A STEP-BY-STEP GUIDE TO SELF-ADMINISTER
KYNAMRO® (mipomersen sodium) injection 200 mg/mL

Please see Important Safety Information on pages 7-9 and full Prescribing Information, including Boxed Warning and Medication Guide.
How do I take KYNAMRO® ( mipomersen sodium) injection?

KYNAMRO is a once-weekly, self-administered injection.

Your health care provider (HCP) will teach you how to use the pre-filled syringe to administer KYNAMRO just under the surface of your skin (subcutaneously).

Your dedicated KYNAMRO Cornerstone® Case Manager can also arrange injection training at your home or a place convenient to you.

It is important to take KYNAMRO on the same day of each week. To help you remember, make a note on your calendar, set an alarm on your smartphone, or an email alert on your computer or tablet.

Store KYNAMRO in a refrigerator between 36°F to 46°F until you are ready to use it. Let it warm to room temperature before use, as this may reduce injection site reactions.

Do not use the KYNAMRO pre-filled syringe if:

- The expiration date on the barrel of the container has passed
- The packaging or seals are torn or broken, or the syringe looks cracked or damaged when you receive your KYNAMRO
- The medicine in the pre-filled syringe is discolored (it should be colorless to slightly yellow), or if it is cloudy or has any visible particles in it (it should be completely clear)

To learn more about KYNAMRO Cornerstone, please visit KYNAMRO Cornerstone at KYNAMRO.com or call 1-877-596-2676.

Please see Important Safety Information on pages 7-9 and full Prescribing Information, including Boxed Warning and Medication Guide.

These instructions are only for KYNAMRO pre-filled syringes

Supplies needed for your KYNAMRO injection:

- KYNAMRO pre-filled syringe

  NOTE It is important that KYNAMRO be at room temperature prior to the injection. Allow KYNAMRO to come to room temperature for at least 30 minutes. When KYNAMRO is cold, it may cause redness or sensitivity after your injection. KYNAMRO should not be heated and should be kept in original packaging to protect it from light.

- Alcohol wipe
- Cotton ball
- Puncture-proof container to dispose of the used syringes
Arrange supplies and wash hands

Place the supplies you will need on a clean, flat surface in a well-lit area. Wash and dry your hands well.

Choose an injection site

KYNAMRO® ( mipomersen sodium) injection is injected under the skin and into the fat layer between the skin and the muscles (subcutaneous). KYNAMRO should be injected into the abdomen (belly), thigh, or back of the upper arm. If you choose your abdomen, do not use the area 2 inches around your belly button (navel).

NOTE Choose a different site each time you give yourself an injection to reduce the chance of redness or pain. Avoid injecting KYNAMRO into areas of skin that are damaged, such as scars or tattoos, or areas that have active skin disease, sunburns, rashes, inflammation, skin infections, or active areas of psoriasis.

Clean the injection site

Use an alcohol wipe and allow the site to dry.

Remove the syringe from the tray

Peel back the foil lid from the tray. Grasp the syringe from the center and pull straight out of the tray.

NOTE Do not remove the syringe by pulling on the plunger or the cap, as you may bend the needle or move the plunger.

Remove the cap

Pull the cap straight off the syringe to avoid bending the needle.

NOTE Hold the barrel of the syringe in one hand like a pencil or a dart. Do not touch the needle.

Insert the needle

Gently pinch and lift the skin around the injection site. Stick the needle straight down into your skin with a quick, firm motion. Be careful not to stick the needle into the fingers of your other hand.

Slowly, over a period of at least 10 seconds, push down the plunger with your thumb until the syringe is empty

Once the syringe is empty, pull the needle straight out, release the skin, and hold a clean cotton ball at the injection site. Do not rub the area; rubbing may cause reddening or pain at your injection site.

Activate safety shield

Point the needle down and away from yourself and others, and then fully push down on the plunger to activate the safety shield. Do not try to recap the needle with the cap.

Dispose properly of used syringes

Put your used syringes into an FDA-cleared sharps disposal container right away after use.

Please see Important Safety Information on pages 7-9 and full Prescribing Information, including Boxed Warning and Medication Guide.
How should I store KYNAMRO® ( mipomersen sodium) injection?

