CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203568Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 29, 2013

Reviewer(s): Cynthia LaCivita, Pharm.D., Risk Management Analyst, Team Leader, Division of Risk Management (DRISK)
Joyce Weaver, Pharm.D., Risk Management Analyst, DRISK
Kate Heinrich Oswell, M.A., Health Communications Analyst, DRISK

Division Director: Claudia Manzo, Pharm.D., Director DRISK

Subject: Evaluation of the proposed REMS

Drug Name(s): Kynamro™ ( mipomersen)

Therapeutic Class: Cholesterol-lowering agent

Dosage and Route: 200mg once weekly subcutaneous injection

Application Type/Number: 203568

Applicant/sponsor: Genzyme

OSE RCM #: 2012-793

*** This document contains proprietary and confidential information that should not be released to the public. ***
1 INTRODUCTION
This review documents DRISK’s evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for Kynamro™ ( mipomersen), new drug application (NDA) 203568. Genzyme is seeking approval of Kynamro, the agreed upon indication is as an adjunct to tolerated 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) in individuals with homozygous familial hypercholesterolemia (HoFH).

2 MATERIALS REVIEWED
- Genzyme’s REMS amendment to the proposed modification, submission received on January 29, 2013, sequence no 0024.
- Email submissions to amend the proposed REMS received on January 10, 21, 22, and 28, 2013
- DRISK Review in DARRTS, dated December 19, 2012 by Joyce Weaver evaluating the proposed REMS

3 RECOMMENDATIONS

DRISK finds the REMS and REMS Supporting Document to be acceptable. DRISK recommends approval of the Kynamro REMS.

Attachment: Kynamro REMS
I. GOALS

The goals of the KYNAMRO REMS Program are:

- To educate prescribers about:
  - the risk of hepatotoxicity associated with the use of KYNAMRO; and
  - the need to monitor patients during treatment with KYNAMRO as per product labeling.

- To restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

II. REMS Elements

A. Elements to Assure Safe Use (ETASU)

1. Healthcare Providers (HCP) who prescribe KYNAMRO are specially certified.

   a. Genzyme will ensure HCPs who prescribe KYNAMRO are specially certified.

      To become specially certified to prescribe KYNAMRO, prescribers must enroll in the KYNAMRO REMS Program. Prescribers must complete the following requirements:

      i. Review the Prescribing Information (PI).
ii. Complete the KYNAMRO REMS prescriber training by reviewing the materials in the KYNAMRO REMS Prescriber Education and Enrollment Kit.

iii. Complete and sign the Prescriber Enrollment Form and submit it to the KYNAMRO REMS Program.

b. Genzyme will:

i. Ensure that the KYNAMRO REMS Prescriber Education and Enrollment Kit is available through the REMS website at www.KynamroREMS.com or from the KYNAMRO REMS Program coordinating center at 877-596-2676. The KYNAMRO REMS Prescriber Education and Enrollment Kit consists of:
   - the PI,
   - Prescriber Training slide set,
   - Summary of Monitoring Recommendations,
   - Prescriber Enrollment Form, and
   - Prescription Authorization Form.

ii. Ensure that prescriber enrollment can be completed by faxing the forms to the KYNAMRO REMS Program coordinating center at 877-778-9008.

iii. Ensure that HCPs complete the Prescriber Training and the Prescriber Enrollment Form before activating prescribers’ certification in the KYNAMRO REMS Program.

iv. Ensure that prescribers are notified when they have been successfully certified by the KYNAMRO REMS Program.

v. Inform certified prescribers following substantive changes to the KYNAMRO REMS or KYNAMRO REMS Program. Substantive changes include: significant changes to the operation of the KYNAMRO REMS Program or changes to the PI that affect the risk-benefit profile of KYNAMRO.

vi. To facilitate prescriber certification, Genzyme will communicate information to HCPs and professional associations through the KYNAMRO REMS Program website and Dear Healthcare Provider and Dear Professional Association letters.
1) **Dear Healthcare Provider** letter - Genzyme will distribute a *Dear Healthcare Provider* letter within 60 days of KYNAMRO REMS approval to inform potential prescribers about the REMS and the REMS requirements. The *Dear Healthcare Provider* letter will be distributed to HCPs certified by the American Board of Clinical Lipidology, directors of apheresis centers, and to HCPs known to be experienced in treating patients with HoFH. The letter will be accompanied by the PI, the *Healthcare Professional Information Brochure*, and the *Summary of Monitoring Recommendations* and will be available from the KYNAMRO REMS Program website (www.KynamroREMS.com) at the time of the mailing and will remain on the website for 12 months after the mailing, or can be requested from the KYNAMRO REMS Program coordinating center by phone at 877-596-2676. Genzyme will distribute the letter via electronic mail, mail, or facsimile.

2) **Dear Professional Association** letter - Genzyme will send a *Dear Professional Association* letter within 60 days of KYNAMRO REMS approval to the leadership of the following professional associations and will request that these associations disseminate the content of the letter to their professional membership:

   a) National Lipid Association
   
   b) The Endocrine Society
   
   c) The American Association of Clinical Endocrinologists
   
   d) American Heart Association
   
   e) American College of Cardiology
   
   f) American Society of Preventive Cardiology
   
   g) Preventive Cardiology Nurses Association
   
   h) American Society for Apheresis

The letter will be provided to MedWatch at the same time it is provided to the professional associations.
3) KYNAMRO REMS website - A KYNAMRO REMS website (www.KynamroREMS.com) will be available at the time of approval.

The following materials are part of the KYNAMRO REMS and are appended:

- Dear Healthcare Provider letter
- Healthcare Professional Information Brochure
- Dear Professional Association letter
- KYNAMRO REMS Prescriber Education and Enrollment Kit:
  - Prescriber Training slide set
  - Summary of Monitoring Recommendations
  - Prescriber Enrollment Form
  - Prescription Authorization Form
- KYNAMRO REMS website

2. KYNAMRO will be dispensed only by specially certified pharmacies.

a. Genzyme will ensure that KYNAMRO will be dispensed only by certified pharmacies.

b. To become certified to dispense KYNAMRO, the authorized pharmacy representative must agree to the following:

   i. To educate all pharmacy staff involved in the dispensing of KYNAMRO on the KYNAMRO REMS Program requirements.

   ii. Put processes and procedures in place to verify, prior to dispensing KYNAMRO, that:

       1) the prescriber is certified in the KYNAMRO REMS Program;

       2) the KYNAMRO REMS Prescription Authorization Form is received for each new prescription.

   iii. To be audited to ensure that all processes and procedures are in place and are being followed for the KYNAMRO REMS Program.

   iv. To provide prescription data to the KYNAMRO REMS program.
3. KYNAMRO will be dispensed only to patients with evidence or other documentation of safe-use conditions.

a. KYNAMRO will be dispensed only to patients whose prescribers are specially certified in the KYNAMRO REMS Program and attest on the KYNAMRO REMS Prescription Authorization Form that:

i. they understand that KYNAMRO is indicated 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 HoFH;

ii. they affirm that their patient has a clinical or laboratory diagnosis consistent with HoFH;

iii. they understand that KYNAMRO has not been adequately studied in patients less than 18 years of age; and

iv. liver-related laboratory tests have been obtained as directed in the PI.

B. Implementation System

1. Genzyme will ensure that KYNAMRO is distributed to and dispensed only by certified pharmacies.

2. Genzyme will maintain, monitor, and evaluate the implementation of the KYNAMRO REMS Program.

a. Genzyme will develop and follow written procedures and scripts to implement the REMS.

b. Genzyme will maintain a secure, validated database of all certified prescribers and pharmacies that is in compliance with 21 CFR Part 11 regulations.

c. Genzyme will send confirmation of certification to each certified pharmacy.

d. Genzyme will maintain a KYNAMRO REMS Program coordinating center with a call center to support patients, prescribers, and pharmacies in interfacing with the KYNAMRO REMS Program.
e. Genzyme will ensure that all materials listed in or appended to the KYNAMRO REMS Program will be available through the KYNAMRO REMS website at www.KynamroREMS.com or from the KYNAMRO REMS Program coordinating center at 877-596-2676.

f. If there are substantive changes to the KYNAMRO REMS or KYNAMRO REMS Program, Genzyme will update all affected materials and notify enrolled prescribers and certified pharmacies, as applicable. Substantive changes include significant changes to the operation of the KYNAMRO REMS Program or changes to the PI that affect the risk-benefit profile of KYNAMRO.

g. Genzyme will monitor and audit the certified pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the KYNAMRO REMS Program. Corrective action will be instituted by Genzyme if noncompliance is found.

h. Based on monitoring and evaluation of the KYNAMRO REMS elements to assure safe use, Genzyme will take reasonable steps to improve implementation of these elements and to maintain compliance with the KYNAMRO REMS Program requirements, as applicable.

C. Timetable for Submission of Assessments

Genzyme will submit REMS Assessments to FDA at 6 months, 12 months, and annually thereafter from the date of initial approval of the KYNAMRO REMS. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Genzyme will submit each assessment so that it will be received by FDA on or before the due date.
APPENDIX 1

WEBSITE SCREEN SHOT - TRAINING SLIDE SET

APPEARS THIS WAY ON ORIGINAL
An Overview of the KYNAMRO™ Risk Evaluation and Mitigation Strategy (REMS) Program

Prescriber Training
Contents

- Introduction

- KYNAMRO Product Information
  - Indication and Limitations of Use
  - Appropriate Patient Selection
  - Serious Risks
  - Warnings and Precautions
  - Dosing and Administration
  - Patient Monitoring

- KYNAMRO REMS Program
  - Overview
  - Program Goals
  - Prescriber Certification and Enrollment
  - Prescription Authorization Form
  - Prescription Ordering and Dispensing
  - Learning Check

This training module contains important information about the risk of hepatotoxicity associated with the use of KYNAMRO and the need to monitor patients during treatment, and about the KYNAMRO REMS Program requirements.
Introduction

• This training module has been developed as part of the KYNAMRO REMS Program to:
  – Educate prescribers on the risk of hepatotoxicity associated with the use of KYNAMRO and the need to monitor patients during treatment with KYNAMRO per product labeling
  – Provide information to prescribers on the KYNAMRO REMS Program requirements, including how to enroll in the KYNAMRO REMS Program

• This training module focuses on the risk of hepatotoxicity associated with KYNAMRO. This is not the only risk associated with the use of KYNAMRO. Please see the Prescribing Information (PI) for a complete description of risks associated with the use of KYNAMRO.
KYNAMRO PRODUCT INFORMATION

KYNAMRO ( mipomersen sodium ) injection

This site is intended for United States residents only.

Copyright ©2013 Genzyme Corporation, a Sanofi company. All rights reserved.

KYNAMRO is a trademark of Genzyme Corporation.
Genzyme is a registered trademark of Genzyme Corporation. NP0022-0113
Indication and Limitations of Use

- KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)

- Limitations of use
  - The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH
  - The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
  - The use of KYNAMRO as an adjunct to LDL apheresis is not recommended
Appropriate Patient Selection

- KYNAMRO is indicated for use in patients with HoFH
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- KYNAMRO has not been adequately studied in patients less than 18 years of age
Serious Risks, Warnings and Precautions

- The use of KYNAMRO is contraindicated in the following conditions:
  - Moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
  - Known hypersensitivity to any component of the product

This is not a comprehensive description of the risks associated with the use of KYNAMRO. Please see the Prescribing Information for a complete description of risks associated with the use of KYNAMRO.
Boxed Warning for Serious Risk

WARNING: RISK OF HEPATOTOXICITY

KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or partial thromboplastin time (PTT).

KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 28 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are ≥3 x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.
Risk of Hepatotoxicity

- **KYNAMRO** can cause elevations in transaminases and hepatic steatosis. There is concern that KYNAMRO could induce steatohepatitis, which can progress to cirrhosis over several years.

- Elevation of transaminases
  - **KYNAMRO** can cause increases in serum transaminases (ALT and/or AST). If transaminase elevations are accompanied by clinical symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with KYNAMRO and identify the probable cause.

- Hepatic steatosis
  - **KYNAMRO** increases hepatic fat (steatosis) with or without concomitant increases in transaminases. The long-term consequences of hepatic steatosis associated with KYNAMRO therapy are unknown.
Risk of Hepatotoxicity

- Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYYNAMRO should consume no more than one alcoholic drink per day.

