CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203568Orig1s000

Trade Name: **Kynamro Injection 200 mg/mL**

Generic Name: **Mipomersen Sodium**

Sponsor: **Genzyme Corporation**

Approval Date: **January 29, 2013**

Indications: Provides for the use of Kynamro (mipomersen sodium) Injection as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoproteincholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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APPLICATION NUMBER:

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203568

NDA APPROVAL

Genzyme Corporation
Attention: Jill Hillier, PhD
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Hillier:

Please refer to your New Drug Application (NDA) dated March 29, 2012, received March 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kynamro (mipomersen sodium) Injection, 200 mg/mL.

We acknowledge receipt of your amendments dated April 4, 11, and 12, May 11 and 25, June 4, 8, and 20, July 12, 16, and 25, September 5, 6, 11,13,14, 25, and 28, October 1, 3, and 24, November 30, December 20, 2012, and January 29, 2013. We also acknowledge receipt of your emails dated January 14, 23, 24, and 25, 2013, that includes the agreed-upon labeling.

This new drug application provides for the use of Kynamro (mipomersen sodium) Injection as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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 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, Instructions for Use (vial presentation), Instructions for Use (prefilled syringe]. 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.

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

EXPIRY DATING PERIOD

Sufficient stability data has been submitted to support a 30-month expiration date for the glass vial presentation and an 18-month expiration date for the prefilled glass syringe presentation when stored at 2-8°C (36-46°F).

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-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 *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 "**Final Printed Carton and Container Labels for approved NDA 203568**." 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.

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 a known serious risk of hepatic transaminase elevations and hepatic steatosis, or to assess signals of a serious risk of

malignancy (hepatocellular adenoma or carcinoma, and fibroma, fibrosarcoma, and fibrous histiocytoma of the skin and subcutis), or to identify an unexpected serious risk when available data indicate the potential for a serious risk of immune-mediated disorders.
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:

1999-1 Development and validation of a sensitive assay to assess for the presence of antibodies to double-stranded (ds) DNA to allow for testing of patients treated with Kynamro (mipomersen sodium).

The timetable you submitted on January 23, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: December 31, 2013

1999-2 A study to assess for the presence of antibodies that bind native double-stranded (ds) DNA among patients treated with Kynamro (mipomersen sodium). The study may be conducted with stored serum samples from patients treated with Kynamro (mipomersen sodium) in the clinical development program, but should include samples from patients who test negative as well as patients who test positive for antibodies to mipomersen. Among patients who develop anti-drug antibodies, samples should be included from patients shortly after seroconversion as well as from sustained responders.

The timetable you submitted on January 23, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: July 31, 2014

1999-3 A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Kynamro (mipomersen sodium) to evaluate known and potential serious risks related to the use of Kynamro (mipomersen sodium), including hepatotoxicity (hepatic transaminase elevations, hepatic steatosis), malignancy (hepatocellular adenoma and carcinoma, and fibroma, fibrosarcoma, and fibrous histiocytoma of the skin and subcutis), and new diagnoses of autoimmune disorders (lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, glomerulonephritis). The registry will include a sample of patients prescribed Kynamro (mipomersen sodium) and continue for 10 years from the date of last patient enrollment.

The timetable you submitted on January 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 29, 2013
Interim Report Submissions:	November 29, 2014
	November 29, 2015
	November 29, 2016
	November 29, 2017
	November 29, 2018
	November 29, 2019
	November 29, 2020
	November 29, 2021
	November 29, 2022
	November 29, 2023
	November 29, 2024
	November 29, 2025
Study Completion:	November 29, 2026
Final Report Submission:	May 29, 2027

1999-4 An assessment and analysis of spontaneous reports of serious hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with Kynamro (mipomersen sodium) for a period of 10 years from the date of approval. Specialized follow-up should be obtained on these cases to collect additional information on the reports.