- Store KYNAMRO in a refrigerator between 36°F to 46°F (2°C to 8°C). If a refrigerator is not available, KYNAMRO can be stored at or below 86°F (30°C) for up to 14 days if it is kept away from heat.
- Protect KYNAMRO from light and store in the original carton.
- Safely throw away medicine that is out of date or no longer needed.
- Keep KYNAMRO and all medicines out of the reach of children.

These instructions have been approved by the US Food and Drug Administration.

WHAT IS KYNAMRO?

KYNAMRO® ( mipomersen sodium) injection 200 mg/mL is a prescription medicine used along with other lipid-lowering medications and diet in people with homozygous familial hypercholesterolemia (HoFH) to reduce:

- Low-density lipoprotein (LDL) cholesterol, commonly known as “bad” cholesterol.
- Total cholesterol.
- A protein that carries LDL cholesterol in the blood (apolipoprotein B).
- Non-high-density lipoprotein cholesterol (non–HDL–C).
- It is not known if KYNAMRO is safe and effective in people with high cholesterol but who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).
- It is not known whether KYNAMRO can decrease problems from high cholesterol, such as heart attack, stroke, death, or other health problems.
- The safety and effectiveness of KYNAMRO as a treatment given in addition to LDL apheresis, a dialysis-like procedure that removes cholesterol from the blood, is not known or recommended.

Please see Important Safety Information on pages 7-9 and full Prescribing Information, including Boxed Warning and Medication Guide.
WARNINGS AND PRECAUTIONS

KYNAMRO® [mipomersen sodium] injection can cause increases in liver enzymes and liver fat.

Prior to starting your therapy with KYNAMRO, your doctor should perform liver tests including measurements of liver enzymes called alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase. If the results of any of these tests are abnormal, your doctor may perform additional tests to explain or resolve these abnormalities before starting your treatment with KYNAMRO.

During the first year of therapy, your doctor will conduct liver-related tests on a monthly basis.

After the first year, these tests should be conducted at least once every 3 months. Your doctor should stop your treatment with KYNAMRO if the tests show significant or constant increases in enzyme levels.

If liver enzyme levels are elevated and you are showing symptoms of liver injury or liver disease (e.g., nausea, vomiting, fever, loss of appetite, feeling more tired than usual, yellowing of your eyes or skin, dark urine, itching, or stomach pain), your physician should stop treatment and identify the possible cause.

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.

Caution should be exercised when KYNAMRO is used with other medications that may cause liver problems as the effect of these combinations is unknown. More frequent liver-related tests may be necessary.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Before starting a new medicine while taking KYNAMRO, even if you will only be taking it for a short time, ask your doctor or pharmacist if it is safe to take while you are using KYNAMRO.

The effect of taking KYNAMRO at the same time as other LDL-lowering drugs that can increase liver fat has not been studied. Therefore, it is not recommended.

Skin reactions at the site of injection were reported at least once in 84% of patients, including redness or discoloration of the skin, pain, tenderness, itching, and swelling around the injection site. Proper injection technique is recommended to help minimize the potential for reactions at the site of injection. These reactions did not occur on all injections. A total of 5% of patients discontinued therapy due to injection site reactions.

Flu-like symptoms, including fever, chills, aches, and tiredness, have been reported in 30% of patients taking KYNAMRO. These symptoms did not occur with all injections. These symptoms usually happen within 2 days after an injection. A total of 3% of patients discontinued therapy due to flu-like symptoms.

USE IN SPECIFIC POPULATIONS

Before you take KYNAMRO tell your doctor if you are pregnant or plan to become pregnant. KYNAMRO may cause harm to your unborn baby. If you are a female who can get pregnant, you should use effective birth control while using KYNAMRO. Talk with your doctor to find the best method of birth control for you. If you become pregnant while taking KYNAMRO, stop taking KYNAMRO and call your doctor right away.

Before you take KYNAMRO tell your doctor if you are breastfeeding or plan to breastfeed. It is not known if KYNAMRO passes into your breast milk. You and your doctor should decide if you will use KYNAMRO or breastfeed. You should not do both.

The safety and effectiveness of KYNAMRO in children under the age of 18 has not been established.

It is not known whether KYNAMRO is safe and effective in people with kidney problems, including people who are receiving kidney dialysis.

ADVERSE REACTIONS

In drug trials the most commonly reported side effects were injection site reactions (84%), flu-like symptoms (30%), nausea (14%), headache (12%), and elevations in liver enzymes, specifically ALT (10%).