- Caution should be exercised when KYYNAMRO is used with other medications known to have potential for hepatotoxicity for example isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of KYYNAMRO with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted.

- KYYNAMRO has not been studied concomitantly with other LDL-lowering agents that can also increase hepatic fat. Therefore, the combined use of such agents is not recommended.
Dosing and Administration

- The recommended dose of KYNAMRO is 200 mg once weekly as a subcutaneous injection:
  - KYNAMRO is available in a single-use vial or pre-filled syringe
  - Each vial or pre-filled syringe of KYNAMRO provides 200 mg of mipomersen sodium in a deliverable volume of 1 mL of solution and is intended for single use only
  - KYNAMRO should be removed from refrigerated storage and allowed to reach room temperature for at least 30 minutes prior to administration
  - The first injection of KYNAMRO should be performed under the guidance and supervision of an appropriately qualified healthcare provider (HCP). Patients and caregivers should be instructed by an appropriately qualified HCP in the proper technique for administering subsequent injections
  - KYNAMRO should be injected into the abdomen, thigh region, or outer area of the upper arm. Patients and caregivers should be instructed to alternate sites for subcutaneous injections
## Monitoring of Hepatic Transaminases

<table>
<thead>
<tr>
<th>PERIOD ON TREATMENT</th>
<th>TREATMENT AND MONITORING RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning treatment</td>
<td>• Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin</td>
</tr>
<tr>
<td>During first year</td>
<td>• Conduct liver-related tests monthly (ALT and AST, at a minimum)</td>
</tr>
<tr>
<td>After first year</td>
<td>• Conduct liver-related tests at least every 3 months (ALT and AST, at a minimum)</td>
</tr>
</tbody>
</table>
Monitoring of Hepatic Transaminases

- For patients who develop elevated transaminases during therapy with KYNAMRO, follow the monitoring recommendations summarized below:

<table>
<thead>
<tr>
<th>ALT OR AST</th>
<th>TREATMENT AND MONITORING RECOMMENDATIONS*</th>
</tr>
</thead>
</table>
| ≥3x and < 5x ULN | - Confirm elevation with a repeat measurement within 1 week  
|               | - If confirmed, withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause  
|               | - If resuming KYNAMRO after transaminases resolve to <3x ULN, consider monitoring liver-related laboratory tests more frequently |
| ≥5x ULN     | - Withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause  
|             | - If resuming KYNAMRO after transaminases resolve to <3x ULN, monitor liver-related laboratory tests more frequently |

* Recommendations based on an ULN of approximately 30-40 international units/L.
Adverse Reaction Reporting

- To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 800-745-4447 or FDA at 800-FDA-1088 or www.fda.gov/medwatch
Overview

• To ensure that the benefits of KYNAMRO outweigh the risks, KYNAMRO is only available through the KYNAMRO REMS Program

• The elements of the KYNAMRO REMS Program are:
  – Healthcare providers who prescribe KYNAMRO must be specially certified
    • To become certified to prescribe KYNAMRO, prescribers must be trained and enrolled in the KYNAMRO REMS Program
  – Pharmacies that dispense KYNAMRO must be specially certified
    • Only certified pharmacies can dispense KYNAMRO
  – KYNAMRO will be dispensed only to patients with evidence or other documentation of safe-use conditions
    • Patients must have a clinical or laboratory diagnosis consistent with HoFH as documented on the KYNAMRO Prescription Authorization Form
Program Goals

- To educate prescribers about:
  - The risk of hepatotoxicity associated with the use of KYNAMRO
  - The need to monitor patients during treatment with KYNAMRO as per product labeling

- To restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with HoFH
Prescriber Certification and Enrollment

- Only healthcare providers specially certified in the KYNAMRO REMS Program can prescribe KYNAMRO

- To become specially certified in the KYNAMRO REMS Program, you must:
  - Complete the training by reviewing the materials provided in the KYNAMRO REMS Prescriber Education and Enrollment Kit
    - Prescribing Information
    - Prescriber Training Slide Set
    - Summary of Monitoring Recommendations
    - Prescriber Enrollment Form
    - Prescription Authorization Form
  - Complete, sign, and submit the Prescriber Enrollment Form certifying that you have completed the required training and agree to follow the procedures required by the KYNAMRO REMS Program

- If you have any questions on the KYNAMRO REMS Program, visit www.KynamroREMS.com or call 877-596-2676
Prescriber Enrollment Form

1. Complete the Prescriber Information at the top of the form
2. Carefully review the attestations on the bottom half of the form
3. Sign and date the form to attest and agree to comply with the KYNAMRO REMS Program requirements
Prescriber Enrollment Attestations

3 In signing the Prescriber Enrollment Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce low LDL-C, apo B, TC, and non-HDL-C in patients with HoFH
- You understand that KYNAMRO is only available through the KYNAMRO REMS Program and that you must comply with the program requirements in order to prescribe KYNAMRO
- You have completed the KYNAMRO REMS Prescriber Training
- You understand that there is a risk of hepatotoxicity associated with KYNAMRO
- You understand that serum ALT, AST, alkaline phosphatase, and total bilirubin must be measured before initiating therapy with KYNAMRO
- You understand that during the first year of treatment with KYNAMRO, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly
- You understand that after the first year, liver-related laboratory tests (ALT and AST at a minimum) should be measured at least every 3 months
- You agree that personnel from the KYNAMRO REMS Program may contact you to gather further information or resolve discrepancies or to provide other information related to KYNAMRO or the KYNAMRO REMS Program
- You will complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription
- You agree that Genzyme, its agents, and contractors such as the pharmacy providers may contact you via phone, mail, or email to survey you on the effectiveness of the program requirements for the KYNAMRO REMS Program
Prescriber Enrollment Form

Fax the signed form to the KYNAMRO REMS Program at 877-778-8008 or scan and email to KynamroREMS@LashGroup.com

A confirmation letter will be sent when the form has been received and verified.
Prescription Authorization Form

For a patient to receive KYNAMRO, the Prescription Authorization Form must be completed by the prescriber.

1. Patient Information and Insurance Information should be completed at the top of the form.
2. Prescriber Information should be completed within the third box of the form.
3. Carefully review the Attestation of REMS Requirements on the bottom half of the form.
Prescription Authorization Form Requirements

In completing the Prescription Authorization Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH
- The patient has a clinical or laboratory diagnosis consistent with HoFH
- You understand that KYNAMRO has not been adequately studied in pediatric patients <18 years of age
- You have obtained the appropriate liver-related laboratory tests for the patient as directed in the KYNAMRO PI
Prescription Authorization Form

The KYNAMRO Prescription should be written in the last box on the form.

The Prescription Authorization Form should be provided by the prescriber to a certified pharmacy via the KYNAMRO REMS Program by faxing the completed form to the KYNAMRO REMS Program at 877-778-9008.
KYNAMRO Prescription Ordering and Dispensing

- KYNAMRO is only available through a designated network of pharmacies that are certified in the KYNAMRO REMS Program

- Prescriptions for KYNAMRO must be written using the Prescription Authorization Form
  - Completed prescriptions should be submitted to the KYNAMRO REMS Program by fax at 877-778-9008
  - If you need assistance submitting a KYNAMRO prescription, contact the KYNAMRO REMS Program at 877-596-2876
Learning Check

- Prescribers should be able to answer these questions about the KYNAMRO REMS Program

- If you have problems answering any of these questions, please review information from the previous slides to ensure you are able to answer these questions correctly
Learning Check – Question 1

1. KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with all forms of familial hypercholesterolemia
   - True
   - False
Learning Check – Answer to Question 1

1. KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with all forms of familial hypercholesterolemia

   - [ ] True
   - [x] False

ANSWER

KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH.
Learning Check – Question 2

2. Which of the following liver-related laboratory tests should be performed prior to initiating a patient on treatment with KYNAMRO?
   - Alkaline phosphatase
   - Liver transaminases (ALT and AST)
   - Total bilirubin
   - All of the above
Learning Check – Answer to Question 2

2. Which of the following liver-related laboratory tests should be performed prior to initiating a patient on treatment with KYNAMRO?
   - [ ] Alkaline phosphatase
   - [ ] Liver transaminases (ALT and AST)
   - [ ] Total bilirubin
   - [x] All of the above

**ANSWER**

Measure a full liver panel to include ALT, AST, total bilirubin, and alkaline phosphatase before initiation of treatment with KYNAMRO.
Learning Check – Question 3

3. At what frequency should liver transaminase levels be obtained for patients while on treatment with KYNAMRO? (check all that apply)
   - During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly
   - After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months
   - For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 month
   - All of the above
Learning Check – Answer to Question 3

3. At what frequency should liver transaminase levels be obtained for patients while on treatment with KYNAMRO? (check all that apply)

- During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly
- After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months
- For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 month
- All of the above

**ANSWER**

During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly. After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months. For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 week.
Learning Check – Question 4

4. Which of the following statements is false? (check all that apply)
   - The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
   - KYNAMRO can be used as an adjunct to LDL apheresis
   - Patients must have a clinical or laboratory diagnosis consistent with HoFH
   - The use of KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
4. Which of the following statements is false? (check all that apply)

- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
- **KYNAMRO can be used as an adjunct to LDL apheresis**
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- The use of KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases

**ANSWER**

Limitations of use include: the effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined and the use of KYNAMRO as an adjunct to LDL apheresis is not recommended. KYNAMRO has not been adequately studied in patients <18 years of age. The use of KYNAMRO is contraindicated in the following conditions: moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases, and known hypersensitivity to any component of the product.
Learning Check – Question 5

5. Which of the following statements are true?
   - KYNAMRO can cause elevations in liver transaminases
   - KYNAMRO increases hepatic fat, with or without concomitant increases in liver transaminases
   - Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYNAMRO should consume no more than 1 alcoholic drink per day
   - Exercise caution when KYNAMRO is used with other medications known to have potential for hepatotoxicity. More frequent monitoring of liver-related tests may be warranted.
   - All of the above
Learning Check – Answer to Question 5

5. Which of the following statements are true (check all that apply)
   - KYNAMRO can cause elevations in liver transaminases
   - KYNAMRO increases hepatic fat, with or without concomitant increases in liver transaminases
   - Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYNAMRO should consume no more than 1 alcoholic drink per day
   - Exercise caution when KYNAMRO is used with other medications known to have potential for hepatotoxicity. More frequent monitoring of liver-related tests may be warranted.

☑ All of the above

ANSWER

KYNAMRO is associated with a risk of hepatotoxicity.
Learning Check – Question 6

6. **KYNAMRO** is available from any pharmacy.
   - True
   - False
Learning Check – Answer to Question 6

6. KYNAMRO is available from any pharmacy.
   - True
   - False

ANSWER

KYNAMRO is only available from KYNAMRO REMS-certified pharmacies. Prescriptions must be submitted using the Prescription Authorization Form to the KYNAMRO REMS Program at 877-778-9008.
Summary

For additional information on the KYNAMRO REMS Program, call 877-596-2676 or visit www.KynamroREMS.com
APPENDIX 2

PRESCRIBER TRAINING SLIDE SET

APPEARS THIS WAY ON ORIGINAL
An Overview of the KYNAMRO™ Risk Evaluation and Mitigation Strategy (REMS) Program

Prescriber Training
Contents

• Introduction

• KYNAMRO Product Information
  – Indication and Limitations of Use
  – Appropriate Patient Selection
  – Serious Risks
  – Warnings and Precautions
  – Dosing and Administration
  – Patient Monitoring

• KYNAMRO REMS Program
  – Overview
  – Program Goals
  – Prescriber Certification and Enrollment
  – Prescription Authorization Form
  – Prescription Ordering and Dispensing
  – Learning Check

This training module contains important information about the risk of hepatotoxicity associated with the use of KYNAMRO and the need to monitor patients during treatment, and about the KYNAMRO REMS Program requirements.

