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 Program Coordinating Center at 877-778-9008, and by accessing the KYNAMRO REMS Program website.
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.
KYNAMRO® REMS Program

KYNAMRO (mipomersen sodium) injection
Risk Evaluation and Mitigation Strategy (REMS) Program: An Introduction

Only health care professionals who are trained and enrolled in the KYNAMRO REMS Program may prescribe KYNAMRO.

KYNAMRO is available only through a designated network of specialty pharmacies.

Train, enroll, and start prescribing KYNAMRO for your homozygous familial hypercholesterolemia (HoFH) patients.

**Train**
- Review the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction
- Complete the KYNAMRO REMS Program Certification Training Module, and successfully complete the Knowledge Assessment

**Enroll**
- Enroll in the KYNAMRO REMS program by completing the KYNAMRO REMS Program Prescriber Enrollment Form, and fax the form to the KYNAMRO REMS Program Coordinating Center

**Prescribe**
- 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 a copy to the patient
- Complete the KYNAMRO REMS Program Patient-Prescriber Acknowledgment Form for each patient, and fax the form to the KYNAMRO REMS Program Coordinating Center
- Prescribe KYNAMRO for each patient by completing the KYNAMRO REMS Program Prescription Authorization Form, and faxing the form to the KYNAMRO REMS Program Coordinating Center

The materials needed to train and enroll into the KYNAMRO REMS Program are available at www.KYNAMROREMS.com.

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

1. 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.
2. KYNAMRO is dispensed only to patients with a clinical or laboratory diagnosis consistent with HoFH.
3. Patients are informed about the risk of hepatotoxicity associated with the use of KYNAMRO and the need for baseline and periodic monitoring.

Questions concerning the KYNAMRO REMS Program?
Contact the KYNAMRO REMS Coordinating Center

Phone: 1-877-596-2676 | Fax: 1-877-778-9008 | www.KYNAMROREMS.com

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Reference ID: 4171886
**Note to Reviewer:**

- The KYNAMRO® REMS Program Prescriber Certification Training Module and Knowledge Assessment can be accessed online by clicking the link at KYNAMROREMS.com

- The participant will need to register prior to starting the Training Module and Knowledge Assessment

  - To register, participants will be required to enter their name, practice name, city, state, zip code, and NPI number. The participant’s email address will also be requested; however, if this is not provided, the participant will be able to start the module. The registration information will be used to populate a **Certificate of Completion** that will be generated upon completion of the Knowledge Assessment. The participant will be required to fax the certificate and a completed **Prescriber Enrollment Form** to the KYNAMRO REMS Program Coordinating Center to be confirmed as REMS certified to prescribe KYNAMRO
An Overview of the KYNAMRO® Risk Evaluation and Mitigation Strategy (REMS) Program

KYNAMRO REMS Program Prescriber Certification Training Module and Knowledge Assessment
Contents

Introduction

KYNAMRO® ( mipomersen sodium) Injection
Product Information
  – Indication and Limitations of Use
  – Appropriate Patient Selection
  – Contraindication
  – Boxed Warning for Hepatotoxicity
  – Risk of Hepatotoxicity
  – Dosing and Administration
  – Patient Monitoring
  – Adverse Reactions

KYNAMRO REMS Program
  – Overview & Program Goals
  – Prescriber Training & Enrollment
  – Counsel Patients
  – Prescription & Dispensing

KYNAMRO Knowledge Assessment
INTRODUCTION
Introduction

• This training module has been developed as part of the KYNAMRO REMS Program to:
  – Educate prescribers on the approved indication in patients with HoFH, 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

• The interactive Knowledge Assessment will follow the training module. You must correctly answer each of the 6 questions to become REMS certified to prescribe KYNAMRO

  • Estimated time to complete the Training Module and Knowledge Assessment is 30 minutes
KYNAMRO PRODUCT INFORMATION

KYNAMRO®
(mipomersen sodium) injection
200mg/ml
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)

• Selected Limitations of use
  – The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH)
Appropriate Patient Selection

• KYNAMRO is only indicated for use in patients with HoFH

• Patients must have a clinical or laboratory diagnosis consistent with HoFH
• 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

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 Hepatotoxicity

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) $\geq 3x$ 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 $\geq 3x$ 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. Prescribe KYNAMRO only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH.
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.
  – In the clinical trial, 4 (12%) of the 34 subjects with HoFH treated with KYNAMRO compared to 0% of the 17 subjects treated with placebo had an elevation in ALT >3x ULN, and 3 (9%) of those treated with KYNAMRO compared to 0% treated with placebo had at least one elevation in ALT >5x ULN.
Risk of Hepatotoxicity

• Hepatic steatosis
  – KYNAMRO increases hepatic fat (steatosis) with or without concomitant increases in transaminases.
  – Hepatic steatosis is a risk factor for advanced liver disease including steatohepatitis and cirrhosis.
  – During the clinical trial 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% baseline, measured by magnetic resonance imaging (MRI).
Dosing and Administration

• The recommended dose of KYNAMRO is 200 mg once weekly as a subcutaneous injection:
  – KYNAMRO is available in a pre-filled syringe
  – Each 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
## Recommendations for Monitoring Hepatic Transaminases

