An Overview of the KYNAMRO® Risk Evaluation and Mitigation Strategy (REMS) Program

Prescriber Training
Contents

• Introduction

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

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

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

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

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

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

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

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

- Moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
- Known hypersensitivity to any component of the product

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reference Id: 5798259
Adverse Reaction Reporting

- To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 800-745-4447 or FDA at 800-FDA-1088 or www.fda.gov/medwatch
To ensure that the benefits of KYNAMRO outweigh the risks, KYNAMRO is only available through the KYNAMRO REMS Program.

The elements of the KYNAMRO REMS Program are:

- Healthcare providers who prescribe KYNAMRO must be specially certified
  - To become certified to prescribe KYNAMRO, prescribers must be trained and enrolled in the KYNAMRO REMS Program

- Pharmacies that dispense KYNAMRO must be specially certified
  - Only certified pharmacies can dispense KYNAMRO

- KYNAMRO will be dispensed only to patients with evidence or other documentation of safe-use conditions
  - Patients must have a clinical or laboratory diagnosis consistent with HoFH as documented on the KYNAMRO Prescription Authorization Form
Program Goals

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

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

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

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

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

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

Reference ID: 3798253
In signing the Prescriber Enrollment Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH
- You understand that KYNAMRO is only available through the KYNAMRO REMS Program and that you must comply with the program requirements in order to prescribe KYNAMRO
- You have completed the KYNAMRO REMS Prescriber Training
- You understand that there is a risk of hepatotoxicity associated with KYNAMRO
- You understand that serum ALT, AST, alkaline phosphatase, and total bilirubin must be measured before initiating therapy with KYNAMRO
- You understand that during the first year of treatment with KYNAMRO, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly
- You understand that after the first year, liver-related laboratory tests (ALT and AST at a minimum) should be measured at least every 3 months
- You agree that personnel from the KYNAMRO REMS Program may contact you to gather further information or resolve discrepancies or to provide other information related to KYNAMRO or the KYNAMRO REMS Program
- You will complete and submit a KYNAMRO REMS Prescription Authorization Form for each new prescription
- You agree that Genzyme, its agents, and contractors such as the pharmacy providers may contact you via phone, mail, or email to survey you on the effectiveness of the program requirements for the KYNAMRO REMS Program
Fax the signed form to the KYNAMRO REMS Program at 877-778-9008 or scan and email to KynamroREMS@Genzyme.com

A confirmation letter will be sent when the form has been received and verified.
For a patient to receive KYNAMRO, the Prescription Authorization Form must be completed by the prescriber.

1. **Prescriber Information** should be completed at the top of the form.

2. **Patient Information and Insurance Information** should be completed in the second and third box of the form.

3. **Carefully review the Attestation of REMS Requirements** on the bottom half of the form.
In completing the Prescription Authorization Form, you attest that:

- You understand that KYNAMRO is indicated as an adjunct to lipid lowering medications and diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH

- The patient has a clinical or laboratory diagnosis consistent with HoFH

- You understand that KYNAMRO has not been adequately studied in pediatric patients <18 years of age

- You have obtained the appropriate liver-related laboratory tests for the patient as directed in the KYNAMRO PI
The KYNAMRO Prescription should be written in the last box on the form. The Prescription Authorization Form should be provided by the prescriber to a certified pharmacy via the KYNAMRO REMS Program by faxing the completed form to the KYNAMRO REMS Program at 877-778-9008 or by scanning and emailing to KynamroREMS@Genzyme.com.
KYNAMRO Prescription Ordering and Dispensing

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

- Prescriptions for KYNAMRO must be written using the Prescription Authorization Form
  
  - Completed prescriptions should be submitted to the KYNAMRO REMS Program by faxing the completed form to the KYNAMRO REMS Program at 877-778-9008 or by scanning and emailing to KynamroREMS@Genzyme.com
  
  - If you need assistance submitting a KYNAMRO prescription, contact the KYNAMRO REMS Program at 877-596-2676
LEARNING CHECK

Reference ID: 3798253
Learning Check

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

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

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

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

- False

**ANSWER**

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

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

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

**ANSWER**

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

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

✔ During the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted monthly

✔ After the first year of treatment with KYNAMRO, ALT and AST tests (at a minimum) should be conducted at least every 3 months

☐ For patients who develop ALT or AST elevations ≥3x and <5x ULN, the elevation should be confirmed with a repeat measurement within 1 month

☐ All of the above

ANSWER

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

☑️ The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined

☑️ KYNAMRO can be used as an adjunct to LDL apheresis

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

☑️ The use of KYNAMRO is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), or active liver disease, including unexplained persistent elevations of serum transaminases
4. Which of the following statements is false? (check all that apply)

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

**ANSWER**

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

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

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

☑️ All of the above

**ANSWER**

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

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

- True
- False

ANSWER

KYNAMRO is only available from KYNAMRO REMS-certified pharmacies. Prescriptions must be submitted using the Prescription Authorization Form to the KYNAMRO REMS Program by faxing the completed form to the KYNAMRO REMS Program at 877-778-9008 or by scanning and emailing to KynamroREMS@Genzyme.com.
For additional information on the KYNAMRO REMS Program, call 877-596-2676 or visit www.KynamroREMS.com
Kynamro®
(mipomersen sodium) injection
200 mg/mL