Initial REMS Approval: 01/2013
Most Recent Modification: 10/2017

NDA 203568
KYNAMRO® ( mipomersen sodium)
Drug Class: Oligonucleotide Inhibitor of Apolipoprotein B-100 Synthesis

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of the KYNAMRO REMS is to mitigate the risk of hepatotoxicity associated with the use of KYNAMRO by ensuring that:

• prescribers are educated about the approved indication for KYNAMRO, the risk of hepatotoxicity associated with the use of KYNAMRO, and the need to monitor patients during treatment with KYNAMRO as per product labeling
• KYNAMRO is dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH)
• patients are informed about the risk of hepatotoxicity associated with the use of KYNAMRO and the need for baseline and periodic monitoring.

II. REMS Elements

A. Elements to Assure Safe Use

1. Healthcare providers (HCP) who prescribe KYNAMRO must be certified.
   a. To become certified to prescribe KYNAMRO, healthcare providers must:
      i. Review the Prescribing Information for KYNAMRO.
      ii. Review KYNAMRO REMS Program: An Introduction.
      iii. Complete the KYNAMRO REMS Program Prescriber Certification Training Module, and successfully complete the Knowledge Assessment.
iv. Enroll in the KYNAMRO REMS Program by completing the *Prescriber Enrollment Form* and submit to the KYNAMRO REMS Program Coordinating Center.

b. As a condition of certification, prescribers must:
   
i. Review the *KYNAMRO REMS Program Patient Guide* with each patient to counsel the patient about the appropriate use and risks associated with KYNAMRO and provide the patient a copy.

   ii. Complete the *Patient-Prescriber Acknowledgment Form* for each patient and submit to the KYNAMRO REMS Program Coordinating Center.

   iii. Perform the following on an ongoing basis for each patient: Complete and submit a *Prescription Authorization Form* for each new KYNAMRO prescription.

c. Kastle Therapeutics must:
   
i. Ensure that healthcare providers who prescribe KYNAMRO are certified, in accordance with the requirements described above.

   ii. Provide all of the following mechanisms for healthcare providers to complete the certification process for the KYNAMRO REMS Program: by faxing the *Prescriber Enrollment Form* to the KYNAMRO REMS Program Coordinating Center at 877-778-9008, by calling the KYNAMRO REMS Program Coordinating Center at 877-596-2676, by mailing to the KYNAMRO REMS Program Coordinating Center at 610 Crescent Executive Court, Suite 200, Lake Mary, FL 32746, and online at www.KynamroREMS.com.

   iii. Ensure that healthcare providers are notified when they have been certified by the KYNAMRO REMS Program Coordinating Center.

iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe KYNAMRO in the KYNAMRO REMS Program.

v. Ensure that healthcare providers meet the REMS requirements and decertify healthcare providers who do not maintain compliance with the REMS requirements.

vi. Provide the Prescribing Information for KYNAMRO, *KYNAMRO REMS Program: An Introduction, KYNAMRO REMS Program Prescriber Certification Training Module and Knowledge Assessment, KYNAMRO REMS Program Patient Guide, Patient-Prescriber Acknowledgment Form*, and the *Prescription Authorization Form* to healthcare providers who (1)
attempt to prescribe KYNAMRO and are not yet certified, or (2) inquire about how to become certified.

vii. Send a REMS Letter for Healthcare Providers within 60 calendar days of the approval of the REMS modification (10/25/2017) to certified prescribers. The letter must be accompanied by the KYNAMRO REMS Program: An Introduction and the Prescribing Information for KYNAMRO. The letter must also be available from the KYNAMRO REMS Program website (www.KynamroREMS.com) at the time of the mailing and will remain on the website for 6 months after the mailing, or can be requested from the KYNAMRO REMS Program Coordinating Center by phone at 877-596-2676.

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

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

2. Pharmacies that dispense KYNAMRO must be certified.

   a. To become certified to dispense KYNAMRO, pharmacies must:

      i. Designate an authorized pharmacy representative to complete the certification process by submitting the completed Pharmacy Enrollment Form on behalf of the pharmacy.

      ii. Ensure that the authorized pharmacy representative oversees implementation and compliance with the KYNAMRO REMS Program requirements by the following:

          1) Review the Prescribing Information for KYNAMRO.