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<thead>
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<th>Time</th>
<th>Recommendation</th>
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| Before initiating treatment | • Measure liver-related tests (ALT, AST), alkaline phosphatase, and total bilirubin  
• If abnormal, consider initiating KYNAMRO only after an appropriate work-up and the baseline abnormalities have been explained or resolved  
• KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevation of serum transaminases |
| During first Year           | • Measure liver-related tests (ALT and AST, at a minimum), alkaline phosphatase, and total bilirubin monthly                                       |
| After first year            | • Measure liver-related tests (ALT and AST, at a minimum), alkaline phosphatase, and total bilirubin, at least every 3 months                  |
| At anytime during treatment | • If transaminases are abnormal, withhold dose of KYNAMRO and monitor as recommended [see Dosage and Administration (2.3)]  
• Discontinue KYNAMRO for persistent or clinically significant elevations  
• If transaminase elevations are accompanied by clinical symptoms of liver injury (such as 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 |
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 &amp; Monitoring Recommendations *</th>
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| ≥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 Kastle Therapeutics at 877-279-2308 or FDA at 800-FDA-1088 or [www.fda.gov/medwatch](http://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:
  – Prescriber must be certified to prescribe KYNAMRO
    o To become certified to prescribe KYNAMRO, prescribers must be trained and enrolled in the KYNAMRO REMS Program
  – Patients must be educated about risk of hepatotoxicity and have clinical or laboratory diagnosis of HoFH
  – Pharmacies must be certified in order to dispense KYNAMRO
Program Goals

• The goal of the KYNAMRO REMS Program is to mitigate the risk of hepatotoxicity associated with the use of KYNAMRO by ensuring that:
  – Prescribers are educated about:
    o the approval indication of KYNAMRO
    o the risk of hepatotoxicity associated with the use of KYNAMRO
    o the need to monitor patients during treatment with KYNAMRO 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
Prescriber Certification Training

Overview

• Prescriber must complete the following KYNAMRO REMS Program training before prescribing KYNAMRO for their HoFH patient:

TRAIN
• Review the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction
• Complete the KYNAMRO REMS Program Certification Training Module, successfully complete the Knowledge Assessment and fax to the KYNAMRO REMS Program Coordinating Center

ENROLL
• Complete the KYNAMRO REMS Program Prescriber Enrollment Form and submit the form to the KYNAMRO REMS Program Coordinating Center

• Prescriber needs to only complete the KYNAMRO REMS Program training once before starting his/her first patient on KYNAMRO
  – Recertification may be required if there are any updates to the KYNAMRO REMS Program
Prescribing KYNAMRO
Overview

PRESCRIBE

1. Review the KYNAMRO REMS Program Patient Guide with each patient to counsel about the appropriate use and risks associated with KYNAMRO, and provide a copy to the patient

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

3. Prescribe KYNAMRO for each patient by completing the KYNAMRO REMS Program Prescription Authorization Form and submit to KYNAMRO REMS Program Coordinating Center
Prescribing KYNAMRO
KYNAMRO REMS PROGRAM Patient Guide

• Review the KYNAMRO REMS Program Patient Guide with each patient to counsel about the appropriate use of risks associated with KYNAMRO, and provide the patient with a copy of the guide.

• Next, please review the Patient-Prescriber Acknowledgment Form

• The Patient Guide and Patient-Prescriber Acknowledgment Form can be accessed at www.KYNAMROREMS.com
Summary of KYNAMRO Benefits and Risks

Patient must sign to acknowledge that they've reviewed the benefits and risks with the prescriber.

Prescriber must sign to acknowledge they reviewed the benefits and risks with the patient.

Fax to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008.
For a patient to receive KYNAMRO, the Prescription Authorization Form must be completed in its entirety.

1. Patient information and insurance information should be completed in the first and second box of the form.

2. Prescriber information should be completed in the third section of the form.

3. Carefully review the Attestation of the REMS Program requirements.

4. Prescription information should be completed in the last section of the form.

5. Once form has been completed, fax the signed form to the REMS Program Coordinating Center at 1-877-778-9008.
KYNAMRO REMS PROGRAM
Training, Enrolling and Prescribing Summary

TRAIN
- Review the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction

ENROLL
- Complete the KYNAMRO REMS Program Certification Training Module
- Complete the KYNAMRO REMS Program Prescriber Enrollment Form
- Fax both completed Prescriber Enrollment Form & Certificate to 1-877-778-9008
- REMS Coordinating Center will fax confirmation that prescriber is REMS certified

PRESCRIBE
- Review the KYNAMRO REMS Program Patient Guide with each patient and provide a copy to the patient
- Complete the KYNAMRO REMS Program Patient-Prescriber Authorization Form for each patient, and fax to 1-877-778-9008
- Complete the KYNAMRO REMS Program Prescription Authorization Form for each patient and fax to 1-877-778-9008

Reference ID: 4171886
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KNOWLEDGE ASSESSMENT
Knowledge Assessment

- You must answer all 6 questions correctly

- If your answer is incorrect, you will be directed to review the relevant section within the training module. Once you have completed the review, you will be able to return to answer the question again. You will not be able to continue the assessment until you have answered the question correctly.

- Upon completion, you will be directed to print your Certificate of Completion, and then fax it to the KYNAMRO REMS Program Coordinating Center along with your Prescriber Enrollment Form.
1. KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apoB, TC, and non-HDL-C in patients with all forms of familial hypercholesterolemia

- True
- False
Knowledge Assessment – 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 transaminase (ALT and AST)
- Total bilirubin
- 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
Knowledge Assessment – Question 4

4. 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
- Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended.
- Because the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS.
- All of the above
Knowledge Assessment – Question 5

5. Which actions must a REMS-certified prescriber take in order to complete the prescription process? Check all that apply

- Once the prescriber has reviewed the risks and benefits of KYNAMRO, the prescriber can prescribe KYNAMRO by completing a Prescription Authorization Form and sending it to into their preferred pharmacy
- Prescriber must review the Patient Guide with the patient to discuss the risks and benefits of KYNAMRO, and provide them a copy of the Patient Guide
- Prescriber and patient must complete the Patient-Prescriber Acknowledgement Form, and then fax the signed form to the KYNAMRO REMS Program Coordinating Center
- Prescriber must complete the Prescription Authorization Form and fax it to the KYNAMRO REMS Program Coordinating Center
Knowledge Assessment – Question 6

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

You have successfully completed the Prescriber Training Module and Knowledge Assessment.

