RISK EVALUATION AND MITIGATION STRATEGY (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.

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

- KYNAMRO REMS Prescriber Education and Enrollment Kit:
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 9-1

WEBSITE SCREEN SHOT - TRAINING SLIDE SET

Website training slide view is identical to training slide view in Appendix 9-2.
APPENDIX 9-2

PRESCRIBER TRAINING SLIDE SET