Tell your doctor right away about any side effect that bothers you or that does not go away.
IMPORTANT SAFETY INFORMATION

KYNAMRO (mipomersen sodium) Injection 200 mg/mL may cause serious side effects, including liver problems. KYNAMRO can cause liver problems such as increased liver enzymes or increased fat in the liver.

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 1 elevation in levels of liver enzymes that was at least 3 times higher than normal. There were no important changes in other measures of liver function. KYNAMRO also increases liver fat, with or without accompanying increases in liver enzymes. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and high cholesterol, the median absolute increase in liver fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Fatty liver is a risk factor for advanced liver disease.

Your doctor will measure your liver enzyme levels and liver function before starting treatment and then regularly during treatment, as recommended. If enzyme levels or liver function are abnormal, treatment will be withheld or discontinued depending on severity.

Because of the risk of liver problems, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS. Your doctor must be enrolled in the program in order for you to be prescribed KYNAMRO. KYNAMRO is only for patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia.

CONTRAINDICATIONS

Do not take KYNAMRO if you:

• Have moderate or severe liver problems or active liver disease, including unexplained abnormal liver tests
• Are allergic to mipomersen or any of the ingredients in KYNAMRO
KYNAMRO (mipomersen sodium) injection, for subcutaneous use

Solution for Subcutaneous Injection

Initial U.S. Approval: 2013

FULL PRESCRIBING INFORMATION

See full prescribing information for complete boxed warning.

KYNAMRO can cause elevations in transaminases (5.1).

- Measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended.
- During treatment, withhold the dose of KYNAMRO if the ALT or AST is ≥3 times the upper limit of normal (ULN) (2.3, 5.1).
- Discontinue KYNAMRO for clinically significant liver toxicity (2.3, 5.1).
- KYNAMRO increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases (5.1).
- Hepatic steatosis associated with KYNAMRO may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis (5.1).

Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program called the KYNAMRO REMS (5.2). 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 (1).

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) (1).
- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined (1).
- The use of KYNAMRO as an adjunct to LDL apheresis is not recommended (1).

DOSEAGE AND ADMINISTRATION

200 mg once weekly as a subcutaneous injection (2.1)
Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin (2.1)

DOSEAGE FORMS AND STRENGTHS
- Single-use pre-filled syringe containing 1 mL of a 200 mg/mL solution (3)

CONTRAINDICATIONS
- Moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases (4)
- Known sensitivity to product components (4)

WARNINGS AND PRECAUTIONS
- Injection site reactions occur in 84% of patients and typically consist of one or more of the following: erythema, pain, tenderness, pruritus and local swelling (5.3)
- Flu-like symptoms, which typically occur within 2 days after an injection, occur in 30% of patients and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue (5.4)

ADVERSE REACTIONS
- The most commonly reported adverse reactions (incidence ≥ 10% and greater than placebo) are injection site reactions, flu-like symptoms, nausea, headache and elevations in serum transaminases, specifically ALT (5.4, 6).

USE IN SPECIFIC POPULATIONS
- Nursing mothers: Discontinue drug or nursing (8.3).
- Pediatric Patients: Safety and effectiveness not established (8.4).

To report SUSPECTED ADVERSE REACTIONS, contact Kastle Therapeutics at 1-877-278-2308 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 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) (1).

Limitations of Use:
- The safety and effectiveness of KYNAMRO as an adjunct to LDL apheresis have not been established (1).
- The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH (1).
- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined (1).
- The use of KYNAMRO as an adjunct to LDL apheresis is not recommended (1).

*Sections or subsections omitted from the full prescribing information are not listed

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) (see Warnings and Precautions (5.1)). 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 (see Warnings and Precautions (5.1)).

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and 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 (see Dosage and Administration (2.3) and Warnings and Precautions (5.1)).

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 (5.2). 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 (1).

1. INDICATIONS AND USAGE
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).

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).
- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined.
- The safety and effectiveness of KYNAMRO as an adjunct to LDL apheresis have not been established; therefore, the use of KYNAMRO as an adjunct to LDL apheresis is not recommended.

12 CLINICAL PHARMACOLOGY
- Toxicology

14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
TREATMENT AND MONITORING RECOMMENDATIONS

- Measure liver-related tests (ALT and AST, at a minimum) at least every 3 months.

Adverse Reactions (6.1)

Before initiating KYNAMRO and during treatment, monitor transaminases as recommended in Table 2.