Reference ID: 3252211
Introduction

• This training module has been developed as part of the KYNAMRO REMS Program to:
  – Educate prescribers on the risk of hepatotoxicity associated with the use of KYNAMRO and the need to monitor patients during treatment with KYNAMRO per product labeling
  – Provide information to prescribers on the KYNAMRO REMS Program requirements, including how to enroll in the KYNAMRO REMS Program

• This training module focuses on the risk of hepatotoxicity associated with KYNAMRO. This is not the only risk associated with the use of KYNAMRO. Please see the Prescribing Information (PI) for a complete description of risks associated with the use of KYNAMRO.
KYNAMRO PRODUCT INFORMATION
Indication and Limitations of Use

• KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)

• Limitations of use
  – The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH
  – The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
  – The use of KYNAMRO as an adjunct to LDL apheresis is not recommended
Appropriate Patient Selection

- KYNAMRO is indicated for use in patients with HoFH
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- KYNAMRO has not been adequately studied in patients less than 18 years of age
Serious Risks, Warnings and Precautions

- The use of KYNAMRO is contraindicated in the following conditions:
  - Moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
  - Known hypersensitivity to any component of the product

This is not a comprehensive description of the risks associated with the use of KYNAMRO. Please see the Prescribing Information for a complete description of risks associated with the use of KYNAMRO.
WARNING: RISK OF HEPATOTOXICITY

KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or partial thromboplastin time (PTT).

KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are ≥3 x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.
Risk of Hepatotoxicity

• KYNAMRO can cause elevations in transaminases and hepatic steatosis. There is concern that KYNAMRO could induce steatohepatitis, which can progress to cirrhosis over several years.

• Elevation of transaminases
  – KYNAMRO can cause increases in serum transaminases (ALT and/or AST). If transaminase elevations are accompanied by clinical symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with KYNAMRO and identify the probable cause.

• Hepatic steatosis
  – KYNAMRO increases hepatic fat (steatosis) with or without concomitant increases in transaminases. The long-term consequences of hepatic steatosis associated with KYNAMRO therapy are unknown.
Risk of Hepatotoxicity

• Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYNAMRO should consume no more than one alcoholic drink per day.

• Caution should be exercised when KYNAMRO is used with other medications known to have potential for hepatotoxicity for example isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of KYNAMRO with other hepatotoxic medications is unknown. More frequent monitoring of liver-related tests may be warranted.

• KYNAMRO has not been studied concomitantly with other LDL-lowering agents that can also increase hepatic fat. Therefore, the combined use of such agents is not recommended.
Dosing and Administration

- The recommended dose of KYNAMRO is 200 mg once weekly as a subcutaneous injection:
  - KYNAMRO is available in a single-use vial or pre-filled syringe
  - Each vial or pre-filled syringe of KYNAMRO provides 200 mg of mipomersen sodium in a deliverable volume of 1 mL of solution and is intended for single use only
  - KYNAMRO should be removed from refrigerated storage and allowed to reach room temperature for at least 30 minutes prior to administration
  - The first injection of KYNAMRO should be performed under the guidance and supervision of an appropriately qualified healthcare provider (HCP). Patients and caregivers should be instructed by an appropriately qualified HCP in the proper technique for administering subsequent injections
  - KYNAMRO should be injected into the abdomen, thigh region, or outer area of the upper arm. Patients and caregivers should be instructed to alternate sites for subcutaneous injections
# Monitoring of Hepatic Transaminases

<table>
<thead>
<tr>
<th>PERIOD ON TREATMENT</th>
<th>TREATMENT AND MONITORING RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning treatment</td>
<td>• Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin</td>
</tr>
<tr>
<td>During first year</td>
<td>• Conduct liver-related tests monthly (ALT and AST, at a minimum)</td>
</tr>
<tr>
<td>After first year</td>
<td>• Conduct liver-related tests at least every 3 months (ALT and AST, at a minimum)</td>
</tr>
</tbody>
</table>
Monitoring of Hepatic Transaminases

- For patients who develop elevated transaminases during therapy with KYNAMRO, follow the monitoring recommendations summarized below:

<table>
<thead>
<tr>
<th>ALT OR AST</th>
<th>TREATMENT AND MONITORING RECOMMENDATIONS*</th>
</tr>
</thead>
</table>
| ≥3x and < 5x ULN | • Confirm elevation with a repeat measurement within 1 week  
• If confirmed, withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause  
• If resuming KYNAMRO after transaminases resolve to <3x ULN, consider monitoring liver-related laboratory tests more frequently |
| ≥5x ULN | • Withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause  
• If resuming KYNAMRO after transaminases resolve to < 3x ULN, monitor liver-related laboratory tests more frequently |

*Recommendations based on an ULN of approximately 30-40 international units/L.
Adverse Reaction Reporting

• To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 800-745-4447 or FDA at 800-FDA-1088 or www.fda.gov/medwatch
KYNAMRO REMS PROGRAM
Overview

• To ensure that the benefits of KYNAMRO outweigh the risks, KYNAMRO is only available through the KYNAMRO REMS Program

• The elements of the KYNAMRO REMS Program are:
  – Healthcare providers who prescribe KYNAMRO must be specially certified
    • To become certified to prescribe KYNAMRO, prescribers must be trained and enrolled in the KYNAMRO REMS Program
  – Pharmacies that dispense KYNAMRO must be specially certified
    • Only certified pharmacies can dispense KYNAMRO
  – KYNAMRO will be dispensed only to patients with evidence or other documentation of safe-use conditions
    • Patients must have a clinical or laboratory diagnosis consistent with HoFH as documented on the KYNAMRO Prescription Authorization Form

Reference ID: 3252211
Program Goals

• To educate prescribers about:
  – The risk of hepatotoxicity associated with the use of KYNAMRO
  – The need to monitor patients during treatment with KYNAMRO as per product labeling

• To restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with HoFH
Prescriber Certification and Enrollment

• Only healthcare providers specially certified in the KYNAMRO REMS Program can prescribe KYNAMRO

• To become specially certified in the KYNAMRO REMS Program, you must:
  
  – Complete the training by reviewing the materials provided in the KYNAMRO REMS Prescriber Education and Enrollment Kit
    • Prescribing Information
    • Prescriber Training Slide Set
    • Summary of Monitoring Recommendations
    • Prescriber Enrollment Form
    • Prescription Authorization Form
  
  – Complete, sign, and submit the Prescriber Enrollment Form certifying that you have completed the required training and agree to follow the procedures required by the KYNAMRO REMS Program

• If you have any questions on the KYNAMRO REMS Program, visit www.KynamroREMS.com or call 877-596-2676

Reference ID: 3252211
Prescriber Enrollment Form

1. Complete the Prescriber Information at the top of the form
2. Carefully review the attestations on the bottom half of the form
3. Sign and date the form to attest and agree to comply with the KYNAMRO REMS Program requirements

Reference ID: 3252211
In signing the Prescriber Enrollment Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce low LDL-C, apo B, TC, and non-HDL-C in patients with HoFH
- You understand that KYNAMRO is only available through the KYNAMRO REMS Program and that you must comply with the program requirements in order to prescribe KYNAMRO
- You have completed the KYNAMRO REMS Prescriber Training
- You understand that there is a risk of hepatotoxicity associated with KYNAMRO
- You understand that serum ALT, AST, alkaline phosphatase, and total bilirubin must be measured before initiating therapy with KYNAMRO
- You understand that during the first year of treatment with KYNAMRO, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly
- You understand that after the first year, liver-related laboratory tests (ALT and AST at a minimum) should be measured at least every 3 months
- You agree that personnel from the KYNAMRO REMS Program may contact you to gather further information or resolve discrepancies or to provide other information related to KYNAMRO or the KYNAMRO REMS Program
- You will complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription
- You agree that Genzyme, its agents, and contractors such as the pharmacy providers may contact you via phone, mail, or email to survey you on the effectiveness of the program requirements for the KYNAMRO REMS Program
Prescriber Enrollment Form

Fax the signed form to the KYNAMRO REMS Program at 877-778-9008 or scan and email to KynamroREMS@LashGroup.com

A confirmation letter will be sent when the form has been received and verified

<table>
<thead>
<tr>
<th>Name of Indication/Name</th>
<th>Procedure/Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Name]</td>
<td>[Procedure/Expiry Date]</td>
</tr>
</tbody>
</table>

4. Faxing the form to the KYNAMRO REMS Program

5. A confirmation letter will be sent when the form has been received and verified.
Prescription Authorization Form

For a patient to receive KYNAMRO, the Prescription Authorization Form must be completed by the prescriber.

1. **Patient Information and Insurance Information** should be completed at the top of the form.

2. **Prescriber Information** should be completed within the third box of the form.

3. **Carefully review the Attestation of REMS Requirements** on the bottom half of the form.

The KYNAMRO Prescription Authorization Form is available at www.kynamro.com. Please visit www.kynamro.com for prescribing information for KYNAMRO. KYNAMRO® is a trademark of Genzyme Corporation.
In completing the Prescription Authorization Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH
- The patient has a clinical or laboratory diagnosis consistent with HoFH
- You understand that KYNAMRO has not been adequately studied in pediatric patients <18 years of age
- You have obtained the appropriate liver-related laboratory tests for the patient as directed in the KYNAMRO PI
The KYNAMRO Prescription should be written in the last box on the form.

The Prescription Authorization Form should be provided by the prescriber to a certified pharmacy via the KYNAMRO REMS Program by faxing the completed form to the KYNAMRO REMS Program at 877-778-9008.
KYNAMRO Prescription Ordering and Dispensing

- KYNAMRO is only available through a designated network of pharmacies that are certified in the KYNAMRO REMS Program

- Prescriptions for KYNAMRO must be written using the Prescription Authorization Form
  - Completed prescriptions should be submitted to the KYNAMRO REMS Program by fax at 877-778-9008
  - If you need assistance submitting a KYNAMRO prescription, contact the KYNAMRO REMS Program at 877-596-2676
LEARNING CHECK
Learning Check

• Prescribers should be able to answer these questions about the KYNAMRO REMS Program

• If you have problems answering any of these questions, please review information from the previous slides to ensure you are able to answer these questions correctly
Learning Check – Question 1

1. KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with all forms of familial hypercholesterolemia
   - True
   - False
1. KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with all forms of familial hypercholesterolemia

- True
- False

**ANSWER**

KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH.
2. Which of the following liver-related laboratory tests should be performed prior to initiating a patient on treatment with KYNAMRO?

- Alkaline phosphatase
- Liver transaminases (ALT and AST)
- Total bilirubin
- All of the above
2. Which of the following liver-related laboratory tests should be performed prior to initiating a patient on treatment with Kynamro?

- [ ] Alkaline phosphatase
- [ ] Liver transaminases (ALT and AST)
- [ ] Total bilirubin
- [✓] All of the above

**ANSWER**

Measure a full liver panel to include ALT, AST, total bilirubin, and alkaline phosphatase before initiation of treatment with Kynamro.
3. At what frequency should liver transaminase levels be obtained for patients while on treatment with KYNAMRO? (check all that apply)

- During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly.
- After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months.
- For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 month.
- All of the above.
3. At what frequency should liver transaminase levels be obtained for patients while on treatment with KYNAMRO? (check all that apply)

- During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly
- After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months
- For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 month
- All of the above

**ANSWER**

During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly. After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months. For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 week.
4. Which of the following statements is false? (check all that apply)

- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
- KYNAMRO can be used as an adjunct to LDL apheresis
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- The use of KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
Learning Check – Answer to Question 4

4. Which of the following statements is false? (check all that apply)

- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
- KYNAMRO can be used as an adjunct to LDL apheresis
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- The use of KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases

ANSWER

Limitations of use include: the effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined and the use of KYNAMRO as an adjunct to LDL apheresis is not recommended. KYNAMRO has not been adequately studied in patients <18 years of age. The use of KYNAMRO is contraindicated in the following conditions: moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases; and known hypersensitivity to any component of the product.
Learning Check – Question 5

5. Which of the following statements are true?

- KYNAMRO can cause elevations in liver transaminases
- KYNAMRO increases hepatic fat, with or without concomitant increases in liver transaminases
- Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYNAMRO should consume no more than 1 alcoholic drink per day
- Exercise caution when KYNAMRO is used with other medications known to have potential for hepatotoxicity. More frequent monitoring of liver-related tests may be warranted.
- All of the above
5. Which of the following statements are true (check all that apply)

- KYNAMRO can cause elevations in liver transaminases
- KYNAMRO increases hepatic fat, with or without concomitant increases in liver transaminases
- Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. Patients taking KYNAMRO should consume no more than 1 alcoholic drink per day
- Exercise caution when KYNAMRO is used with other medications known to have potential for hepatotoxicity. More frequent monitoring of liver-related tests may be warranted.