Click here to print your Certificate of Completion

NEXT STEPS

• Download and print the pdf of your Certificate of Completion (see link, above)
• Complete and sign the Prescriber Enrollment Form.
  A downloadable pdf of the form can be accessed at www.KYNAMROREMS.com
• Fax the Certificate of Completion and the Prescriber Enrollment Form to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008

Click here to print the Training Module to be used as an overview reference for the KYNAMRO REMS Program

If all certification requirements are met, the KYNAMRO REMS Program Coordinating Center will confirm, by fax, that you are REMS certified to prescribe KYNAMRO.

Reference ID: 4171886
CERTIFICATE OF COMPLETION

KYNAMRO Risk Evaluation and Mitigation Strategy (REMS) Program

This certifies that

[HCP NAME],
[HPI: #### #### ####], of [Practice Name]

has successfully completed the KYNAMRO REMS Program Prescriber Certification Training Module & Knowledge Assessment

[Month/Day/Year]
KYNAMRO® REMS Program

Prescriber Enrollment Form

KYNAMRO (mipomersen sodium) injection is available only through KYNAMRO Risk Evaluation and Mitigation Strategy (REMS).

In order to be REMS certified, a prescriber must:

1. Review the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction.
2. Complete the KYNAMRO REMS Program Prescriber Certification Training Module and successfully complete the Knowledge Assessment.
3. Complete this one-time KYNAMRO REMS Program Prescriber Enrollment Form.

Fax forms as described below to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008.

If you have taken the online version of the Prescriber Certification Training Module, fax:
1) Your Certification of Completion and 2) both pages of this Prescriber Enrollment Form

If you have taken the print version of the Prescriber Certification Training Module, fax:
1) The completed Knowledge Assessment form and 2) both pages of this Prescriber Enrollment Form

Prescriber Information (all information required)

Name (first, middle, last) Credentials
[ ] MD [ ] DO [ ] NP [ ] PA [ ] Other

Name of Institution/Practice Name

Practice Setting:
[ ] Hospital-Based Practice [ ] Private/Group Practice [ ] University (Academic) Center

Prescriber Specialty (board certification):
[ ] Cardiology [ ] Endocrinology [ ] Family Medicine [ ] Internal Medicine [ ] Other (please specify)

Practice Address

City State Zip Code Preferred Method of Contact
[ ] Fax [ ] Phone

Email Address Office Phone Number Office Contact Name Office Fax Number

Primary State License Number/State of Issue National Provider Identification (NPI) Number

Please read the Prescriber Attestation on page 2. Sign form and submit both pages.

Questions? Contact the KYNAMRO REMS Program Coordinating Center
Phone: 1-877-596-2676 | Fax: 1-877-778-9008 | www.KYNAMROREMS.com
All of the KYNAMRO REMS Program documents are available at www.KYNAMROREMS.com
Please see Full Prescribing Information on KYNAMRO.com

Reference ID: 4171886
Prescriber Enrollment Form Page 1 of 2
Prescriber Attestation

By signing this form, I attest that:

I understand that KYNAMRO® is available only through the KYNAMRO REMS Program and that I must comply with the program requirements in order to prescribe KYNAMRO.

Use:

- 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 the safety and effectiveness of KYNAMRO has not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH)

Hepatotoxicity Risk:

- I understand that there is a risk of hepatotoxicity associated with KYNAMRO
- I understand the Recommendations for Monitoring Transaminases with KYNAMRO treatment:
  - Before initiating therapy, measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin
  - During the first year, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly
  - After the first year, these parameters should be measured at least every 3 months

REMS Requirements:

- I have reviewed the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction
- I have completed the KYNAMRO REMS Program Prescriber Certification Training Module, including Knowledge Assessment
- I agree to counsel patient on the risk of hepatotoxicity with KYNAMRO and the need for regular monitoring using the KYNAMRO REMS Program Patient Guide
- I will complete and submit a KYNAMRO REMS Program Patient-Prescriber Acknowledgment Form
- I will complete and submit a KYNAMRO REMS Program Prescription Authorization Form for each new prescription
- I understand that KYNAMRO is available only through the KYNAMRO REMS Program and that I must comply with the program requirements in order to prescribe KYNAMRO
- 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 agree that Kastle Therapeutics, 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________________________

Print Name____________________________________________________

Fax both pages to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008.
Please refer to the KYNAMRO Medication Guide for complete information.

**What is KYNAMRO?**

KYNAMRO is a prescription medicine for the treatment of homozygous familial hypercholesterolemia (HoFH) that is used with diet and other lipid-lowering treatments to reduce:

- LDL ("bad") cholesterol
- Total cholesterol (TC)
- A protein that carries "bad" cholesterol in the blood (apolipoprotein B)
- Non–high-density lipoprotein cholesterol (non-HDL-C)

Because of the risk of liver problems, KYNAMRO should be taken only by people with HoFH. It is not known if KYNAMRO is safe and effective in people with high cholesterol who do not have HoFH, including in people who have heterozygous familial hypercholesterolemia (HeFH).

**What is the most serious risk with taking KYNAMRO?**

KYNAMRO can cause liver problems such as increased liver enzymes or increased fat in the liver. Your doctor will order a blood test to check your liver before you start KYNAMRO and while you are taking KYNAMRO. Blood test results will tell your doctor if certain liver enzyme levels are higher than normal. Enzyme levels higher than normal can be an early sign of liver problems. If your test shows signs of liver problems, your doctor may stop KYNAMRO.