Elevation of Transaminases

- Patients with a known hypersensitivity to any component of this product [see Adverse Reactions (6.1)].

5.4 Flu-Like Symptoms

- Patients taking KYNAMRO should consume no more than one alcoholic drink per day.

Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. It is recommended that patients taking KYNAMRO should consume no more than one alcoholic drink per day. Caution should be exercised when KYNAMRO is used with other medications known to have potential for hepatotoxicity, for example isotretnoin, amiodarone, acetaminophen (>4 g/day), 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.

Mipomersen 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.
for the KYNAMRO group and 28% for the placebo group. Sixty-two percent of patients receiving KYNAMRO developed a 5% or greater increase in hepatic fat versus 8% of patients receiving placebo.

In general, these elevations in fat fraction decreased when assessed by MRI performed 24 weeks after cessation of KYNAMRO in the Phase 3 trial of patients with high-risk hypercholesterolemia. In the open-label extension trial, among individuals with a measurement at baseline and at 12 months or longer on KYNAMRO, 25% had an average liver fat fraction > 20% or at least one occasion.

### Injection Site Reactions

The most commonly-reported adverse reactions were injection site reactions occurring in 84% of patients receiving KYNAMRO versus 33% of placebo-treated patients. The most common injection site reactions were erythema (59%), pain (56%), hematoma (32%), pruritis (28%), swelling (18%) and discoloration (17%). Injection site reactions did not occur with every injection. Injection site reactions resulted in discontinuation of KYNAMRO in 5% of patients. Recall reactions, consisting of local erythema, tenderness and/or pruritis at previous injection sites when subsequent injections were administered, were observed in 8% of patients, all of whom were receiving KYNAMRO.

### Flu-like Symptoms

Flu-like symptoms, defined as any one of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue occurring within 2 days of injection, have been reported more frequently in patients receiving KYNAMRO (29.9%) versus placebo (16.3%) in the pooled Phase 3 studies. Flu-like symptoms did not occur with all injections. Flu-like symptoms resulted from bi-weekly injections in 2.7% of patients. In the open-label extension trial, in which all patients received KYNAMRO therapy, 66% reported flu-like symptoms, 25% discontinued treatment due to flu-like symptoms and 9% experienced severe flu-like symptoms.

### Immune-mediated events

In the pooled Phase 3 trials, 38% of KYNAMRO-treated patients tested positive for anti-KYNAMRO antibodies during the 6-month trials. Efficacy results in the Phase 3 trials in patients who tested positive for anti-KYNAMRO antibodies were similar to patients who remained negative for antibodies (mean LDL-C percent change from baseline was -32% for antibody-positive and -34% for antibody-negative participants). In the open-label extension trial, approximately 72% of patients receiving KYNAMRO therapy tested positive for anti-KYNAMRO antibodies (35% with titers >3200). The incidence of flu-like symptoms and the incidence of discontinuation of KYNAMRO were higher in antibody-positive patients. Antibodies to KYNAMRO were associated with higher trough levels for the drug. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to KYNAMRO with the incidence of antibodies to other products may be misleading.

### SEVERE GASTRIC DISORDERS

Severe gastrointestinal disorders were reported in 5% of patients receiving placebo. Data from Phase 3 supportive trials in patients with heterozygous familial hypercholesterolemia and coronary artery disease and in patients with high risk hypercholesterolemia demonstrated after 26 weeks of treatment, a median nominal increase in fat fraction of 9.6% relative to baseline following KYNAMRO therapy versus a nominal 0.02% change in the placebo group (mean increases were 12.2% mipomersen vs 0.4% placebo). The maximum change in fat fraction was 46%
8.6 Females of Reproductive Potential
KYNAMRO may cause fetal harm [see Use in Specific Populations (8.1)]. Females who become pregnant during KYNAMRO therapy should notify their healthcare provider.

Contraindications
Females of reproductive potential should use effective contraception during KYNAMRO therapy.

8.7 Renal Impairment
The safety and efficacy of KYNAMRO treatment in patients with known renal impairment or in patients undergoing renal dialysis have not been established. Due to the lack of clinical data and KYNAMRO’s renal safety profile, KYNAMRO is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis.