The timetable you submitted on January 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 29, 2013
Interim Report Submissions:	February 28, 2014
	August 29, 2014
	February 28, 2015
	August 29, 2015
	February 28, 2016
	August 29, 2016
	February 28, 2017
	February 28, 2018
	February 28, 2019
	February 28, 2020
	February 28, 2021
	February 28, 2022
	February 28, 2023
	February 28, 2024
Study Completion:	November 29, 2024
Final Report Submission:	May 29, 2025

Submit the protocols to your IND 070969, 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.

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 Kynamro (mipomersen sodium) to ensure the benefits of the drug outweigh the risk of hepatotoxicity.

Pursuant to 505-1(f)(1), we have also determined that Kynamro (mipomersen sodium) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of elevated liver transaminases and hepatic steatosis, a risk factor for advanced liver disease including steatohepatitis and cirrhosis, that are listed in the labeling. The elements to assure safe use will educate prescribers about the risk of hepatotoxicity associated with the use of Kynamro (mipomersen sodium), the need to monitor patients during treatment with Kynamro (mipomersen sodium) as per product labeling, and to restrict access to therapy with Kynamro (mipomersen sodium) to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

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 on January 29, 2013, 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 Kynamro (mipomersen sodium) into interstate commerce.

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

1. A survey study to evaluate healthcare providers' knowledge of the risk of hepatotoxicity associated with the use of Kynamro (mipomersen sodium), the need to monitor liver-related laboratory tests before and during treatment with Kynamro (mipomersen sodium) as described in product labeling, and that FDA's determination of the safety and efficacy of Kynamro (mipomersen sodium) is limited to patients diagnosed with homozygous familial hypercholesterolemia.

    a. The target level of healthcare provider knowledge for each educational goal of the REMS.

    b. If the target levels for healthcare provider knowledge are not met, provide possible causes for the deficiencies and proposed measures to improve knowledge.

2. An assessment of enrollment in the Kynamro REMS Program, including the following:

    a. Number of healthcare providers certified during the reporting period and cumulatively

        i. Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location)
        ii. Volume of prescriptions for each prescriber and each specialty

    b. Number of pharmacies certified during the reporting period and cumulatively.

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

3. Metrics regarding Kynamro (mipomersen sodium) distribution and dispensing to assess pharmacy compliance with the Kynamro REMS:

    a. The number of Kynamro (mipomersen sodium) orders shipped to pharmacies during the reporting period and cumulatively, including number of cartons, carton size, number of vials, and number of pre-filled syringes.

b. Pharmacy compliance with Kynamro REMS Program requirements (e.g., shipped to a Kynamro REMS-certified pharmacy versus a non-certified pharmacy).

c. The number of prescriptions dispensed for Kynamro (mipomersen sodium), including quantity of vials and quantity of pre-filled syringes, during the reporting period and cumulatively, overall and subset by compliance with the Kynamro REMS Program requirements (e.g., received from Kynamro REMS-certified versus non-certified healthcare providers, number of prescriptions dispensed without a signed attestation on the Kynamro *Prescription Authorization Form*). Dispensing details are to be obtained from the pharmacies.

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

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

f. Report of number, length, and reasons for shipment delays to patients.

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

4. Summary of issues and complaints received by Kynamro REMS coordinating center; summary of resolution of the issues and complaints.

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 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.

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.

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 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:

NDA 203568 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 203568
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203568
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 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.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Acting Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Package Insert
Medication Guide
Instructions for Use (vial)

- Instructions for Use (Prefilled Syringe)
- Carton and Container Labeling
  - Vial Container Label
  - Vial Carton Label (single and 4-pack)
  - Prefilled Syringe Container Label
  - Prefilled Syringe Lid
  - Prefilled Syringe Carton Label (single and 4-pack)
- REMS
  - Prescriber Training slide set
  - Summary of Monitoring Recommendations
  - Prescriber Enrollment Form
  - Prescription Authorization Form
  - Dear Healthcare Provider Letter
  - Dear Professional Association Letter
  - Healthcare Professional Information Brochure
  - Web site 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/

CHRISTINE P NGUYEN
01/29/2013