Tell your doctor right away if you have any of the following symptoms, as they may be signs of liver problems:

- Nausea, vomiting, or stomach pain that gets worse, changes, or does not go away
- Fever
- Yellowing of your eyes or skin
- Feeling more tired than normal
- Flu-like symptoms

Tell your doctor if you have had liver problems, including liver problems while taking other medications. Drinking alcohol may increase your chance of having liver problems or make your liver problems worse. You should not have more than 1 alcoholic drink each day while using KYNAMRO. There are other side effects associated with the use of KYNAMRO. Talk to your doctor about the other risks associated with KYNAMRO.

**What is the KYNAMRO REMS Program?**

- Because of the possible risk of liver problems, KYNAMRO is available only through a special program called the KYNAMRO REMS Program
- Your doctor will discuss the benefits and risks of KYNAMRO with you
- You and your doctor will sign the KYNAMRO REMS Program Patient-Prescriber Acknowledgment Form. You must sign this form in order to receive KYNAMRO

**How do I receive KYNAMRO?**

- KYNAMRO is available only through a REMS-certified pharmacy
- The KYNAMRO REMS Program Coordinating Center will call you to tell you the name and phone number of the certified pharmacy that will fill your KYNAMRO prescription
- The certified pharmacy will call you to arrange the date to ship KYNAMRO to you
- Call the KYNAMRO REMS Program Coordinating Center at 1-877-KYNAMRO (1-877-596-2676) if you need assistance with your prescription

For more information about KYNAMRO, please see the KYNAMRO Medication Guide available at www.KYNAMROREMS.com.
**Instructions for Health Care Providers**

1. Counsel the patient on the benefits and risks of KYNAMRO ( mipomersen sodium) injection.
2. Complete each section of the form with the patient as required.
3. Provide a signed copy of this form to the patient along with the KYNAMRO REMS Program Patient Guide.
4. Fax completed Acknowledgment Forms to the KYNAMRO REMS Coordinating Center at 1-877-778-9008.

Please note that without this form completed, the KYNAMRO prescription for your patient will be delayed.

**Patient Acknowledgment of KYNAMRO Benefits and Risks**

**Benefits:**
- KYNAMRO is used along with diet and other lipid-lowering treatments in people with homozygous familial hypercholesterolemia (HoFH) to reduce:
  - LDL (“bad”) cholesterol
  - Total cholesterol
  - A protein that carries “bad” cholesterol in the blood (apolipoprotein B)
  - Non-high-density lipoprotein cholesterol (non-HDL-C)

**Risks:**
- KYNAMRO may cause liver problems, such as increased liver enzymes or increased fat in the liver
- Because of these serious side effects, KYNAMRO is only for people with HoFH
- I will need to have blood tests before and during KYNAMRO treatment to check my liver’s enzymes. If my tests show some liver problems, my doctor may stop treatment with KYNAMRO

By signing this form, I acknowledge that:
- I received, read, and understand the information in the KYNAMRO REMS Program Patient Guide
- My health care provider told me about the benefits and risks of KYNAMRO therapy
- My health care provider answered all of my questions or concerns about my treatment with KYNAMRO
- The risks listed on this form are not all of the risks of KYNAMRO treatment

**Written Permission to Share Information**

- I permit my health care provider to share this form with Kastle Therapeutics and their contractors. The Program Sponsors and Contractors agree to keep my information secure. They will use it only to make sure KYNAMRO REMS Program rules are being followed
- My permission lasts until the KYNAMRO REMS Program ends. I can cancel my permission at any time by providing written notice to my health care provider

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<th>Signature of patient</th>
<th>Signature of patient representative</th>
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<th>Printed patient name</th>
<th>Printed patient representative name</th>
<th>Relationship of patient representative to patient (if applicable)</th>
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**Health Care Provider Acknowledgment**

I acknowledge that prior to the initiation of this new course of KYNAMRO therapy:
- I counseled the patient on the benefits and risks of KYNAMRO by reviewing the Acknowledgment Form
- I discussed all concerns and answered all questions the patient had about treatment with KYNAMRO
- The patient or patient representative signed the Acknowledgment Form, and I provided a copy of the signed KYNAMRO REMS Program Patient Guide to the patient

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<th>Signature of health care provider</th>
<th>Printed name of health care provider</th>
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**Questions? Contact the KYNAMRO REMS Program Coordinating Center**

Phone: 1-877-596-2676 | Fax: 1-877-778-9008 | www.KYNAMROREMS.com

All of the KYNAMRO REMS Program documents are available at www.KYNAMROREMS.com

Please see Full Prescribing Information on KYNAMRO.com

Reference ID: 4171888
Complete all sections of this form. Please note that processing of your patient's prescription could be delayed if any section is incomplete.
Fax the completed form to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008.

### PATIENT INFORMATION

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### PATIENT INSURANCE INFORMATION

Please complete below or attach a copy of both sides of the patient's insurance and/or prescription card(s)

- Patient has no insurance [ ] [If your patient does not have insurance, no further information is required in this section after you have checked this box]

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<td>Policyholder's Date of Birth</td>
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<td>Relationship to Patient</td>
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- Have you provided a copy of all insurance cards? [ ]
- Medical Card [ ]
- Prescription Card [ ]

### KYNAMRO REMS CERTIFIED PRESCRIBER INFORMATION

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<th>Name (first, middle, last)</th>
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Attestation of KYNAMRO REMS Program Requirements:

- I understand that KYNAMRO is indicated only as an adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, 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.
  - Before initiating therapy, measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin.
  - During the first year, liver-related tests (ALT, and AST, at a minimum) must be measured monthly.
  - After the first year, these parameters should be measured at least every 3 months.