8.8 Hepatic Impairment
The safety and efficacy of KYNAMRO treatment in patients with known hepatic impairment have not been established. KYNAMRO is contraindicated in patients with clinically significant hepatic dysfunction, which may include persistent elevations of transaminases. [See Contraindications (4) and Precautions (5.1)]

10 OVERDOSAGE
There have been no reports of overdose with KYNAMRO treatment. In clinical trials, patients receiving higher doses of KYNAMRO (300 mg and 400 mg once weekly for 13 weeks) experienced adverse reactions similar to the adverse reactions experienced by patients receiving treatment with 200 mg once weekly but at slightly higher rates and greater severity. Liver-related tests should be monitored. Although there is no information on the effect of hemodialysis in treating an overdose with mipomersen, hemodialysis is unlikely to be useful in overdose management since mipomersen is highly bound to plasma proteins.

11 DESCRIPTION
KYNAMRO ( mipomersen sodium ) Injection is a sterile, preservative-free, clear, colorless to slightly yellow, aqueous solution for subcutaneous injection. KYNAMRO is supplied in single-use, 1 mL, clear glass pre-filled syringes filled to deliver 1 mL of solution containing 200 mg of mipomersen sodium (200 mg per 1 mL). KYNAMRO is formulated in water for injection and may include hydrochloric acid and/or sodium hydroxide for pH adjustment to 7.5 – 8.5.

Mipomersen sodium is an oligonucleotide inhibitor of apo B-100 synthesis. ApoB is the principal apolipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen inhibits synthesis of apoB by sequence-specific binding to its messenger ribonucleic acid (mRNA) resulting in degradation of the mRNA through enzyme-mediated pathways or disruption of mRNA function through binding alone.

Mipomersen sodium is a synthetic phosphorothioate oligonucleotide sodium salt, 20 nucleotides in length, with the following sequence: 5’-GpCpCPpUPpUCpSpAGTpCpTGpCTpCCpGpCApCPcC-3’, where the underlined residues are 2’-O(2-methoxyethyl) nucleosides; all other residues are 2’-deoxynucleosides. Substitution at the 5-position of the cytosine (C) and uracil (U) bases with a methyl group is indicated by Me.

Mipomersen sodium is represented by the following structural formula:

The molecular formula of mipomersen sodium is C188H268N42O39P5S19Na10 and the molecular weight is 7594.9 g/mol.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Mipomersen is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apo B-100, the principal apolipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein.

The in vitro pharmacologic activity of mipomersen was characterized in human hepatoma cell lines (HepG2, HepB) and in human and cynomolgus monkey primary hepatocytes. In these experiments, mipomersen selectively reduced apo B mRNA, protein and secreted protein in a concentration- and time-dependent manner. The effects of mipomersen were shown to be highly sequence-specific. The binding site for mipomersen lies within the coding region of the apo B mRNA at the position 3249-3268 relative to the published sequence GenBank accession number NM_000384.1.

12.2 Pharmacodynamics
Cardiac ECG Effects
At a concentration of 3.8 times the Cmax of the maximum recommended dose (200 mg subcutaneous injection), mipomersen does not prolong the QTc interval to any clinically relevant extent.
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a subcutaneous carcinogenicity study in mice, mipomersen sodium was administered for up to 104 weeks at doses of 5, 10, 20 mg/kg/week. There were statistically significant increases in the incidences of hepatocellular adenoma and combined adenoma and carcinoma in female mice at 60 mg/kg/week (2-times the systemic clinical exposure at 200 mg/kg/week based on a body surface area comparison) for both mipomersen sodium and the mouse-specific analog. This dose also resulted in statistically significant increases in the incidence of hemangiosarcomas in female mice and fibrosarcomas of the skin/subcutis in male mice.

In a subcutaneous carcinogenicity study in rats, mipomersen sodium was administered for up to 104 weeks at doses of 5, 10, 20 mg/kg/week. The incidence of fibrosarcomas of the skin/subcutis and the combination of fibroma, fibrosarcomas and malignant fibrous histiocytoma of the skin/subcutis was statistically significantly increased in female rats at 10 mg/kg/week, at less than clinical exposure at the 200 mg/kg dose based on body surface area comparisons. Both sexes of rats also had statistically significant increases in the incidence of malignant fibrous histiocytoma of the skin/subcutis at 20 mg/kg/ wk (at clinical exposure at the 200 mg/kg dose based on body surface area comparisons).