☑️ All of the above

ANSWER

KYNAMRO is associated with a risk of hepatotoxicity.
6. **KYNAMRO** is available from any pharmacy.

- True
- False
6. **KYNAMRO** is available from any pharmacy.

- [ ] True
- [x] False

**ANSWER**

KYNAMRO is only available from KYNAMRO REMS-certified pharmacies. Prescriptions must be submitted using the Prescription Authorization Form to the KYNAMRO REMS Program at 877-778-9008.
For additional information on the KYNAMRO REMS Program, call 877-596-2676 or visit www.KynamroREMS.com
APPENDIX 3

SUMMARY OF MONITORING RECOMMENDATIONS
## SUMMARY OF RECOMMENDATIONS*

### Monitoring Patients Receiving KYNAMRO™

<table>
<thead>
<tr>
<th>TIMING</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to Initiating treatment</td>
<td>Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin</td>
</tr>
<tr>
<td>During the first year of treatment</td>
<td>Instruct patients to report symptoms of possible liver problems</td>
</tr>
<tr>
<td></td>
<td>Conduct liver-related tests monthly (ALT and AST, at minimum)</td>
</tr>
<tr>
<td>After the first year of treatment</td>
<td>Instruct patients to report symptoms of possible liver problems</td>
</tr>
<tr>
<td></td>
<td>Conduct liver-related tests at least every 3 months (ALT and AST, at a minimum)</td>
</tr>
<tr>
<td>If liver enzyme elevations are</td>
<td>• If elevations in ALT or AST levels ≥3X and &lt;5X ULN are observed, confirm</td>
</tr>
<tr>
<td>observed:</td>
<td>elevation with a repeat measurement within 1 week. If confirmed, withhold</td>
</tr>
<tr>
<td></td>
<td>dosing, obtain additional liver-related tests if not already measured (such</td>
</tr>
<tr>
<td></td>
<td>as total bilirubin, alkaline phosphatase, and INR) and investigate to identify</td>
</tr>
<tr>
<td></td>
<td>the probable cause</td>
</tr>
<tr>
<td></td>
<td>• If elevations in ALT or AST levels ≥5X ULN are observed, withhold dosing,</td>
</tr>
<tr>
<td></td>
<td>obtain additional liver-related tests if not already measured (such as total</td>
</tr>
<tr>
<td></td>
<td>bilirubin, alkaline phosphatase, and INR) and investigate to identify the</td>
</tr>
<tr>
<td></td>
<td>probable cause</td>
</tr>
<tr>
<td></td>
<td>• If resuming KYNAMRO after transaminases resolve to &lt;3X ULN, consider</td>
</tr>
<tr>
<td></td>
<td>monitoring liver-related laboratory tests more frequently</td>
</tr>
</tbody>
</table>

For patients with:
- Persistent or clinically significant elevations in transaminases
- Transaminase elevations accompanied by clinical symptoms of liver injury, increases in bilirubin ≥2X ULN, or active liver disease
- Clinically significant liver toxicity

Discontinue treatment with KYNAMRO and Investigate to identify the probable cause

*Please see the Prescribing Information for more information.

Report all suspected adverse events associated with KYNAMRO. Please contact Genzyme at 1-800-745-4447 or the FDA at 1-800-FDA-1088 (332-1088) or www.fda.gov/medwatch.

*KYNAMRO® is a trademark of Genzyme Corporation*
KYNAMRO™ (mipomersen sodium) is only available through the KYNAMRO Risk Evaluation and Mitigation Strategy (REMS) Program. In order to prescribe KYNAMRO, a prescriber must:

1. Complete the KYNAMRO REMS prescriber training by reviewing the materials in the KYNAMRO REMS Prescriber Education and Enrollment Kit.
2. Complete this one-time KYNAMRO REMS Program Prescriber Enrollment Form.
3. Complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription.

Complete this enrollment form and submit to the KYNAMRO REMS Program by fax at 877-778-9008 or scan and email to KynamroREMS@LashGroup.com

---

Prescriber Enrollment Form

KYNAMRO™ (mipomersen sodium) is only available through the KYNAMRO Risk Evaluation and Mitigation Strategy (REMS) Program. In order to prescribe KYNAMRO, a prescriber must:

1. Complete the KYNAMRO REMS prescriber training by reviewing the materials in the KYNAMRO REMS Prescriber Education and Enrollment Kit.
2. Complete this one-time KYNAMRO REMS Program Prescriber Enrollment Form.
3. Complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription.

Complete this enrollment form and submit to the KYNAMRO REMS Program by fax at 877-778-9008 or scan and email to KynamroREMS@LashGroup.com

---

Prescriber Information (Please print. All information required.)

| Name (first, middle, last) | Credentials | MD | DO | NP | PA | Other 
|---------------------------|-------------|----|----|----|----|------
| Name of Institution/Practice Name | Physician Specialty |
| Office Address |
| City | State | Zip Code | Preferred Method of Contact | Mail | Email |
| Email Address |
| Office Address |
| City | State | Zip Code | Preferred Method of Contact | Mail | Email |
| Email Address |
| Primary State License Number/State of Issue |
| National Provider Identification (NPI) Number |

By signing this form, I attest that:

- I understand that KYNAMRO is indicated 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).
- I understand that KYNAMRO is only available through the KYNAMRO REMS Program and that I must comply with the program requirements in order to prescribe KYNAMRO.
- I have completed the KYNAMRO REMS Prescriber Training.
- I understand that there is a risk of hepatotoxicity associated with KYNAMRO.
- I understand that serum ALT, AST, alkaline phosphatase, and total bilirubin must be measured before initiating therapy with KYNAMRO.
- I understand that during the first year of treatment with KYNAMRO, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly.
- I understand that after the first year, these parameters should be measured at least every 3 months.
- I agree that personnel from the KYNAMRO REMS Program may contact me to gather further information or resolve discrepancies or to provide other information related to KYNAMRO or the KYNAMRO REMS Program.
- I will complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription.
- I agree that Genzyme, its agents, and contractors such as the pharmacy providers may contact me via phone, mail, or email to survey me on the effectiveness of the program requirements for the KYNAMRO REMS Program.

Prescriber Signature ___________________________ Date ___________________________

If you have any questions, contact the KYNAMRO REMS Program.

Phone: 877-596-2676 | Fax: 877-778-9008 | www.KynamroREMS.com

The KYNAMRO Prescriber Enrollment Form is available at www.KynamroREMS.com.

Please see Prescribing Information for KYNAMRO.

KYNAMRO is a trademark of Genzyme Corporation.

Reference ID: 3252211
# REMS Prescription Authorization Form

Please complete all sections of this form and fax it to the KYNAMRO™ REMS Program at 877-778-9008. If you have any questions, contact the KYNAMRO REMS Program at 877-596-2676.

## Patient Information (Please print. All information marked with an * is required.)

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Name (first, middle, last)*</td>
<td>Gender* □ M □ F</td>
</tr>
<tr>
<td>Address*</td>
<td>City*</td>
</tr>
<tr>
<td>Preferred Phone Number*</td>
<td>Alternate Phone Number</td>
</tr>
<tr>
<td>Email Address</td>
<td>Alternate Contact/Phone</td>
</tr>
<tr>
<td>Date of Birth*</td>
<td>Zip*</td>
</tr>
</tbody>
</table>

## Shipping Information

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ship to</td>
<td>Patient's Home Address (address above) □ Other Address (indicate below)</td>
</tr>
<tr>
<td>Name</td>
<td>Address</td>
</tr>
<tr>
<td>City</td>
<td>State</td>
</tr>
<tr>
<td>State</td>
<td>Zip</td>
</tr>
<tr>
<td>Phone Number</td>
<td></td>
</tr>
</tbody>
</table>

## Insurance Information (Please print.)

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Insurance Name</td>
<td>Primary Insurance Phone</td>
</tr>
<tr>
<td>Policy Holder's Name</td>
<td>Policy Holder's Date of Birth</td>
</tr>
<tr>
<td>Policy/Rx ID</td>
<td>Group Number</td>
</tr>
<tr>
<td>Secondary Insurance Name</td>
<td>Secondary Insurance Phone</td>
</tr>
<tr>
<td>Policy Holder's Name</td>
<td>Policy Holder's Date of Birth</td>
</tr>
<tr>
<td>Policy/Rx ID</td>
<td>Group Number</td>
</tr>
<tr>
<td>Prescription Card</td>
<td>□ Yes (complete information below) □ Not applicable</td>
</tr>
<tr>
<td>Carrier</td>
<td>ID #</td>
</tr>
<tr>
<td>Policy/Group #</td>
<td>Cardholder's Full Name</td>
</tr>
<tr>
<td></td>
<td>Cardholder's Date of Birth</td>
</tr>
</tbody>
</table>

## Prescriber Information (Please print. All information marked with an * is required.)

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber's Full Name*</td>
<td>NPI*</td>
</tr>
<tr>
<td>Phone Number*</td>
<td>Fax Number*</td>
</tr>
<tr>
<td>Practice Street Address*</td>
<td>City*</td>
</tr>
<tr>
<td></td>
<td>State*</td>
</tr>
<tr>
<td></td>
<td>Zip*</td>
</tr>
</tbody>
</table>

## Attestation of REMS Requirements:

- I understand that KYNAMRO is indicated 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).
- I affirm that my patient has a clinical or laboratory diagnosis consistent with HoFH.
- I understand that KYNAMRO has not been adequately studied in pediatric patients less than 18 years of age.
- I attest that I have obtained the liver-related laboratory tests for this patient as directed in the KYNAMRO Prescribing Information.

## KYNAMRO Prescription (Please print. All information marked with an * is required.)

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Instructions*</td>
<td>Refills NR 1 2 3 4 5 6</td>
</tr>
<tr>
<td></td>
<td>□ Dispense as Written</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Field</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date*</td>
<td>Prescriber Signature*</td>
</tr>
</tbody>
</table>

The KYNAMRO Prescription Authorization Form is available at [www.KynamroREMS.com](http://www.KynamroREMS.com)

Please see Prescribing Information for KYNAMRO.

KYNAMRO is a trademark of Genzyme Corporation.
APPENDIX 6

DEAR HEALTHCARE PROVIDER LETTER

APPEARS THIS WAY ON ORIGINAL
IMPORTANT DRUG WARNING

SUBJECT:  
- Risk of hepatotoxicity with KYNAMRO™ ( mipomersen sodium) injection  
- Appropriate patient selection and monitoring  
- Prescriber Action: Training and enrollment as part of KYNAMRO REMS Program

Dear Healthcare Provider:

Genzyme Corporation, a Sanofi company, would like to inform you of the approval of KYNAMRO™ ( mipomersen sodium) by the Food and Drug Administration (FDA). KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated 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).

FDA has required a Risk Evaluation and Mitigation Strategy (REMS) for KYNAMRO. The purpose of the REMS is to help ensure that the benefits of treatment with KYNAMRO outweigh the risk of hepatotoxicity. Please see enclosed brochure for detailed risk information.

KYNAMRO has a Boxed Warning in the prescribing information.

WARNING: RISK OF HEPATOTOXICITY

- KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or partial thromboplastin time (PTT).
- KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.
- Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are ≥3 x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.
- Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS.

KYNAMRO is a trademark of Genzyme Corporation.
Appropriate Patient Selection

- KYNAMRO is indicated for use in patients with HoFH
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- KYNAMRO has not been adequately studied in patients less than 18 years of age

Prescriber Action

KYNAMRO will only be available through the KYNAMRO REMS Program. In order to prescribe KYNAMRO, prescribers must:

- Review the KYNAMRO Prescribing Information and complete the Prescriber Training;
- Complete and submit the one-time KYNAMRO REMS Program Prescriber Enrollment Form;
- Complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription; and
- Comply with the requirements of the KYNAMRO REMS Program.