By signing below, I attest to the REMS requirements above and also authorize the KYNAMRO REMS Program Coordinating Center to forward this prescription on my behalf to a certified pharmacy to dispense KYNAMRO to the patient named above.

### KYNAMRO PRESCRIPTION

- Rx: KYNAMRO® (mipomersen sodium) Injection 200 mg/mL, 1 mL Prefilled Syringe
- Dx: [ ] Clinical or laboratory diagnosis consistent with HoFH (there is currently no HoFH-specific ICD-10 code)
- Sig: [ ] Inject 1 mL of 200 mg/mL subcutaneously once a week OR [ ]
- Dispense: [ ] Box of 4 prefilled syringes OR [ ] Box of 1 prefilled syringe
- Refills: [ ] 11 refills [ ] ___ refills [ ] NR
- [ ] Dispense as written [ ] Request for Home Injection Training

Prescriber Signature __________________________ Date ____________

Print Name ___________________________

Questions? Contact the KYNAMRO REMS Program Coordinating Center
Phone: 1-877-595-2676 | Fax: 1-877-778-9008 | www.KYNAMROREMS.com

Reference ID: 4171886

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RECERTIFICATION REQUIRED
KYNAMRO REMS Program Changes For Healthcare Professionals

Dear Healthcare Professional:

This letter is to inform you of recent changes in the KYNAMRO® ( mipomersen sodium) injection Risk Evaluation and Mitigation Strategy (REMS) Program. To continue to prescribe KYNAMRO, healthcare professionals must recertify in the KYNAMRO REMS Program by Month, Day, 2017.

Action Required
All currently enrolled healthcare professionals must recertify by Month, Day, 2017 in order to continue to prescribe KYNAMRO. To recertify in the KYNAMRO REMS Program, healthcare professionals must:

- Review the KYNAMRO Prescribing Information and the KYNAMRO REMS Program: An Introduction.
- Complete the updated KYNAMRO REMS Program Certification Training Module and successfully complete the Knowledge Assessment.
- Enroll in the KYNAMRO REMS program by completing the KYNAMRO REMS Program Prescriber Enrollment Form and submit to the KYNAMRO REMS Program Coordinating Center.

How To Enroll or Re-Certify in the KYNAMRO REMS Program
- Call the KYNAMRO REMS Program Coordinating Center at 1-877-596-2676.
- Contact your Kastle Clinical Science Specialist
- Learn more at www.KYNAMROREMS.com

The KYNAMRO REMS Program now has additional requirements for both healthcare professionals and patients. Before prescribing KYNAMRO you must:

1. 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 a copy to the patient.
2. Complete the KYNAMRO REMS Program Patient - Prescriber Acknowledgment Form with each patient, and submit it to the KYNAMRO REMS Program Coordinating Center.
3. Prescribe KYNAMRO for each patient by completing the KYNAMRO REMS Program Prescription Authorization Form and submit to the KYNAMRO REMS Program Coordinating Center.

Please see the accompanying Prescribing Information for your reference. As always, please report any adverse events to Kastle Drug Info at 1- 877-279-2308 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Sincerely,

Stuart Kupfer
Chief Medical Advisor, Kastle Therapeutics
The FDA has required a REMS Program for KYNAMRO ( mipomersen sodium) injection so that the benefits of the drug outweigh the risks to patients. The KYNAMRO REMS Program Coordinating Center is here to help healthcare providers and pharmacists complete the training, enroll, and be certified in the KYNAMRO REMS Program.

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

- Healthcare providers 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 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.

Both healthcare providers and pharmacies need to be trained, enrolled, and thereby certified in the KYNAMRO REMS Program before healthcare providers can prescribe KYNAMRO and pharmacies can dispense KYNAMRO.

For healthcare providers to become certified in the KYNAMRO REMS Program:

1. **Train**
   - Click to open and review all of the educational materials below, including the KYNAMRO REMS Certification Training Module and Knowledge Assessment.
   - The Training Module, Introduction, and Knowledge Assessment are intended to be read in conjunction with your preparation for certification. The interactive Knowledge Assessment will follow the Training Module. You must correctly answer each of the 5 questions to become REMS certified to prescribe KYNAMRO. The estimated time to complete the Training Module and Knowledge Assessment is 30 minutes.

2. **Enroll**
   - Download and complete the Prescriber Enrollment Form below. Fax completed form to 1-877-778-9008.

3. **Prescribe**
   - Review the KYNAMRO REMS Program Patient Guide below with each patient to counsel the patient about the appropriate use and risks associated with KYNAMRO, and provide a copy to the patient.
   - Complete the KYNAMRO REMS Program Patient Prescriber Acknowledgment Form below for each patient, and fax the form to the KYNAMRO REMS Program Coordinating Center.
   - Prescribe KYNAMRO for each patient by completing the KYNAMRO REMS Program Prescription Authorization Form below, and faxing the form to the KYNAMRO REMS Program Coordinating Center (1-877-778-9008).