          2) Review KYNAMRO REMS Program: An Introduction
3) Complete the **KYNAMRO REMS Program Pharmacy Certification Training Module** and successfully complete the **Knowledge Assessment**.

4) Ensure all relevant staff involved in the dispensing of KYNAMRO are trained on the KYNAMRO REMS Program requirements as described in the **KYNAMRO REMS Program Pharmacy Certification Training Module and Knowledge Assessment** and maintain a record of training.

5) Put processes and procedures to ensure the following requirements are completed prior to dispensing KYNAMRO:

   a) Verify the prescriber is certified in the KYNAMRO REMS Program by reviewing the weekly data file provided by the KYNAMRO REMS Program Coordinating Center.

   b) Verify the **Patient-Prescriber Acknowledgment Form** is completed and on file at the KYNAMRO REMS Program Coordinating Center.

   c) Verify a **Prescription Authorization Form** is received for each new KYNAMRO prescription.

b. As a condition of certification:

   i. The certified pharmacy must recertify in the KYNAMRO REMS Program if the pharmacy designates a new authorized pharmacy representative.

   ii. Maintain documentation that all processes and procedures are in place and are being followed for the KYNAMRO REMS Program and provide upon request to Kastle Therapeutics, FDA, or a third party acting on behalf of Kastle Therapeutics or FDA.

   iii. Comply with audits by Kastle Therapeutics, FDA, or a third party acting on behalf of Kastle Therapeutics or FDA to ensure that all processes and procedures are in place and are being followed for the KYNAMRO REMS Program.

   iv. Provide prescription data to Kastle Therapeutics.

c. Kastle Therapeutics must:

   i. Ensure that pharmacies that dispense KYNAMRO are certified, in accordance with the requirements described above.

   ii. Provide all the following mechanisms for pharmacy to complete the certification process for the KYNAMRO REMS Program: by faxing the **Pharmacy Enrollment Form** to the KYNAMRO REMS Program Coordinating Center at 877-778-9008, by calling the KYNAMRO REMS
iii. Ensure that pharmacies are notified when they have been certified by the KYNAMRO REMS Program Coordinating Center.

iv. Ensure that certified pharmacies are provided access to a database of certified prescribers and patients who have a completed Patient-Prescriber Acknowledgment Form.

v. Verify every 12 months that the authorized representative’s name and contact information corresponds to that of the current designated authorized representative for the certified pharmacy. If different, the pharmacy must be required to re-certify with a new authorized representative.

vi. Send a REMS Letter for Pharmacists within 60 calendar days of the approval of the REMS modification (10/25/2017) to certified pharmacies. The letter must be accompanied by the KYNAMRO REMS Program: An Introduction and the Prescribing Information for KYNAMRO.

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

- KYNAMRO REMS Program Pharmacy Certification Training Module and Knowledge Assessment
- Pharmacy Enrollment Form
- REMS Letter for Pharmacists

3. **KYNAMRO must be dispensed only to patients with evidence or other documentation of safe-use conditions.**

   a. Patients/caregivers must sign a Patient-Prescriber Acknowledgment Form indicating that he/she has:
      i. Received and has read the KYNAMRO REMS Program Patient Guide;
      ii. Received counselling from the prescriber regarding:
          1) the risk of hepatotoxicity
          2) periodic liver function monitoring
          3) appropriate patient selection

   b. To authorize a patient to receive KYNAMRO under the KYNAMRO REMS Program, a certified prescriber must complete a Prescription Authorization Form for each new KYNAMRO prescription.

   c. Kastle Therapeutics must:
i. Provide all of the following mechanisms for the certified prescriber to be able to submit the completed *Patient-Prescriber Acknowledgment Form* to the KYNAMRO REMS Program Coordinating Center: faxing to 877-778-9008.

ii. Ensure that the certified pharmacies complete the verifications required under Section A.2. for each patient prior to dispensing.

iii. Ensure that the certified pharmacies are able to verify KYNAMRO is dispensed to patients only if there is evidence or other documentation that they have met the following requirements:

   1) Prescriber is certified.