KYNAMRO REMS training materials are available at the KYNAMRO REMS Program website (www.KynamroREMS.com) or by contacting the KYNAMRO REMS Program by phone at 877-596-2676.

Certified Pharmacies

- KYNAMRO is only dispensed through certified pharmacies.

For more information regarding KYNAMRO REMS Program enrollment or general questions regarding the KYNAMRO REMS Program, visit www.KynamroREMS.com or call 877-596-2676.

Reporting Adverse Events

HCPs should report all suspected adverse events associated with the use of KYNAMRO. Please contact Genzyme at 800-745-4447 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The information in this letter is not a comprehensive description of the risks associated with the use of KYNAMRO. Please see the enclosed Prescribing Information and Medication Guide for a complete description of these risks.

Sincerely,

[Signature, Name, Title]
Genzyme Corporation

Enclosures: KYNAMRO Prescribing Information, Medication Guide, KYNAMRO Healthcare Professional Information Brochure

KYNAMRO is a trademark of Genzyme Corporation.
APPENDIX 7

DEAR PROFESSIONAL ASSOCIATION LETTER

APPEARS THIS WAY ON ORIGINAL
IMPORTANT DRUG WARNING

SUBJECT:  - Risk of hepatotoxicity with KYNAMRO™ (mipomersen sodium) injection
          - Appropriate patient selection and monitoring
          - Prescriber Action: Training and enrollment as part of KYNAMRO REMS Program

Dear Professional Association:

This letter highlights important safety information your members need to know when prescribing KYNAMRO™ (mipomersen sodium). To ensure the safe and appropriate use of KYNAMRO, it is important that you share the information included in this letter with your members who may treat patients with homozygous familial hypercholesterolemia (HoFH).

KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated 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 HoFH.

FDA has required a Risk Evaluation and Mitigation Strategy (REMS) for KYNAMRO. The purpose of the REMS is to help ensure that the benefits of treatment with KYNAMRO outweigh the risk of hepatotoxicity.

KYNAMRO has a Boxed Warning in the prescribing information.

WARNING: RISK OF HEPATOTOXICITY

- KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or partial thromboplastin time (PTT).

- KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.

- Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are ≥3 x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.

- Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS.

KYNAMRO is a trademark of Genzyme Corporation.
Appropriate Patient Selection

- KYNAMRO is indicated for use in patients with HoFH
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
- KYNAMRO has not been adequately studied in patients less than 18 years of age

Prescriber Action

In order to prescribe KYNAMRO, prescribers must review the Prescribing Information and complete the Prescriber Training, and enroll in the KYNAMRO REMS Program.

Certified Pharmacies

KYNAMRO is only dispensed through certified pharmacies.

More specific details about prescriber responsibilities, enrollment and educational materials for the KYNAMRO REMS Program can be found at www.KynamroREMS.com. For more information, you may also contact KYNAMRO REMS Program at 877-596-2676.

The information in this letter is not a comprehensive description of the benefits and risks associated with the use of KYNAMRO. Please see accompanying Prescribing Information and Medication Guide.

Please share the information on the KYNAMRO REMS Program and the materials referenced above with your membership in order to ensure the safe and appropriate use of KYNAMRO. Thank you for your consideration of this request.

Sincerely,

[Signature, Name, Title]
Genzyme Corporation

Enclosures: KYNAMRO Prescribing Information, KYNAMRO Medication Guide

KYNAMRO is a trademark of Genzyme Corporation.
APPENDIX 8

HEALTHCARE PROFESSIONAL INFORMATION BROCHURE

APPEARS THIS WAY ON ORIGINAL
Patient Counseling

Before initiating treatment with KYNAMRO, prescribers must discuss the risks of KYNAMRO with patients and their caregivers:

- Patients should be advised about the risk of hepatotoxicity and the need to have regular blood tests to monitor for evidence of liver injury or dysfunction.
- For additional information on patient counseling, please see the Prescribing Information.

Reporting Adverse Events

Healthcare professionals should report all suspected adverse events associated with KYNAMRO. Please contact Genzyme at 1-800-455-4447 or the FDA at 1-800-FDA-1088 (3332-1088) or www.fda.gov/medwatch.

Please see accompanying Prescribing Information for KYNAMRO for complete information on all the risks associated with KYNAMRO.

KYNAMRO™ (mipomersen sodium) and risk of hepatotoxicity

Healthcare Professional Information Brochure
Important REMS Information for Healthcare Professionals

KYNAMRO is a trademark of Genzyme Corporation

© 2002-2011 Genzyme Corporation

Reference ID: 3252211
About this Brochure

This brochure has been developed as a part of the Risk Evaluation and Mitigation Strategy (REMS) to help educate healthcare professionals on the risk of hepatotoxicity associated with the use of KYNAMRO (mitomycin sodium). Prescribers of KYNAMRO must review training materials and enroll in the KYNAMRO REMS Program in order to prescribe KYNAMRO. Please visit www.KynamroREMS.com to find out more information about the KYNAMRO REMS Program.

The brochure includes information about this risk and how to mitigate this risk through liver transaminase monitoring and dosing recommendations in the presence of increased hepatic transaminases.

This brochure focuses on elevations of hepatic transaminases and hepatic steatosis that have been observed in patients treated with KYNAMRO. These are not the only risks associated with KYNAMRO. Please see the accompanying Prescribing Information for KYNAMRO.

Introduction

KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated 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). HoFH is a rare genetic disorder that causes extremely elevated cholesterol levels and premature cardiovascular disease as a result of genetic mutations that impair the liver's ability to clear LDL particles from the bloodstream.

Use of KYNAMRO in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases is contraindicated. KYNAMRO was approved with a required REMS to ensure that the benefits of KYNAMRO outweigh the risks.

Elevated Hepatic Transaminases and Hepatic Steatosis

Elevated hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed in patients who received KYNAMRO in clinical trials. In phase 3 placebo-controlled trials, 8.4% and 4.2% of patients receiving KYNAMRO experienced elevated ALT and AST enzymes, respectively, >3 times the upper limit of normal (ULN) on 2 or more consecutive measurements at least 7 days apart.

Monitoring for Hepatotoxicity

- Before beginning treatment with KYNAMRO, measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin.
- During the first year of treatment with KYNAMRO:
  - Conduct liver-related tests monthly (ALT and AST, at a minimum).
  - After the first year of treatment with KYNAMRO:
    - Conduct liver-related tests at least every 3 months (ALT and AST, at a minimum).
- For patients who develop elevated transaminases during therapy with KYNAMRO, follow the monitoring recommendations summarized below:

Monitoring for Patients With Elevated Transaminases

<table>
<thead>
<tr>
<th>TREATMENT AND MONITORING RECOMMENDATIONS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3x and &lt;5x ULN</td>
</tr>
<tr>
<td>Confirm elevation with a repeat measurement within 1 week</td>
</tr>
<tr>
<td>If confirmed, withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause</td>
</tr>
<tr>
<td>If resuming KYNAMRO after transaminases resolve to &lt;3x ULN, consider monitoring liver-related laboratory tests more frequently</td>
</tr>
<tr>
<td>≥5x ULN</td>
</tr>
<tr>
<td>Withhold dosing, obtain additional liver-related tests if not already measured (such as total bilirubin, alkaline phosphatase, and INR) and investigate to identify the probable cause</td>
</tr>
<tr>
<td>If resuming KYNAMRO after transaminases resolve to &lt;3x ULN, consider monitoring liver-related laboratory tests more frequently</td>
</tr>
</tbody>
</table>

* Recommendations based on an ULN of approximately 30-40 International units/L.

- Advise patients to promptly report symptoms of possible liver injury.
- Discontinue treatment with KYNAMRO and investigate to identify the probable cause for patients with:
  - Persistent or clinically significant elevations in transaminases
  - Transaminase elevations accompanied by clinical symptoms of liver injury, increases in bilirubin ≥2x ULN, or active liver disease
  - Clinically significant liver toxicity

Reference ID: 3252211
APPENDIX 9
WEBSITE SCREEN SHOT – LANDING PAGE

APPEARS THIS WAY ON ORIGINAL
KYNAMRO™ Risk Evaluation and Mitigation Strategy (REMS)

The FDA has required a REMS program for KYNAMRO so that the benefits of the drug outweigh the risks to patients. The purpose of the KYNAMRO REMS program is:

- To educate prescribers about the risk of hepatotoxicity associated with the use of KYNAMRO.
- To educate prescribers about the need to monitor patients during treatment with KYNAMRO as per the Full Prescribing Information.
- To restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

Healthcare Provider Training

This comprehensive online program provides important safety information and REMS program enrollment requirements that must be completed before you can prescribe Kynmamo to your patients with a clinical or laboratory diagnosis of homozygous familial hypercholesterolemia (HoFH).

Get Started Now

Download and Print Resources

<table>
<thead>
<tr>
<th>Healthcare Providers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>KYNAMRO Full Prescribing Information</td>
<td>Medication Guide</td>
</tr>
<tr>
<td>Prescriber Enrollment Form</td>
<td></td>
</tr>
<tr>
<td>Healthcare Professional Information Brochure</td>
<td></td>
</tr>
<tr>
<td>Dear Healthcare Provider Letter</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthcare Providers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber Training Slide Set</td>
<td></td>
</tr>
<tr>
<td>Prescription Authorization Form</td>
<td></td>
</tr>
<tr>
<td>Summary of Monitoring Recommendations</td>
<td></td>
</tr>
</tbody>
</table>
INDICATIONS

KYNAMRO™ is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated 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).

Limitations of use

- The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH.
- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined.

Important Safety Information

WARNING: RISK OF HEPATOTOXICITY

KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 8% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR) or partial thromboplastin time (PTT).

KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease; including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are ≥3 x ULN. Discontinue KYNAMRO for clinically significant liver toxicity.

Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS.

OTHER WARNINGS AND PRECAUTIONS

Patients are advised to read the KYNAMRO medication guide before starting treatment with KYNAMRO, and each time they receive a refill. There may be new information. This information does not take the place of talking to a doctor about a medical condition or treatment.

KYNAMRO may cause serious side effects, including liver problems. A doctor should be informed of any liver problems, including liver problems while taking other medicines, or if a patient has any of these symptoms of liver problems while taking KYNAMRO: nausea, vomiting, fever, loss of appetite, being (or feeling) more tired than usual, yellowing of eyes or skin, dark urine, itching, or stomach pain.

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. It is recommended that patients taking KYNAMRO should consume no more than one alcoholic drink per day.

Caution should be exercised when KYNAMRO is used with other medications known to have potential for hepatotoxicity.

KYNAMRO should be used during pregnancy only if clearly needed. Females who become pregnant during KYNAMRO therapy should notify their healthcare provider. Safety and effectiveness have not been established in pediatric patients.

KYNAMRO is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis.

The safety and effectiveness of KYNAMRO as an adjunct to LDL apheresis have not been established; therefore, the use of KYNAMRO as an adjunct to LDL apheresis is not recommended.
CONTRAINDICATIONS

KYNAMRO is contraindicated in the following conditions:

- Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases.
- Patients with a known hypersensitivity to any component of this product.

COMMON SIDE EFFECTS

In clinical trials the most commonly-reported adverse reactions were injection site reactions occurring in 84% of patients receiving KYNAMRO versus 33% of placebo treated patients. The most common injection site reactions were erythema (59%), pain (56%), hematoma (32%), pruritus (29%), swelling (18%) and discoloration (17%). Injection site reactions did not occur with every injection but resulted in discontinuation of therapy in 5% of patients in pooled phase 3 trials.

Flu-like symptoms, defined as any one of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue and occurring within 2 days of injection, have been reported more frequently in patients receiving KYNAMRO (30%) versus placebo (16%) in the pooled Phase 3 trials. Flu-like symptoms did not occur with all injections but resulted in discontinuation of therapy in 3% of patients in pooled phase 3 trials.

See full prescribing information for more details about Warnings & Precautions, complete list of Adverse Reactions and Boxed Warning.
KYNAMRO™ Risk Evaluation and Mitigation Strategy (REMS) Program

You're almost there! Please fill in the information below then print and sign the downloadable enrollment form to complete the training and certification program. After completing and signing the enrollment form, you can finalize your REMS registration by faxing it to 877-770-5099 or scan and email your form to KynamroREMS@LaskGroup.com.