Pharmacies wishing to be KYNAMRO REMS certified, please contact the KYNAMRO REMS Program Coordinating Center at 1-877-KYNAMRO (1-877-596-2676) for more information.
An Overview of the KYNAMRO®
Risk Evaluation and Mitigation
Strategy (REMS) Program

KYNAMRO REMS Program Pharmacy Certification Training
Module and Knowledge Assessment
Contents

Introduction

KYNAMRO® (mipomersen sodium) Injection
Product Information
  – Indication and Limitations of Use
  – Appropriate Patient Selection
  – Contraindication
  – Boxed Warning for Hepatotoxicity
  – Risk of Hepatotoxicity
  – Dosing and Administration
  – Adverse Reactions

KYNAMRO REMS Program
  – Pharmacy Training Overview & Program Goals
  – Prescription & Dispensing

KYNAMRO Knowledge Assessment

This training contains important information about your Specialty Pharmacy’s role in the KYNAMRO REMS program

Reference ID: 4171886
INTRODUCTION
Introduction

• This training module has been developed as part of the KYNAMRO REMS Program to:
  – Educate pharmacists on the risk of hepatotoxicity associated with the use of KYNAMRO
  – Provide information on the KYNAMRO REMS Program requirements, including how to enroll in the KYNAMRO REMS Program, and requirements for dispensing KYNAMRO

• 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
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)

• Selected Limitations of use
  – The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH)
Appropriate Patient Selection

- KYNAMRO is only indicated for use in patients with HoFH
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
Contraindication

• 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

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 Hepatotoxicity

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 ≥3x 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. Prescribe KYNAMRO only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH.
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.
  – In the clinical trial, 4 (12%) of the 34 subjects with HoFH treated with KYNAMRO compared to 0% of the 17 subjects treated with placebo had an elevation in ALT >3x ULN, and 3 (9%) of those treated with KYNAMRO compared to 0% treated with placebo had at least one elevation in ALT >5x ULN.
Risk of Hepatotoxicity

• Hepatic steatosis
  – KYNAMRO increases hepatic fat (steatosis) with or without concomitant increases in transaminases.
  – Hepatic steatosis is a risk factor for advanced liver disease including steatohepatitis and cirrhosis.
  – During the clinical trial 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% baseline, measured by magnetic resonance imaging (MRI).
The recommended dose of KYNAMRO is 200 mg once weekly as a subcutaneous injection:

- KYNAMRO is available in a pre-filled syringe
- Each 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
Adverse Reaction Reporting

• To report SUSPECTED ADVERSE REACTIONS, contact Kastle Therapeutics at 877-279-2308 or FDA at 800-FDA-1088 or www.fda.gov/medwatch
KYNAMRO REMS PROGRAM
Program Goals

- The goal of the KYNAMRO REMS Program is to mitigate the risk of hepatotoxicity associated with the use of KYNAMRO by ensuring that:
  - Prescribers are educated about:
    - The approval indication of KYNAMRO
    - The risk of hepatotoxicity associated with the use of KYNAMRO
    - The need to monitor patients during treatment with KYNAMRO 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
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:

- Certified Prescriber
  - ONLY prescribers trained, enrolled and thereby certified can prescribe KYNAMRO
- Patient Education
  - Patients must be educated on the approved indication, the risks and the need for regular monitoring
- Certified Pharmacies
  - ONLY pharmacies trained and thereby certified can dispense KYNAMRO
  - Restrict access to therapy with KYNAMRO to patients with a clinical or laboratory diagnosis consistent with Homozygous familial hypercholesterolemia (HoFH)
  - KYNAMRO can ONLY be dispensed to patients with evidence or other documentation of safe use conditions. This is confirmed on the KYNAMRO Prescription Authorization Form.
Pharmacy Training Overview

Each pharmacy must be REMS certified before KYNAMRO may be dispensed:

**Pharmacy TRAINING**
- Review the KYNAMRO Prescribing Information and **KYNAMRO REMS Program: An Introduction**
- Complete the **KYNAMRO REMS Program Pharmacy Certification Training Module**, successfully complete the **Knowledge Assessment** and fax to the KYNAMRO REMS Program Coordinating Center

**Pharmacy ENROLLMENT**
- Complete the **KYNAMRO REMS Program Pharmacy Enrollment Form** and submit the form to the KYNAMRO REMS Program Coordinating Center

**Pharmacy Dispensing Process**
- The prescriber is certified in the KYNAMRO REMS Program by checking the REMS Certified Prescriber Report prior to dispensing
- The **KYNAMRO REMS Program Prescription Authorization Form** is received for each new prescription
- The **KYNAMRO REMS Program Patient-Prescriber Acknowledgement Form** is on file with the REMS Program Coordinating Center

Reference ID: 4171886
Pharmacy Roles and Responsibilities

Each Certified Pharmacy must:

• Agree to be audited to ensure that all processes and procedures are in place and are being followed for the KYNAMRO REMS program
• Agree to cooperate with Kastle for the investigation of root causes of noncompliance with KYNAMRO REMS program-required dispensing/reporting and any corrective and/or preventive actions taken to address noncompliance;
• Provide KYNAMRO prescription data to Kastle that includes:
  – Number of KYNAMRO prescriptions dispensed, including quantity of pre-filled syringes; number of prescriptions dispensed without a signed attestation on the Prescription Authorization Form
  – Number and demographics (e.g. gender, age, geographic location) of patients who received KYNAMRO;
  – Report of the number, length, and reasons for shipment delays to patients, if any
  – Provide reports in a format and frequency required by Kastle

NOTE: Only Specialty Pharmacy Providers and locations who have received written notification from the Kastle REMS Administrator that they have been REMS certified in the KYNAMRO REMS program, can dispense KYNAMRO.
Pharmacy Certification Training

• Authorized Pharmacy Representative (APR) must complete the following KYNAMRO REMS Program training before SPP location may dispense KYNAMRO:
  1. Review Prescribing Information
  2. Review KYNAMRO REMS Program: An Introduction, which summarizes the risks and requirements of the REMS program
  3. Complete this KYNAMRO REMS Program Pharmacy Certification Training Module
  4. Complete, sign, and fax the KYNAMRO REMS Program Knowledge Assessment and KYNAMRO REMS Program Pharmacy Enrollment Form to KYNAMRO REMS Program Coordinating Center
  5. APR must educate all pharmacy staff involved in the dispensing of KYNAMRO on the KYNAMRO REMS Program requirements and putting in appropriate processes to ensure compliance with the REMS program.