Mipomersen did not exhibit genotoxic potential in a battery of studies, including the in vitro Baxter Reverse Mutation (Ames) assay, an in vitro cytogenetics assay using a mouse lymphoma cell line, and an in vivo micronucleus assay in mice.

Mipomersen sodium had no effect on fertility in mice at doses up to 87.5 mg/kg/week (2-times clinical exposure at the 200 mg/kg dose based on body surface area comparisons).

13.2 Animal Pharmacology and/or Toxicology

The principal target organs for mipomersen pathology are the kidneys and liver. These organs represent the highest distribution of compound, and exhibit microscopic changes reflective of cellular uptake in macrophages. The most widespread toxicological effect of mipomersen was a spectrum of inflammatory changes in numerous organs, including lymphohistiocytic cell infiltrates and increases in lymphoid organ weights, associated with increases in plasma cytokines, chemokines and total serum IgG. In a chronic monkey study, multi-foveal hyperplasia with mixed inflammatory infiltrates was evident in vascular beds in 2 of 6 monkeys treated for 12 months with 30 mg/kg/week with a non-observed-adverse-effect-level (NOAEL) of 10 mg/kg/week (approximately equal to clinical exposures anticipated from a 200 mg/kg dose based on body surface area comparisons across species).

14 CLINICAL STUDIES

The safety and effectiveness of KYNAMRO, given as 200 mg weekly subcutaneous injections, as an adjunct to lipid-lowering medications in individuals with HoFH were evaluated in a multinational, randomized (34 KYNAMRO; 17 placebo), placebo-controlled, 26-week trial in 51 patients with HoFH. A diagnosis of functional HoFH was defined by the presence of at least one of the following clinical or laboratory criteria: (1) history of genetic testing confirming 2 mutated alleles at the LDLr gene locus, or (2) documented history of untreated LDL-C > 500 mg/dL and at least one of the criteria (a) tendonous and/or cutaneous xanthoma prior to age 10 years or (b) documentation of elevated LDL-C > 190 mg/dL prior to lipid-lowering therapy consistent with HoFH in both parents. In case a parent was not available, a history of coronary artery disease in a first degree male relative of the parent younger than 55 years or first degree female relative of the parent younger than 60 years was acceptable.

The baseline demographic characteristics were well-matched between the KYNAMRO and placebo patients. The mean age was 32 years (range, 12 to 53 years), the mean body mass index (BMI) was 26 kg/m², 43% were men, and the majority (75%) were Caucasian. In 50 of 51 (98%) patients, the background therapy of maximally tolerated lipid-lowering medication included statins. In total, 44 of the 50 (88%) patients were on maximum-dose statin therapy with or without other lipid-lowering medications. Thirty-eight of the 50 (76%) patients were also taking at least one other lipid-lowering medication, most commonly ezetimibe in 37 of 74 (74%) patients; patients were not on LDL apheresis. Eighty-two percent of the KYNAMRO group and 100% of the placebo group completed the efficacy endpoint at week 29. Adverse events contributing to premature discontinuation for four patients, all in the KYNAMRO group [see Adverse Reactions (6.2)].

The primary efficacy endpoint was percent change in LDL-C from baseline to Week 28. At Week 28, the mean and median percent changes in LDL-C from baseline were -25% (p<0.001) and -19%, respectively. Changes in lipids and lipoproteins through the efficacy endpoint at Week 28 are presented in Table 5.

Table 5: Response to Addition of KYNAMRO to Maximally Tolerated Lipid Lowering Medication in Patients with HoFH

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Mean Baseline LDL-C/mg/dL (range)</th>
<th>Mean or Median Percent Change from Baseline to End of Treatment*</th>
<th>Mean (95% CI) or Median Treatment Difference from Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>149 (190, 704)</td>
<td>-25 (-36, -14)</td>
<td>-21 (-33, -10)</td>
</tr>
<tr>
<td>Apo B</td>
<td>120 (72, 639)</td>
<td>-22 (-34, -15)</td>
<td>-18 (-31, -9)</td>
</tr>
<tr>
<td>TC</td>
<td>180 (121, 331)</td>
<td>-19 (-31, -9)</td>
<td>-18 (-31, -9)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>180 (121, 331)</td>
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<td>-18 (-31, -9)</td>
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<tr>
<td>HDL-C</td>
<td>35 (4, 11)</td>
<td>-15 (-28, -0)</td>
<td>-15 (-28, -0)</td>
</tr>
</tbody>
</table>

*End of treatment represents two weeks following final dose of KYNAMRO. Last observation carried forward (LOCF).