All fields required unless specified.

Email Address: [Input Field]

First Name: [Input Field]

Last Name: [Input Field]

Job Title: [Input Field]

Telephone: [Input Field]

City: [Input Field]

State / Province: [Input Field]

Institution / Facility: [Input Field]

Submit
KYYNAMRO™ Risk Evaluation and Mitigation Strategy (REMS) Program

Thank you for finalizing your enrollment in the KYYNAMRO™ ( mipomersen sodium) REMS Program.

Don't forget to fax your signed copy of the REMS Prescriber Enrollment Form to 677-776-9000, or scan and email your form to KYYNAMROREMS@LashGroup.com
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CYNTHIA L LACIVITA
01/29/2013

CLAUDIA B MANZO
01/29/2013
concur
Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Kynamro (mipomersen sodium) to ensure that the benefits of the drug outweigh the risk of hepatotoxicity. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with homozygous familial hypercholesterolemia is approximately 300, based on a prevalence of 1 in 1 million persons. This estimate is based on a 1993 article in Lancet entitled “Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia.”\(^1\)

B. Homozygous familial hypercholesterolemia (HoFH) is a life-threatening genetic disease characterized by marked elevations in LDL-C, tendon xanthomas, and premature coronary atherosclerosis. HoFH patients frequently suffer major adverse cardiovascular events such as heart attack and stroke in adolescence and early adulthood. This aggressive and premature

cardiovascular disease often requires interventions such as coronary bypass surgery, coronary stenting, carotid endarterectomy, and aortic valve replacement.

C. When added to background lipid-lowering therapy, Kynamro ( mipomersen sodium) led to a mean placebo-adjusted reduction in LDL-C of 21.4% from baseline to week 26. Four (11.8%) individuals in the Kynamro (mipomersen sodium) group had a >50% decrease in LDL-C levels from baseline to week 26, compared with no individuals in the placebo group, and two (6%) individuals were able to achieve an on-treatment LDL-C level <100 mg/dL versus none in the placebo group.

D. The expected duration of treatment is lifelong.

E. Kynamro (mipomersen sodium) can cause elevations in transaminases. In the Kynamro (mipomersen sodium) pivotal trial, 12% of individuals treated with Kynamro (mipomersen sodium) compared to 0% of individuals treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). Kynamro also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 10% after 26 weeks of treatment with mipomersen, versus 0% with placebo, as measured by magnetic resonance imaging (MRI). Hepatic failure was observed in one individual treated with Kynamro (mipomersen sodium) in the clinical development program; however, the case was confounded and causality to Kynamro (mipomersen sodium) could not be established. Hepatic steatosis is a risk factor for steatohepatitis, which can progress over several years to advanced liver disease and cirrhosis. Given the small size and relatively short duration of Kynamro (mipomersen sodium) exposure in the pivotal trial, it is not surprising that this potential adverse effect has not yet been well-characterized. In addition to the most serious risk of hepatotoxicity, Kynamro (mipomersen sodium) has been associated with injection site reactions and flu-like symptoms.

F. Kynamro (mipomersen sodium) is a new molecular entity.

The elements of the REMS will be elements to assure safe use, including that healthcare professionals who prescribe Kynamro (mipomersen sodium) are specially certified (ETASU A), pharmacies that dispense Kynamro (mipomersen sodium) are specially certified (ETASU B), and Kynamro (mipomersen sodium) will be dispensed to patients with evidence or other documentation of safe-use conditions (ETASU D), an implementation system, and a timetable for submission of assessments of the REMS.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-----------------------------------------------
AMY G EGAN
01/24/2013
Date: December 19, 2012
Reviewer(s): Joyce Weaver, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)
Team Leader: Cynthia LaCivita, Pharm.D., Team Leader
DRISK
Division Director Claudia Manzo, Pharm.D, Director
DRISK
Drug Name(s): Mipomersen
Therapeutic Class: Cholesterol-lowering agent
Dosage and Route: 200mg once weekly subcutaneous injection
Application Type/Number: 203568
Applicant/sponsor: Genzyme
OSE RCM #: 2012-793

*** This document contains proprietary and confidential information that should not be released to the public. ***
CONTENTS

1 INTRODUCTION ............................................................................................................... 1
  1.1 Background .............................................................................................................. 1
  1.2 Regulatory History ................................................................................................. 2
2 MATERIALS REVIEWED .......................................................................................... 3
  2.1 Data and Information Sources ............................................................................. 3
3 RESULTS OF REVIEW ............................................................................................. 4
  3.1 Clinical Development Program ......................................................................... 4
4 FDA’S ASSESSMENT OF NEED FOR A REMS ....................................................... 4
5 SPONSOR’S REVISED REMS PROPOSAL ........................................................... 5
  5.1 Goals ...................................................................................................................... 6
  5.2 Proposed REMS Elements .................................................................................. 6
  5.3 Proposed REMS Assessment .............................................................................. 7
6 ADVISORY COMMITTEE PANEL RECOMMENDATIONS ..................................... 7
7 FDA’S PROPOSED REMS .......................................................................................... 7
  7.1 Goals ...................................................................................................................... 7
  7.2 REMS Elements ................................................................................................. 8
    7.2.1 Elements to Assure Safe Use ....................................................................... 8
    7.2.2 Implementation System ............................................................................. 10
    7.2.3 Timetable for Submission of Assessments ................................................. 11
  7.3 REMS Assessment Plan .................................................................................... 11
8 DISCUSSION ............................................................................................................. 13
9 CONCLUSIONS ....................................................................................................... 14
10 RECOMMENDATIONS FOR DMEP ...................................................................... 14
11 COMMENTS FOR THE SPONSOR ......................................................................... 14
1 INTRODUCTION

This review documents DRISK’s evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for mipomersen. Genzyme is seeking approval of mipomersen as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo-B), total cholesterol, non-high-density lipoprotein cholesterol (non-HDL) and lipoprotein (a) in individuals with homozygous familial hypercholesterolemia (HoFH).

1.1 BACKGROUND

Familial Hypercholesterolemia.¹ Familial Hypercholesterolemia (FH) is an autosomal codominant disorder caused by a large number (>1000) of mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL-C with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. The elevated levels of LDL-C in FH are due to an increase in the production of LDL from intermediate-density lipoprotein (IDL) and a delayed removal of LDL from the blood. Patients with HoFH have mutations in both LDL receptor alleles and have much higher LDL-C levels than those with heterozygous familial hypercholesterolemia (HeFH) who have only one mutant allele. Patients with HoFH are categorized in two groups based on the amount of LDL receptor activity measured in their skin fibroblasts: receptor-negative (<2% of normal LDL receptor activity) and receptor-defective (2–25% of normal LDL receptor activity). Most patients with HoFH are diagnosed in childhood and present with cutaneous xanthomas (hands, wrists, elbows, knees, heels, or buttocks), have total cholesterol levels of >500 mg/dL (can be >1000 mg/dL), and have accelerated atherosclerosis. Receptor-negative patients rarely survive beyond the second decade unless treated; receptor-defective patients have a better prognosis but develop atherosclerotic vascular disease by age 30 or sooner. Treatment for patients with HoFH includes a low fat diet, lipid lowering agents and LDL apheresis. Unfortunately, patients with HoFH are minimally responsive to available lipid lowering drugs and, even with maximal pharmacologic doses of these drugs, generally have LDL-C levels >300 mg/dL.

Mipomersen. Mipomersen is an antisense oligonucleotide (ASO) inhibitor targeted to human messenger ribonucleic acid (mRNA) for apo B-100, the principal apolipoprotein of LDL-C and its metabolic precursor, very-low density lipoprotein (VLDL). Mipomersen inhibits translation of the apo B-100 protein, producing reductions of apo B and LDL-C in patients with HoFH. The proposed dosing regimen is 200 milligrams (mg) once weekly as a subcutaneous injection.

1.2 Regulatory History

Following are pertinent milestones in the regulatory history of mipomersen:^2:

- **November 18, 2005**—IND 70969 submitted by ISIS Pharmaceuticals.
- **April 12, 2006**—Fast-track designation request submitted.
- **May 23, 2006**—Orphan Drug Designation (No. 06-2214) for treatment of HoFH was granted.
- **May 30, 2006**—Fast-track designation denied as the development program was not designed to address whether treatment with mipomersen in HoFH patients (or lower risk populations) reduces cardiovascular morbidity and mortality.
- **January 29, 2008**—IND placed on partial clinical hold because of vasculitis findings in monkeys. Because of the vasculitis safety concerns and the lack of a validated biomarker for vasculitis, it was determined that, at this time, studies should be limited to patients at high risk for cardiovascular disease. Risk-benefit profile only supports treatment of patients at high risk for cardiovascular events defined as 10-year risk for CVD > 20%, on maximum statin dose and not at LDL goal.
- **February 15, 2008**—Regulatory briefing to discuss preclinical toxicity concerns; i.e., increase in aPTT, complement activation and proinflammatory changes/vasculitis, liver effects (increase in liver transaminases, hepatic steatosis) and renal effects (glomerulonephritis, declines in renal function). Discussion included the following issues: (1) whether the available preclinical data on the immunostimulatory effects (pro-inflammatory tissue changes, complement activation, vasculitis) of this compound are concerning; (2) would additional preclinical studies clarify the potential clinical significance of ISIS 301012’s immunostimulatory effects; (3) can the immunostimulatory effects of ISIS 301012 and the potential forvasculitis be adequately monitored (e.g., measurement of proinflammatory biomarkers) in clinical studies; and (4) if the currently available preclinical data support the use of ISIS 301012 in: a) patients at high-risk for cardiovascular disease; and b) in patients at low-to-moderate risk for cardiovascular disease.
- **December 13, 2010**—Pre-NDA meeting to discuss safety issues; discussion included whether the Phase 3 study ISIS 301012-CS5, along with the open-label extension study CS6, supports an indication for the treatment of patients with HoFH will be determined after a full review of the relevant data and, most likely, input from an FDA advisory committee.
- **December 16, 2010**—Applicant notified that after additional internal discussions

Examinations of the study sample sizes used to support NDAs for orphan conditions with prevalence rates similar to severe HeFH support a request for one-year placebo-controlled data in a minimum of 300 severe HeFH patients (e.g., 200 on active drug vs. 100 on placebo). Additional safety concerns which will require further investigation include differentiating “benign” vs. clinically significant transaminase elevations during mipomersen treatment and the nature of the relationship between the transaminase elevations and steatotic changes in the

---

^2 Regulatory history provided by Dr. Eileen Craig in the July 25, 2012 REMS Oversight Committee Briefing Document
liver after mipomersen administration. Since hepatic steatosis may progress to steatohepatitis and cirrhosis, additional information is needed on the long-term use of mipomersen on intrahepatic triglyceride content and hepatic lipid changes particularly in patients with varying degrees of hepatic steatosis at baseline (e.g., patients with diabetes, obesity, hypertriglyceridemia, heavy alcohol use). Careful monitoring of antibodies, renal function (quantitative urine protein measurement, measurement of glomerular filtration rates etc), blood pressure changes and adverse events will also be necessary in ongoing and future studies of mipomersen.

- **June 13, 2011**—Special Protocol Assessment (SPA) request for Protocol MIPO3801011: *A Phase 3, Randomized, Double-Blind, Placebo- Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Uncontrolled Low-Density Lipoprotein Cholesterol.*

- **July 22, 2011**—No agreement to SPA for Protocol MIPO3801011. FDA requested the firm to extend the duration of the trial in order to provide 52 weeks at the fully titrated dose. Provide which hepatic biomarkers will be utilized and the supporting evidence for choosing these biomarkers. The hepatic biomarkers should be determined prior to starting the protocol.

- **September 27, 2011**—No agreement to SPA for Protocol MIPO3801011. FDA requested the firm to extend the duration of the trial in order to provide 52 weeks at the fully titrated dose. Provide which hepatic biomarkers will be utilized and the supporting evidence for choosing these biomarkers. The hepatic biomarkers should be determined prior to starting the protocol.

- **March 29, 2012**—Genzyme Corporation submitted NDA for mipomersen sodium, an apolipoprotein B synthesis inhibitor, as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, non-high density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia.