• APR needs to only do complete the KYNAMRO REMS Program training once before first dispensing KYNAMRO
  • Recertification is required if there is a change in the authorized representative.
Required Dispensing Process – Receipt of Prescription Authorization Form Directly From Kastle

- KYNAMRO is only available through a designated network of Specialty Pharmacy Providers (SPPs) that are certified in the KYNAMRO REMS Program
- Prescriptions for KYNAMRO must be written by the prescriber using the REMS Prescription Authorization Form (PAF) and sent to the KYNAMRO REMS Coordinating Center
- Upon receipt of a completed Prescription Authorization Form, KYNAMRO REMS Coordinating Center will:
  - Confirm prescriber is REMS-certified
  - Perform complete insurance benefit investigation, prior authorization support, etc.
  - Confirm SPP is REMS-certified
- When above work is completed, KYNAMRO REMS Program Coordinating Center will send the Prescription Authorization Form to REMS-certified SPP
- Upon receipt of the Prescription Authorization Form, the SPP will:
  1. Verify the prescriber is REMS-certified in the KYNAMRO REMS Program by checking the REMS Certified Prescriber Report prior to dispensing
  2. The KYNAMRO REMS Program Prescription Authorization Form is received for each new prescription
  3. The KYNAMRO REMS Program Patient-Prescriber Acknowledgement Form is on file with the REMS Program Coordinating Center

Note: SPP are to redirect any Prescription Authorization Forms received directly from prescribers to the KYNAMRO REMS Program Coordinating Center.
Dispensing Process – Filling a Prescription

- SPP will order Kynamro from Kastle’s 3PL provider, and maintain adequate inventory to service its current patient census without delay in prescription shipments or interruption in patient treatment.

- SPP will only dispense prescriptions written on Prescription Authorization Forms from REMS Certified prescribers that have been triaged to them from the KYNAMRO REMS Program Coordinating Center.

- Refills for existing patients can continue uninterrupted until refills are exhausted and a new Prescription Authorization Form is required. The new Prescription Authorization Form should be sent by the prescriber to the KYNAMRO REMS Program Coordinating Center and not directly to the SPP.

Reference ID: 4171886
Records and Reporting

SPPs are required to provide the following information to the KYNAMRO REMS Program Coordinating Center on a weekly basis, as specified by Kastle:

- Information on Kynamro prescriptions dispensed:
  - PrescriptionNumber
  - Prescriber name and NPI number
  - Confirmation of Prescriber REMS Certification
  - Confirmation of Completed Prescription Authorization Form with Prescriber signature to attest for patient qualification
  - Date dispensed, number of cartons and sizes dispensed
  - Dispensing Pharmacy address
  - Ship-To address

- Information on patients who received KYNAMRO:
  - Kynamro Cornerstone Program Patient ID
  - Patient First and Last Names
  - Patient Date of Birth
  - Patient Gender
  - Patient Address

- Information on special alerts:
  - Initial fill/New PatientFlag
  - Refill/Existing Patient Flag

- Information on shipping delays to patients (including number, length, and reasons)

Copies of submitted information must be retained by the SPP for at least 2 years from the date of report submittal to the REMS program.
Summary – Points to Remember

• Only Pharmacies that are REMS-Certified can dispense KYNAMRO
• Only prescribers that are REMS-Certified can prescribe KYNAMRO and only by using the Prescription Authorization Form
  - Be sure to check the weekly REMS certification report for list of certified prescribers
• Pharmacy staff must be trained on the dispensing process for KYNAMRO
  - Documentation showing compliance (training, dispensing records, etc) will be needed for auditing
• Pharmacies must provide prescription information to Kastle on a weekly basis

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

KYNAMRO is a registered trademark of Kastle Therapeutics LLC
KYNAMRO REMS PROGRAM
Pharmacist Training, Enrolling and Prescribing Summary

TRAIN
- Review the KYNAMRO Prescribing Information and KYNAMRO REMS Program: An Introduction
- Complete the KYNAMRO REMS Program Pharmacy Certification Training Module
- Complete the Knowledge Assessment Form

ENROLL
- Complete the KYNAMRO REMS Program Pharmacy Enrollment Form
- Fax both completed Knowledge Assessment Form and Pharmacy Enrollment Form to 1-877-778-9008
- Train all pharmacy staff at pharmacy location on the KYNAMRO REMS Program requirements & ensure processes for program compliance

DISPENSE
- Review & ensure all information on KYNAMRO REMS Program Prescription Authorization Form is complete
- Before dispensing KYNAMRO, confirm:
  1. The prescriber is certified in the KYNAMRO REMS Program by checking the REMS Certified Prescriber Report prior to dispensing
  2. The KYNAMRO REMS Program Prescription Authorization Form is received for each new prescription
  3. The KYNAMRO REMS Program Patient-Prescriber Acknowledgement Form is on file with the REMS Program Coordinating Center
- Ensure all data requirements are reported back to the KYNAMRO REMS Program Coordinating Center
Knowledge Assessment
Knowledge Assessment

- You must answer all 5 questions correctly

- 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.