The treatment effect was not consistent across the Phase 3 trials.

KYNAMRO is supplied in single-use, 1 mL clear pre-filled syringes with sealed needles. Each single-use pre-filled syringe of KYNAMRO is filled to deliver 1 mL of 200 mg/mL solution containing 200 mg of mipomersen sodium.

Store refrigerated KYNAMRO at 2-8°C (36-46°F). KYNAMRO should be protected from light and kept in the original carton until time of use. When refrigeration is not available KYNAMRO may be stored at or below 30°C (86°F), away from heat sources, for up to 14 days. Do not use KYNAMRO after the expiration date on the carton.

17 PATIENT COUNSELING INFORMATION

See FDA-approved labeling (Medication Guide) Advise patients of the following:

Risk of hepatotoxicity [see Warnings and Precautions (5.1)]

- KYNAMRO can cause elevations in transaminases and hepatic steatosis. Discuss with the patient the importance of monitoring liver-related laboratory tests before taking KYNAMRO and periodically thereafter.
- Patients should be advised of the potential for increased risk of liver injury if alcohol is consumed while taking KYNAMRO. It is recommended that patients taking KYNAMRO should consume no more than one alcoholic drink per day.
- Advise patients to promptly report symptoms of possible liver injury, such as nausea, vomiting, fever, liver, anorexia, fatigue, jaundice, dark urine, pruritus, or abdominal pain.

KYNAMRO REMS [see Warnings and Precautions (5.2)]

- KYNAMRO is only available through a restricted program called KYNAMRO REMS and therefore, KYNAMRO is only available from certified pharmacies that are enrolled in the program. Additional information may be obtained at 1-877-KYNAMRO (1-877-596-2676).

Injection Site Reactions [see Warnings and Precautions (5.3)]

- These local reactions typically consist of one or more of the following: erythema, pain, tenderness, pruritus and local swelling.

Flu-like symptoms [see Warnings and Precautions (5.4)]

- Flu-like symptoms have been reported in patients receiving KYNAMRO.
- Flu-like symptoms typically occur within 2 days after an injection and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue.

Dosing [see Dosage and Administration (2.1)]

- The patient or caregiver should be instructed to review the KYNAMRO Medication Guide and Instructions for Use carefully.
- KYNAMRO is administered as a subcutaneous injection given once a week.
- Do not remove the needle cover from the pre-filled syringe while allowing the syringe to reach room temperature.
- The patient or caregiver should be instructed by a physician or an appropriately qualified healthcare professional in the proper technique for administering subcutaneous injections, including the use of aseptic technique.
- The patient and caregiver should be cautioned that needles or syringes must not be re-used and should be disposed of properly. A puncture-resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of the full container.
- KYNAMRO should be injected into the abdomen, thigh region, or outer area of the upper arm. Patients and caregivers should be advised to alternate sites for subcutaneous injections. KYNAMRO should not be injected in areas of active skin disease or injury such as wounds, skin rashes, inflammation, skin infections, active areas of psoriasis, or areas of tattooed skin and scarring.
- Patients and caregivers should be advised to alternate sites for subcutaneous injection. The injection should be performed slowly and steadily and the needle should not be withdrawn until the injection is complete.
- Protect from light. Do not mix or co-administer KYNAMRO with other products.

KYNAMRO is manufactured for: Kastler Therapeutics

Chicago, IL 1-877-596-2676 (phone)

KYNAMRO is a registered trademark of Kastler Therapeutics.

Revised: 5/2016
What is the most important information I should know about KYNAMRO?

- KYNAMRO is available only through certified pharmacies that are enrolled in the KYNAMRO REMS Program. Your doctor must be enrolled in the program in order for you to be prescribed KYNAMRO.

KYNAMRO may cause serious side effects, including liver problems. KYNAMRO can cause liver problems such as increased liver enzymes or increased fat in the liver.

- Your doctor should do blood tests to check your liver before you start KYNAMRO and during your treatment. If your tests show some liver problems, your doctor may stop KYNAMRO.
- Tell your doctor if you have had liver problems, including liver problems while taking other medicines.
- Tell your doctor right away if you have any of these symptoms of liver problems while taking KYNAMRO:
  - nausea
  - vomiting
  - fever
  - dark urine
  - you are more tired than usual
  - yellowing of your eyes or skin
  - itching
  - 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.