- **May 25, 2012**—Division of Metabolism and Endocrinology Products (DMEP) sent a filing communication to Genzyme Corporation accepting the application for standard review with a user fee goal date of January 29, 2013.

- **October 18, 2012**—Advisory Committee meeting voted 9:6 in favor of the approval of mipomersen (with a restrictive REMS) for the treatment of HoFH.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- DMEP Advisory Committee meeting background document.
- Genzyme Corporation Advisory Committee meeting background document.
3 RESULTS OF REVIEW

3.1 CLINICAL DEVELOPMENT PROGRAM

Mipomersen was studied in four randomized, double-blind, placebo-controlled trials evaluating 26 weeks of mipomersen therapy on LDL-C levels in patients who had not achieved lipid control on usual therapy. Patients in the trials were treated for 26 weeks, and the patients were offered participation in a long-term extension trial. In the long-term extension trial, patients continued mipomersen for up to 2 years. The percentage placebo subtracted decrease in LDL-C in the pivotal trial was 21.4. The three supportive trials had placebo subtracted decreases in LDL-C of 43.4%, 33.2%, and 48.4%. The treatment effects persisted for patients who enrolled in the extension trial.

Mipomersen therapy was associated with increased serum transaminases and increased hepatic fat. Nineteen of 261 patients (7.3%) who received mipomersen in the four 26-week trials had hepatic steatosis, compared with two of 129 patients (1.6%) in the placebo group. Increased ALT occurred in 25 (9.6%) of patients receiving mipomersen compared with 1 (0.8%) patient in the placebo group. One patient died of liver failure, with an onset of the event 2 to 3 months after the last dose of mipomersen.

In the long-term extension trial, 25% of patients taking mipomersen had an average liver fat fraction >20%. The fat fraction exceeded 29% in one case.

Five patients in clinical testing had liver biopsies because of increased fat on imaging (all five patients) and elevations in alanine aminotransferase (ALT) greater than or equal to three times the upper limit of normal. Some evidence of inflammation and fibrosis was found on biopsy, findings concerning for the development of non-alcoholic steatohepatitis (NASH).

4 FDA’S ASSESSMENT OF NEED FOR A REMS

The FDA considered whether a REMS is needed to mitigate the risk of hepatotoxicity. Mipomersen increases hepatic fat and it is not known if long-term exposure might cause irreversible liver injury. The potential for progression of non-alcoholic fatty liver (NAFL) to NASH is unknown, but, should this occur, the potential consequences could be severe. Should NAFL progress to NASH, patients would be at risk for cirrhosis and liver-related death. Accepting the potential risk of hepatotoxicity could be reasonable for patients with HoFH, a small population of patients with limited therapeutic options; however, it is not appropriate for the larger population of patients with hypercholesterolemia to assume this risk.

Because of the potential risk of hepatotoxicity, mipomersen could not be approved without the necessary safeguards to restrict prescribing to certified prescribers who understand that mipomersen must be used only for treating patients in whom the benefit is thought to exceed this risk; i.e., HoFH or presumed HoFH. However, we do not believe that access to mipomersen should be contingent on an established diagnosis of HoFH. There are no set, agreed upon diagnostic criteria for HoFH. Diagnosis is generally accomplished using genetic testing or a family medical history. Requiring a diagnosis of HoFH that relies on genetic testing or a family history in order to be prescribed mipomersen is problematic for the following reasons:

Reference ID: 3234537
Genetic testing may not be available to all patients
Not all of the genetic mutations that define HoFH are known
Some patients are likely unaware of their family history

There could be unanticipated consequences to an overly restrictive program; such restrictions could have a negative impact on necessary patient access to mipomersen. On the other hand, it is important to protect the patient population for whom the benefit of treatment with mipomersen has not been demonstrated from the potential risk of drug-induced NASH that may result from chronic use of mipomersen. The following strategy would provide a mechanism to support prescribers in the safe use of mipomersen in the targeted HoFH population, while deterring its use in the larger population of patients with hypercholesterolemia.

Several factors support the implementation of a REMS for mipomersen to address the risk of potential hepatotoxicity. First, mipomersen is an effective therapy for HoFH. The clinical development program demonstrated mipomersen’s efficacy in the reduction of LDL-C in HoFH patients. HoFH is a life threatening condition for which there is medical need for additional effective treatment. Second, mipomersen is a new molecular entity (NME) for which the serious risk of hepatotoxicity is not fully characterized, given its unknown potential for progression of NAFL to NASH is unknown. Third, patients with HoFH would require life-long exposure to this drug, which may increase a patient’s risk of hepatotoxicity requiring ongoing monitoring for evidence of hepatic injury. Fourth, the expected prescriber population requires training in the appropriate patient selection for treatment with mipomersen and in the monitoring and management of the risk of hepatotoxicity. A REMS program would provide an opportunity to train all prescribers regarding the appropriate use and risks associated to the use of mipomersen regardless of their medical training background. Fifth, a REMS program could help minimize use of mipomersen outside of the approved indication.

Currently there are no REMS programs addressing hepatic steatosis and no other approved product used in the treatment of dyslipidemias has a REMS. The particular circumstances associated with mipomersen are not common to other products with a risk of hepatotoxicity with the exception of lomitapide, an NME currently undergoing FDA review.

In summary, the available evidence of mipomersen’s potential risk of hepatotoxicity and the anticipated context for use in clinical practice supports the implementation of a REMS to communicate current knowledge about the potential risk of serious hepatotoxicity, the need for monitoring and managing increased transaminases and hepatic steatosis, and the importance of prescribing this product for the approved indication.

### 5 SPONSOR’S REVISED REMS PROPOSAL

Genzyme proposed a REMS comprising a communication plan (to include a Dear Healthcare Provider letter, a Healthcare Professional Information Brochure, and a Summary of Recommendations tear-off pad), a Medication Guide, and a timetable for submission of assessments. In a teleconference on August 27, 2012, FDA communicated to Genzyme that a REMS with elements to assure safe use (certification and enrollment...
of prescribers, dispensing only by certified pharmacies, and dispensing based on documentation of safe-use conditions) would likely be required for mipomersen. Subsequently, on September 25, 2012, Genzyme submitted a revised REMS proposal that is similar to that recommended by FDA. Following is a description of the revised REMS proposed by the sponsor.

### 5.1 Goals

- The goals of the proposed REMS are:
  - To educate prescribers about the approved indication for use of TRADENAME, the potential risk of hepatotoxicity associated with the use of TRADENAME, and the need to monitor patients during treatment with TRADENAME as per product labeling
  - Limit access to therapy with TRADENAME to patients in whom therapy with TRADENAME is medically appropriate

### 5.2 Proposed REMS Elements

- The elements of the proposed REMS are:
  - Healthcare Providers (HCPs) who prescribe TRADENAME will be specially certified. To become certified to prescribe TRADENAME, each prescriber must:
    - Complete the prescriber training by reviewing the materials in the TRADENAME REMS Prescriber Education and Enrollment Kit (to include the prescribing information, Medication Guide, educational slide deck, Healthcare Professional Information Brochure and Summary of Recommendations, Prescriber Enrollment Form, and Prescription Authorization Form)
    - Agree to review the Medication Guide with each patient and to counsel patients about the risk of hepatotoxicity and the need to have regular blood tests performed to monitor for evidence of hepatic injury or dysfunction
    - Complete, sign, and submit the TRADENAME REMS Prescriber Enrollment Form to the TRADENAME REMS Program.
  - Pharmacies that dispense TRADENAME are specially certified
    - To become certified, the authorized pharmacist for the pharmacy must acknowledge understanding that prescribers must be enrolled in the REMS to prescribe TRADENAME
    - The pharmacy must have a system in place to verify that the prescription was written by an enrolled prescriber and must verify such for each prescription
    - The prescriber must document on the prescription authorization form that TRADENAME is medically appropriate for that patient
  - TRADENAME will be dispensed only to patients with documentation of safe-use conditions
The prescription authorization form will contain an attestation that TRADENAME is medically appropriate for that patient

- The REMS will include an implementation system to implement and monitor the elements to assure safe use
- REMS assessments will be submitted at 6 months and 12 months following initial approval, and then annually thereafter.

5.3 PROPOSED REMS ASSESSMENT

The proposed REMS assessment measures include prescriber surveys of understanding of the indication and risk of potential hepatotoxicity, and metrics of enrolled prescribers and pharmacies, the number of prescriptions dispensed, the number of patients, and compliance with REMS requirements.

6 ADVISORY COMMITTEE PANEL RECOMMENDATIONS

On October 18, 2012, the Endocrinologic and Metabolic Drugs Advisory Committee voted 9:6 in favor of the approval of mipomersen for the treatment of adult patients with HoFH. The panel recommended the REMS program restrict the drug to the approved indication.

7 FDA’S PROPOSED REMS

The following strategy would provide a mechanism to support prescribers in the safe use of mipomersen in the targeted HoFH population, deter its use in the larger population of patients with hypercholesterolemia from the unknown consequences of drug-induced hepatic steatosis with chronic use of mipomersen, but maintain access for the targeted population.

7.1 GOALS

We are proposing that the REMS have the following goals:

The goals of the KYNAMRO REMS are:

- To educate prescribers about:
  - the risk of hepatotoxicity associated with the use of KYNAMRO; and
  - the need to monitor patients during treatment with KYNAMRO as per product labeling.

- To restrict access to therapy with KYNAMRO to patients with a clinical phenotype consistent with homozygous familial hypercholesterolemia (HoFH).
**Rationale for the proposed goals:** The uncertainties regarding the clinical implications of increases in transaminases and steatosis of the liver preclude the formulation of a clear message for patients. Consequently, the proposed goal focuses on prescriber education only. The key actions required from a REMS to maintain the risk:benefit balance for mipomersen are to educate prescribers about the potential risk of serious hepatotoxicity, the need for monitoring increased transaminases and hepatic steatosis, and the importance of prescribing this product for the approved indication.

Requiring a laboratory diagnosis of HoFH for all patients in order to receive mipomersen is problematic for the following reasons:

- Genetic testing may not be available to all patients
- All genetic mutations defining HoFH are not known
- Commercial tests are not available for all genetic mutations

The proposed goals are measurable through the monitoring of prescriber and pharmacy certification statistics; the distribution of letters to prescribers, pharmacists, and professional societies; and via prescriber knowledge surveys.

**7.2 REMS ELEMENTS**

We propose the following components for the REMS.

- Elements to assure safe use to include:
  - Health care professionals (HCP) who prescribe mipomersen are specially certified
  - Pharmacies that dispense mipomersen are specially certified
  - Mipomersen will be dispensed to patients with evidence or other documentation of safe-use conditions

- An implementation system

- A timetable for submission of assessments

**7.2.1 ELEMENTS TO ASSURE SAFE USE**

**Healthcare providers who prescribe mipomersen are specially certified**

- Prescriber Certification (ETASU A) – Certification consists of training and program enrollment. Certification will be linked to ability to prescribe mipomersen.

  **Rationale:** Mandatory Prescriber Certification (ETASU A) including prescriber training and enrollment is required to ensure that prescribers are aware of the potential risks associated with mipomersen, appropriate patient selection, and recommended monitoring parameters and clinical management. DRISK agrees with the sponsor’s proposal for prescriber certification.

  The prescriber enrollment form should include attestation that the prescriber understands the approved indication and appropriate use of mipomersen, the risks associated with its use, and REMS Program requirements.
The requirement for prescriber certification will likely limit the number of healthcare providers able to prescribe mipomersen since many prescribers do not treat patients with HoFH and are therefore not likely to enroll in the program. It is unclear to what extent this will result in a limitation of access to some patients who are candidates for therapy.

- Communications to certified prescribers (ETASU A) – all communications including letters addressed to healthcare providers and professional societies will be distributed as stipulated under ETASU A. A REMS website should be developed and maintained by the sponsor.

**Mipomersen will only be dispensed by pharmacies that are specially certified**

- Pharmacy Certification (ETASU B) – Pharmacy certification will assure that mipomersen is dispensed only when prescribed by certified prescribers and after documentation of safe use conditions. Certification will be linked to ability to purchase and dispense mipomersen.