- Fax both completed **Knowledge Assessment Form & Pharmacy Enrollment Form** to KYNAMRO REMS Program Coordinating Center
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
Knowledge Assessment– Question 2

2. KYNAMRO is indicated for the following patients. Check all that apply

- Patients must have a laboratory diagnosis consistent with HoFH
- KYNAMRO is only indicated for use in patients with HoFH
- Patients with moderate or severe hepatic impairment
- Patients must have a clinical or laboratory diagnosis consistent with HoFH
3. KYNAMRO is available from any pharmacy

- True
- False
4. Each REMS-certified pharmacy must: (Check all that apply)
- Agree to be audited to ensure that all REMS processes and procedures are in place
- Provide detailed prescription data to Kastle on a weekly basis
- May receive prescriptions directly from prescribers and dispense
- Recertify every year
5. Prior to dispensing KYNAMRO, every certified SPP must do the following:

- Verify the prescriber is certified in the KYNAMRO REMS Program by checking the REMS-Certified Prescriber Report distributed by the REMS Coordinating Center
- Receive a Prescription Authorization Form for each new prescription
- Confirm that a Patient-Prescriber Acknowledgement Form is on file with the REMS Coordinating Center
- All of the above
Now that you’ve reviewed and completed the Training Module, please submit the Knowledge Assessment Form & Pharmacy Enrollment Form and fax both to 1-877-778-9008.

The REMS Coordinating Center will review your answers and fax back a confirmation that you are REMS certified to prescribe KYNAMRO along with the Knowledge Assessment Answer Key.

For additional information on the KYNAMRO REMS Program, call 1-877-596-2676 or visit www.KYNAMROREMS.com

KYNAMRO is a registered trademark of Kastle Therapeutics.
KYNAMRO REMS Program Pharmacy Enrollment Form

Note: A separate Enrollment Form should be completed for each individual SPP location (Please print)

To complete certification, you must FAX:

1) both pages of this Pharmacy Enrollment Form and
2) the completed Knowledge Assessment Form to the KYNAMRO REMS Program Coordinating Center at 1-877-778-9008.

Pharmacy Name: ____________________________________________

Address 1: ________________________________________________

Address 2: ________________________________________________

City, State, ZIP: ___________________________________________

NPI Number: ______________________________________________

Authorized Pharmacy Representative for KYNAMRO® REMS: ____________________________________________

Email: ___________________ Phone: ___________________________

Authorized Pharmacy Representative Attestation

KYNAMRO is only available through the KYNAMRO REMS Program. In order to become certified and purchase, dispense and distribute KYNAMRO, pharmacies must agree to 1) recertify if there is a change in the authorized representative 2) be audited 3) provide prescription data to Kastle as requested.

The Authorized Pharmacy Representative, I attest that:

• I have reviewed the KYNAMRO Prescribing Information (PI)

• I have reviewed the KYNAMRO REMS Program: An Introduction that summarizes the requirements of the REMS program.

• I have completed the KYNAMRO REMS Program Pharmacy Certification Training Module and Knowledge Assessment
• I have completed, signed and returned the KYNAMRO REMS Program Pharmacy Enrollment Form to the REMS Program Coordinating Center.

• I agree to train all pharmacy staff involved with KYNAMRO in the requirement of the REMS Program.

• I understand only Health Care Providers (HCPs) that are REMS-Certified can prescribe KYNAMRO and only by using the KYNAMRO REMS Program Prescription Authorization Form.

• I agree to put process and procedures in place to verify, prior to dispensing KYNAMRO, that:
  o The health care prescriber is certified in the KYNAMRO REMS Program by checking the REMS Certified Prescriber Report for list of certified HCPs prior to dispensing
  o The KYNAMRO REMS Program Prescription Authorization Form is received for each new prescription
  o The KYNAMRO REMS Program Patient-Prescriber Acknowledgement Form is on file with the REMS Program Coordinating Center

Signature: ____________________________ Date: _________________

Authorized Pharmacy

Representative: ____________________________

Print Name

Title

Signature: ____________________________ Date: _________________

Kastle Representative: ____________________________

Print Name

Title
RECERTIFICATION REQUIRED
KYNAMRO REMS Program Changes For Pharmacies

Dear Pharmacist:

The purpose of this letter is to inform you of recent changes in the KYNAMRO® ( mipomersen sodium) injection Risk Evaluation and Mitigation Strategy (REMS) Program. To continue to dispense KYNAMRO, pharmacies must recertify in the KYNAMRO REMS Program by Month, Day 2017.

1. **Action Required**
   - **Complete** the updated KYNAMRO REMS Program Pharmacy Certification Training Module and Knowledge Assessment
   - **Submit** a **KYNAMRO REMS Program Pharmacy Enrollment Form** to the KYNAMRO REMS Program Coordinating Center.

2. Pharmacies will need to meet the following requirements to dispense KYNAMRO:
   - Ensure the authorized pharmacy representative oversees implementation and compliance with the KYNAMRO REMS Program requirements:
     - **Train** all relevant staff involved in the dispensing of KYNAMRO on the KYNAMRO REMS Program requirements.
     - **Implement** processes and procedures to ensure the following requirements are completed prior to dispensing KYNAMRO:
       - Verify 1) the prescriber is REMS-certified, 2) a Patient-Prescriber Acknowledge Form is completed and on file and 3) a KYNAMRO REMS Program Prescription Authorization Form is completed and on file
     - **Comply** with requests to be audited by Kastle Therapeutics, FDA, and or a third party.

**How To Enroll or Re-Certify in the KYNAMRO REMS Program**
- Call the KYNAMRO REMS Program Coordinating Center at 1-877-596-2676.

Learn more about the KYNAMRO REMS Program at [www.KYNAMROREMS.com](http://www.KYNAMROREMS.com)

Please see the accompanying Prescribing Information for your reference. As always, please report any adverse events to Kastle Drug Info at 1- 877-279-2308 or the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

Sincerely,

Stuart Kupfer
Chief Medical Advisor, Kastle Therapeutics
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
10/25/2017