What is KYNAMRO?

KYNAMRO is a prescription medicine 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)

It is not known if KYNAMRO can decrease problems from high cholesterol, such as heart attack, stroke, death or other health problems.

It is not known if KYNAMRO is safe and effective in people with high cholesterol but who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

It is not known if KYNAMRO is safe and effective as an additional treatment to LDL-apheresis.

Do not take KYNAMRO if you:

- have moderate or severe liver problems or active liver disease, including people who have unexplained abnormal liver tests.
- are allergic to mipomersen or any of the ingredients in KYNAMRO. See the end of this leaflet for a complete list of ingredients in KYNAMRO.

What should I tell my doctor before taking KYNAMRO?

Before you take KYNAMRO, tell your doctor if you:

- have liver problems
- have kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. KYNAMRO may cause harm to your unborn baby. If you are a female who can get pregnant, you should use effective birth control while using KYNAMRO. Talk with your doctor to find the best method of birth control for you. If you become pregnant while taking KYNAMRO, stop taking KYNAMRO and call your doctor right away.
- are breastfeeding or plan to breastfeed. It is not known if KYNAMRO passes into your breast milk. You and your doctor should decide if you will use KYNAMRO or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Before starting a new medicine while taking KYNAMRO, even if you will only be taking it for a short time, ask your doctor or pharmacist if it is safe to take while you are using KYNAMRO.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KYNAMRO?

- See the Instructions for Use that comes with this Medication Guide for complete information on how to use KYNAMRO.
- KYNAMRO is given by injection under your skin (subcutaneous) 1 time each week. KYNAMRO is available in single-use (1 time) pre-filled syringe.
- Take KYNAMRO exactly as your doctor tells you to take it.
- Make sure that you are or your caregiver is trained by your doctor or other healthcare provider on how to inject KYNAMRO the right way.
- Do not try to give yourself or have another person give you injections at home until you or both of you understand and are comfortable with how to prepare for your dose and give the injection.
- Take KYNAMRO on the same day of the week at the same time of day.
- If you miss a dose or forget to take your dose of KYNAMRO at your usual weekly time, you can take it if you remember, unless it is less than 3 days until your next weekly dose. If it is less than 3 days until your next weekly dose, wait and take your next weekly dose at your regularly scheduled time. Do not take a double dose at the same time to make up for a forgotten or missed dose.
- It is important that KYNAMRO is at room temperature when it is injected.
- Do not mix KYNAMRO with other injectable medicines.
- Do not use KYNAMRO at the same time as other injectable medicines.
- If you use too much KYNAMRO, call your doctor right away.
- Do not stop taking KYNAMRO without talking to your doctor.

What are the possible side effects of KYNAMRO?

KYNAMRO can cause serious side effects, including:

- See “What is the most important information I should know about KYNAMRO?”
- injection site problems. Skin reactions can happen in some people including redness or discoloration of the skin, pain, tenderness, itching, and swelling around the injection site. You may also get a reaction at a former site of injection, when injecting at a different site, or after an injury to an injection site.
- flu-like symptoms, including fever, chills, aches, and tiredness. These symptoms usually happen within 2 days of an injection.

Call your doctor right away if you have any of the serious side effects of KYNAMRO.

The common side effects of KYNAMRO include:

- injection site problems
- flu-like symptoms

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects of KYNAMRO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KYNAMRO?

- Store KYNAMRO in a refrigerator between 36°F to 46°F (2°C to 8°C). If a refrigerator is not available, KYNAMRO may be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 14 days if it is kept away from heat.
- Protect KYNAMRO from light and store in the original carton.
- Safely throw away medicine that is out of date or no longer needed.

Keep KYNAMRO and all medicines out of the reach of children.

General information about the safe and effective use of KYNAMRO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KYNAMRO for a condition for which it was not prescribed. Do not give KYNAMRO to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about KYNAMRO. You can ask your pharmacist or doctor for information about KYNAMRO that is written for healthcare professionals.

For more information:
go to www.KYNAMRO.com or call 1-877-KYNAMRO (1-877-596-2676).

What are the ingredients in KYNAMRO?

Active ingredient: mipomersen sodium

Inactive ingredients: sterile water, hydrochloric acid, and sodium hydroxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.