  *Rationale* – Pharmacy certification is required to ensure that a prescription for mipomersen is dispensed only when the prescriber is certified and has provided documentation of safe use conditions.

The pharmacy certification process must include training of pharmacy staff on the REMS Program requirements. Certified pharmacies would need to have systems in place to verify that only certified prescribers prescribe mipomersen to patients with a clinical phenotype of HoFH. The certified pharmacies would not need to obtain additional documentation in support of the patient’s medical condition other than the prescriber attestation in the authorization form, nor would they need to ensure that the appropriate laboratory testing has been performed prior to dispensing mipomersen.

The sponsor included in their modified proposal a distribution system consistent with the REMS concept of pharmacy certification.

A requirement for pharmacy certification may restrict the number of pharmacies able to dispense mipomersen.

**Mipomersen will be dispensed only to patients with evidence or other documentation of safe-use conditions**

- Safe use conditions – The proposed safe use condition consists of a “Prescription Authorization” form integrated with each new prescription (not refills), includes the following statements attesting to the safe and appropriate use of mipomersen:

  o I understand that KYNAMRO is indicated as an adjunct to lipid-lowering medications and a low-fat 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).

  o I certify that this patient has a clinical phenotype consistent with HoFH.
o I understand that safety and effectiveness of mipomersen have not been established in pediatric patients.

o I attest that I have obtained the liver-related laboratory tests for this patient as directed in TRADENAME’s prescribing information.

The patient would not need to sign the form. The frequency of required documentation of safe use conditions will require further discussion within the Agency.

**Rationale**: This requirement for documentation of safe use conditions is included in FDA’s proposal in support of the second REMS goal, “To limit access to therapy with mipomersen to patients in whom therapy with mipomersen is medically appropriate”. This additional step, required before a prescription is dispensed, ensures that the prescriber will consider whether the use of mipomersen is appropriate therapy for each patient and avoids the need to keep long-term records of authorized patients because the authorization is built into each prescription.

### 7.2.2 **IMPLEMENTATION SYSTEM**

The Implementation System must include the following elements:

1. Genzyme will ensure that KYNAMRO is distributed to and dispensed only by certified pharmacies.

2. Genzyme will maintain, monitor, and evaluate the implementation of the KYNAMRO REM program.
   a. Genzyme will develop and follow written procedures and scripts to implement the REMS.
   b. Genzyme will maintain a secure, validated database of all certified prescribers and pharmacies that is in compliance with 21 CFR Part 11 regulations.
   c. Genzyme will send confirmation of certification to each certified pharmacy.
   d. Genzyme will maintain a KYNAMRO REMS Program Coordinating Center with a Call Center to support patients, prescribers, and pharmacies in interfacing with the KYNAMRO REMS.
   e. Genzyme will ensure that all materials listed in or appended to the KYNAMRO REMS Program will be available through the KYNAMRO REMS Program website (www.KYNAMRO.com/REMSProgram/) or by calling the KYNAMRO REMS Program Call Center at 1-XXX-XXX-XXXX.
   f. If there are substantive changes to the KYNAMRO REMS or KYNAMRO REMS Program, Genzyme will update all affected materials, and notify enrolled prescribers and certified pharmacies, as applicable. Substantive changes are defined as: significant changes to the operation of the KYNAMRO REMS Program or changes to the FPI that affect the risk-benefit profile of KYNAMRO.
   g. Genzyme will monitor and audit the certified pharmacies to ensure that all processes and procedures are in place and functioning to support the
requirements of the KYNAMRO REMS Program. Corrective action will be instituted by Genzyme if noncompliance is found.

h. Based on monitoring and evaluation of the KYNAMRO REMS elements to assure safe use, Genzyme will take reasonable steps to improve implementation of these elements and to maintain compliance with the KYNAMRO REMS Program requirements, as applicable.

The sponsor’s proposed Implementation System for the REMS includes most of the key implementation elements listed above.

7.2.3 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

DRISK concurs with the sponsor’s proposal for REMS assessment submissions at 6 months and 12 months after approval and annually thereafter.

7.3 REMS ASSESSMENT PLAN

The REMS assessment plan should include the following:

- A survey study to evaluate healthcare providers’ knowledge of the approved indication for use of KYNAMRO ( mipomersen), the potential risk of hepatotoxicity associated with the use of KYNAMRO ( mipomersen), the need to monitor liver enzymes during treatment with KYNAMRO ( mipomersen) as described in product labeling, and the need to prescribe KYNAMRO ( mipomersen) only to patients who have a clinical phenotype consistent with homozygous familial hypercholesterolemia. The survey protocol and data collection instrument will be submitted together to FDA for review at least 90 days before the study is conducted.

  o The survey protocol will include the following:

    ▪ Sample size calculations

    ▪ Inclusion and exclusion criteria

    ▪ Healthcare provider recruitment details, including methods to recruit, methods for non-responder follow-up, and honoraria payments (healthcare providers will be recruited from the list of certified healthcare providers in the KYNAMRO ( mipomersen) REMS prescriber database)

    ▪ Details of how the survey will be administered
- Methods to reduce various forms of bias (e.g., selection bias)
- Data analysis and reporting plan
- The target level of healthcare provider knowledge for each educational goal (approved indication for use of KYNAMRO (mipomersen), the potential risk of hepatotoxicity associated with the use of KYNAMRO (mipomersen), the need to monitor liver enzymes during treatment with KYNAMRO (mipomersen) as described in product labeling, including dose adjustments based on the magnitude of liver enzyme elevation, and the need to prescribe KYNAMRO (mipomersen) only to patients who have a clinical phenotype consistent with homozygous familial hypercholesterolemia).
- If the target levels for healthcare provider knowledge are not met, provide possible causes for the deficiencies and proposed measures to improve knowledge.

- An assessment of enrollment in the KYNAMRO (mipomersen) REMS Program, including the following:
  - Number of healthcare providers certified during the reporting period and cumulatively.
    - Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location)
    - Volume of prescriptions for each prescriber and each specialty
  - Number of pharmacies certified during the reporting period and cumulatively.
  - Number of healthcare providers and pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

- Metrics regarding KYNAMRO (mipomersen) distribution and dispensing to assess pharmacy compliance with the KYNAMRO (mipomersen) REMS:
The number of KYNAMRO ( mipomersen) orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size and dosage strength.

Pharmacy compliance with KYNAMRO (mipomersen) REMS Program requirements (e.g., shipped to a KYNAMRO (mipomersen) REMS certified pharmacy vs. a non-certified pharmacy).

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

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

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

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

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.

• Summary of issues and complaints received by REMS call center; summary of resolution of the issues and complaints.

• 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.

8 DISCUSSION
FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a REMS for mipomersen, DRISK balanced the demonstrated benefits of mipomersen in reducing LDL-C in the HoFH patient population and the potential risk of liver toxicity. The REMS proposed by FDA would support appropriate use of mipomersen, allowing it to be approved for use in the targeted patient population while protecting the larger hypercholesterolemic patient population by limiting prescribing of mipomersen to certified prescribers and dispensing to certified pharmacies. Certified pharmacies would dispense mipomersen only if the prescriber is certified and if the prescriber authorizes each prescription by attesting to understand the approved indication and that treatment with mipomersen is appropriate for the patient. In response to the Advisory Committee panel recommendations to strengthen the proposed REMS program, DRISK modified the REMS goals to restrict the use of mipomersen only to patients whose prescribers certify to have a clinical phenotype consistent with HoFH. The prescriber attestation statement included as part of the prescription authorization form will also reflect these changes to the goals.

The proposed safe use conditions that link dispensing of the drug to documentation of specific laboratory or imaging parameters is unwarranted at this time given that there is variability in how the clinical diagnosis is determined. Linking the dispensing to a specific laboratory or imaging parameters may result in limiting access to the drug. Until further clinical data is available, the management of HoFH patients treated with mipomersen will rely on the prescriber’s clinical judgment.

9 CONCLUSIONS
HoFH is a life-threatening disease for which there is a medical need for additional effective therapies. Mipomersen demonstrated to be effective in lowering LDL-C in patients with HoFH. Because of the potential risk of hepatotoxicity, mipomersen cannot be approved without the necessary safeguards to restrict prescribing to certified prescribers who understand that mipomersen must be used only for treating patients in whom the benefit is thought to exceed this risk. DRISK recommends a REMS with prescriber certification, pharmacy certification, and documentation of safe use conditions as described above to ensure that the benefits of mipomersen outweigh the potential risk of serious liver toxicity.

10 RECOMMENDATIONS FOR DMEP
DRISK recommends DMEP request the sponsor to submit a modified REMS proposal incorporating FDA edits as shown on the attached documents.

11 COMMENTS FOR THE SPONSOR
The following REMS assessment plan should be incorporated into the REMS Supporting Document.

The REMS assessment plan should include the following:
A survey study to evaluate healthcare providers’ knowledge of the approved indication for use of KYNAMRO (mipomersen), the potential risk of hepatotoxicity associated with the use of KYNAMRO (mipomersen), the need to monitor liver enzymes during treatment with KYNAMRO (mipomersen) as described in product labeling, and the need to prescribe KYNAMRO (mipomersen) only to patients who have a clinical phenotype consistent with homozygous familial hypercholesterolemia. The survey protocol and data collection instrument will be submitted together to FDA for review at least 90 days before the study is conducted.

- The survey protocol will include the following:
  - Sample size calculations
  - Inclusion and exclusion criteria
  - Healthcare provider recruitment details, including methods to recruit, methods for non-responder follow-up, and honoraria payments (healthcare providers will be recruited from the list of certified healthcare providers in the KYNAMRO (mipomersen) REMS prescriber database)
  - Details of how the survey will be administered
  - Methods to reduce various forms of bias (e.g., selection bias)
  - Data analysis and reporting plan
  - The target level of healthcare provider knowledge for each educational goal (approved indication for use of KYNAMRO (mipomersen), the potential risk of hepatotoxicity associated with the use of KYNAMRO (mipomersen), the need to monitor liver enzymes during treatment with KYNAMRO (mipomersen) as described in product labeling, including dose adjustments based on the magnitude of liver enzyme elevation, and the need to prescribe KYNAMRO (mipomersen) only to patients who have a clinical phenotype consistent with homozygous familial hypercholesterolemia).
If the target levels for healthcare provider knowledge are not met, provide possible causes for the deficiencies and proposed measures to improve knowledge.

- An assessment of enrollment in the KYNAMRO ( mipomersen) REMS Program, including the following:
  - Number of healthcare providers certified during the reporting period and cumulatively.
  - Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location)
  - Volume of prescriptions for each prescriber and each specialty
  - Number of pharmacies certified during the reporting period and cumulatively.
  - Number of healthcare providers and pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

- Metrics regarding KYNAMRO ( mipomersen) distribution and dispensing to assess pharmacy compliance with the KYNAMRO ( mipomersen) REMS:
  - The number of KYNAMRO ( mipomersen) orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size and dosage strength.
  - Pharmacy compliance with KYNAMRO ( mipomersen) REMS Program requirements (e.g., shipped to a KYNAMRO ( mipomersen) REMS certified pharmacy vs. a non-certified pharmacy).
  - The number of prescriptions dispensed for KYNAMRO ( mipomersen), including quantity of tablets (mean, minimum, maximum) and dosage strength during the reporting period and cumulatively, overall and subset by compliance with the KYNAMRO ( mipomersen) REMS Program requirements (e.g., received from KYNAMRO ( mipomersen) certified vs. non-certified healthcare providers, number of initial prescriptions dispensed without a signed attestation on the KYNAMRO ( mipomersen)
Prescription Authorization Form). Dispensing details are to be obtained from the pharmacies.

- The number and demographics (e.g., gender, age, geographic location) of patients who received KYNAMRO ( mipomersen) during the reporting period and annually. The number is to be calculated by reconciling orders dispensed to unique patients.
- Duration of therapy for patients (mean, median, range).
- Report of number, length, and reasons for shipment delays to patients.
- 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.

- Summary of issues and complaints received by REMS call center; summary of resolution of the issues and complaints.
- 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.

Please see our edited version of the REMS and REMS materials. We will have additional comments on the documents.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE P WEAVER
12/19/2012

CLAUDIA B MANZO
12/19/2012
concur