   2) Patient’s *Patient-Prescriber Acknowledgment Form* is completed.

   3) A *Prescription Authorization Form* is received for each new KYNAMRO prescription.

B. Implementation System

1. Kastle Therapeutics must ensure that KYNAMRO is distributed only to certified pharmacies by

   a. Ensuring that wholesalers/distributors that distribute KYNAMRO comply with the program requirements for wholesalers/distributors. The wholesalers/distributors must:

      i. Put processes and procedures in place to verify, prior to distributing KYNAMRO, that the pharmacies are certified.

      ii. Train all relevant staff on the KYNAMRO REMS Program requirements.

   iii. Comply with audits by Kastle Therapeutics, FDA, or a third party acting on behalf of Kastle Therapeutics or FDA to ensure that all processes and procedures are in place and are being followed for the KYNAMRO REMS Program. In addition, wholesalers/distributors must maintain appropriate documentation and make it available for audits.

   iv. Provide distribution data to the KYNAMRO REMS Program to verify compliance with the REMS.

   b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of KYNAMRO and provide the data to the KYNAMRO REMS Program.
2. Kastle Therapeutics must monitor distribution data to ensure all the processes and procedures are in place and functioning to support the requirements of the KYNAMRO REMS Program.

3. Kastle Therapeutics must audit the wholesalers/distributors within 60 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the KYNAMRO REMS Program. Corrective action must be instituted by Kastle Therapeutics if noncompliance is identified.

4. Kastle Therapeutics must maintain a validated, secure database of all certified pharmacies and prescribers in the KYNAMRO REMS Program.

5. Kastle Therapeutics must maintain a validated, secure database of patients who have a completed the Patient-Prescriber Acknowledgment Form.

6. Kastle Therapeutics must maintain records of KYNAMRO distribution and dispensing, certified prescribers, certified pharmacies, wholesalers/distributors, and patients who have a completed the Patient-Prescriber Acknowledgment Form, to meet REMS requirements.

7. Kastle Therapeutics must maintain a KYNAMRO REMS Program Coordinating Center at 1-877- KYNAMRO (596-2676) and KYNAMRO REMS Program website (www.KynamroREMS.com). The KYNAMRO REMS Program website must include the capability to complete prescriber certification online, the option to print the Prescribing Information, Medication Guide, and KYNAMRO REMS Program materials. The KYNAMRO product website must include a prominent REMS-specific link to KYNAMRO REMS Program website. The KYNAMRO REMS Program website must not link back to the product website.

8. Kastle Therapeutics must ensure that the KYNAMRO REMS Program website is fully operational and the REMS materials listed in or appended to the KYNAMRO REMS document are available through the KYNAMRO REMS Program website and by calling the KYNAMRO REMS Program Coordinating Center.

9. Kastle Therapeutics must monitor on an ongoing basis the certified pharmacies to ensure the requirements of the KYNAMRO REMS Program are being met. Kastle Therapeutics must institute corrective action if noncompliance is identified and decertify pharmacies that do not maintain compliance with the REMS requirements.

10. Kastle Therapeutics must maintain an ongoing audit plan and conduct annual audits that involves wholesalers/distributors, and pharmacies.

11. Kastle Therapeutics must audit all certified pharmacies within 120 calendar days after the pharmacy is certified to ensure that all processes and procedures are in
place and functioning to support the requirements of the KYNAMRO REMS Program. The certified pharmacies must be included in Kastle Therapeutics ongoing annual audit plan. Kastle Therapeutics must institute corrective action if noncompliance is identified.

12. Kastle Therapeutics must take reasonable steps to improve implementation of and compliance with the requirements in the KYNAMRO REMS Program based on monitoring and evaluation of the KYNAMRO REMS Program.

C. Timetable for Submission of Assessments

Kastle Therapeutics must submit REMS Assessments to FDA at 6 months, 12 months, and annually thereafter from the date of initial approval of the KYNAMRO REMS (01/29/2013). 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 calendar days before the submission date for that assessment. Kastle Therapeutics must submit each assessment so that it will be received by FDA on or before the due date.