July 8, 2016, as amended and appended to this letter, is approved.

You must implement the modifications to the REMS program within 60 calendar days from the date of this letter. Prescribers and pharmacies have 180 calendar days from the date of this letter to complete the recertification process.

The timetable for submission of assessments of the REMS remains the same as that approved on January 29, 2013.

In order to align with the modified REMS, the REMS assessment plan must be revised. The revised REMS assessment plan must include, but is not limited to, the following:

1. **Knowledge, Attitudes, and Behavior (KAB) Surveys of Prescribers**

   A KAB Survey will be conducted with a random sample of certified prescribers to assess their awareness and understanding of the indication for use, the risk of hepatotoxicity, including appropriate evaluation, monitoring and counseling to minimize this risk, as described in the Prescribing Information (PI), Fact Sheet, and the Prescriber Training Module. The survey will also assess prescribers' awareness of the Kynamro REMS Program materials and knowledge of requirements of the Kynamro REMS Program. In the event of substantive changes to the methodology and protocol for the KAB Survey, or the survey instrument, these documents will be provided to the FDA at least 90 days before the survey is administered.

   The protocol will include:

   a. the target sample size and precision estimates associated with that sample size;

   b. a description of the methodology for recruitment and selection of the prescriber sample;

   c. the specific criteria that will be used to select participants in the survey;

   d. a description of how and when the surveys will be administered;

   e. an explanation of the design features and controls that will be included to minimize bias and compensate for limitations in the methodology; and

   f. a copy of the survey questionnaire.

   Survey results will be provided in each annual REMS Assessment Report starting with the second assessment report following the approval of the modification to the Kynamro REMS Program, due to be submitted on or before January 29, 2019.

2. **Survey to Evaluate Patient Knowledge**

   A survey to evaluate the understanding of patients on their understanding of the REMS goal about the risk of hepatotoxicity and the need for baseline and periodic monitoring will be performed and the data included in the second assessment report following the approval of the modification to the Kynamro REMS Program, due to be submitted on or before January 29, 2019. The protocol or survey instrument will be provided to the FDA at least 90 days before the survey is implemented.

3. **Additional REMS Metrics**

The REMS Assessment will also include evaluation of the following program metrics:

a. Communications with certified prescribers and certified pharmacies:

i. The date of mailing and number of recipients of the REMS Letter for Healthcare Providers and REMS Letter for Pharmacists.

ii. The number of mailings returned.

iii. A copy of all documents included in each mailing.

iv. Summary of issues and complaints received by Kynamro REMS Program Call Center; summary of resolution of the issues and complaints.

v. Summary of the reasons (and numbers per reason) for calls into the Kynamro REMS Program Call Center.

b. Prescriber Certification:

i. The number of Healthcare Prescribers certified (and the number of prescribers that were certified at the time of a requirement for re-certification was instituted) in the Kynamro REMS Program (during the reporting period and cumulatively) and stratified by prescriber degree, practice setting (i.e., type of practice and geographic location) including a full breakdown of prescribing specialties contained in the "other" category.

ii. Volume of prescriptions for each prescriber and each specialty, including a full breakdown of prescribing specialties contained in the "other" category.

iii. Specialties of the "high volume" prescribers, i.e., those who write more than 4 prescriptions in an assessment period and cumulatively, including a full breakdown of prescribing specialties contained in the "other" category.

iv. A summary of the method prescribers used to enroll (fax, email) during the reporting period and cumulatively.

v. Number of healthcare providers that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

c. Wholesaler/Distributor Authorization:

   i. The number of wholesalers/distributors that were authorized in the REMS program during the reporting period and cumulatively.

   ii. Number of wholesalers/distributors that had their authorization revoked during the reporting period and cumulatively and the reason for the revocation.

   iii. The number of Kynamro orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size and dosage strength.

   iv. Number of Kynamro orders shipped to non-certified pharmacies.

d. Pharmacy Enrollment:

   i. The number of pharmacies that were certified (and the number of pharmacies that were certified at the time of a requirement for re-certification was instituted that recertified) in the REMS program during the reporting period and cumulatively.

   ii. Number of pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

e. Pharmacy Metrics:

   i. The number of new prescriptions received, and the number that were not accompanied by the Kynamro REMS Program Prescription Authorization Form.

   ii. The number of prescriptions dispensed for Kynamro, including quantity of capsules (mean, minimum, maximum) and dosage strength, during the reporting period and cumulatively, overall and subset by compliance with the Kynamro REMS Program requirements (e.g., received from Kynamro certified vs. non-certified healthcare providers, number of initial prescriptions dispensed without a signed attestation on the Kynamro REMS Program Prescription Authorization Form). Dispensing details are to be obtained from the pharmacies.

   iii. The number of instances certified pharmacies dispensed Kynamro using a prescription that was not accompanied by a Kynamro REMS Program Patient-Prescriber Acknowledgement Form.

iv. Information on the number of prescribers who have submitted an altered Kynamro REMS Program Prescription Authorization Form (and what alterations were made).

v. Number of instances certified pharmacies dispensed Kynamro in response to a prescription received on an altered Kynamro REMS Program Prescription Authorization Form.

vi. The number and demographics (e.g., including gender, age, geographic location) of unique patients who received Kynamro during the reporting period and annually. The number is to be calculated by reconciling orders dispensed to unique patients.

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

viii. The number of prescriptions pending and canceled, as well as the reason for prescriptions pending and canceled.

ix. Specific criterion used to classify a prescription as canceled.

x. Report of number, length, and reasons for shipment delays to patients and whether or not these reasons were related to the REMS, and any additional information from insurance payers as to what they are stating as the reason for delay/non-payment.

xi. Percentage of fill delays that involve new prescriptions versus refills.

xii. Detailed description of root cause of noncompliance with REMS program-required dispensing and any corrective and/or preventive actions taken to address noncompliance during the reporting period and cumulatively.

f. With regard to the risk of hepatotoxicity associated with Kynamro, provide an analysis of the post-marketing cases of specific hepatic adverse events reported in association with Kynamro to Kastle during the reporting period and cumulatively, including outcome.

g. Specification of measures that would be taken to increase awareness if prescriber surveys indicate that prescriber awareness of the risks associated to Kynamro is not adequate.

4. 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 one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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:

NDA 203568 REMS ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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.

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

NDA 203568 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 203568/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203568/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203568/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 203568/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page

of the submission:

REMS REVISIONS FOR NDA 203568

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

REPORTING REQUIREMENTS

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

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
KYNAMRO REMS Document
KYNAMRO REMS Materials:

- KYNAMRO REMS Program: An Introduction
- KYNAMRO REMS Program Prescriber Certification Training Module and Knowledge Assessment
- Prescriber Enrollment Form
- KYNAMRO REMS Program Patient Guide
- Patient-Prescriber Acknowledgment Form
- Prescription Authorization Form
- REMS Letter for Healthcare Providers
- KYNAMRO REMS website
- KYNAMRO REMS Program Pharmacy Certification Training Module and Knowledge Assessment
- Pharmacy Enrollment Form
- REMS Letter for Pharmacists

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

/s/

JAMES P SMITH
10/25/2017