

Mipomersen (KYNAMRO®)

Criteria for Use

May 2015

VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203568s004lbl.pdf

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx> for further information.

Exclusion Criteria *If one box below is checked, the patient should NOT receive mipomersen.*

Contraindications:

- Patients with moderate or severe liver impairment (e.g., Child-Pugh category B or C) and patients with active liver disease; including those with unexplained persistent elevation of serum transaminases (≥ 3 x ULN)
- Patients with a known hypersensitivity to any component of mipomersen.

Patients without a diagnosis of homozygous familial hypercholesterolemia (HoFH)

**Because of lack of data, mipomersen should not be combined with LDL apheresis.*

Inclusion Criteria *All boxes must be checked in order to meet criteria to receive mipomersen*

Provider is certified to prescribe mipomersen

Diagnosis of homozygous familial hypercholesterolemia (HoFH):

- Confirmed with genetic testing (mutation in LDL receptor: true homozygote or double heterozygote), **OR**
- Untreated LDL of >500 mg/dL **OR**
- Receiving maximal treatment with lipid-lowering therapy and LDL >300 mg/dL (adherence is confirmed), **AND**
- Physical findings including: tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.

Patient is receiving maximally tolerated doses of statins and at least one other lipid-lowering medication.

Patient has been educated regarding the need to follow a lipid-lowering diet.

Dosage and Administration (refer to prescribing information for more detailed information)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203568s004lbl.pdf

Dosing/Administration

- 200 mg is administered subcutaneously into the abdomen, thigh or outer area of the upper arm once a week, on the same day.
- Mipomersen should not be injected into an area of the skin that has active disease or injury (e.g., sunburn, rash, inflammation, infection, active psoriasis, tattooed skin or scarring).
- Mipomersen should not be given intravenously or intramuscularly.
- If a dose is missed, the injection should be given at least 3 days prior to the next weekly dose.
- The first dose should be supervised by an appropriately qualified healthcare professional.

Monitoring (LFTS and Lipid Levels)

- Liver function tests (LFTs) including ALT, AST, total bilirubin and alkaline phosphatase should be measured prior to initiation of mipomersen.
- LFTs (at least ALT and AST) should be done monthly within the first year and every three months thereafter.
- Mipomersen should be stopped for persistent or clinically significant LFT elevation (see table below for recommendations).
- If transaminase elevation occurs with symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy or flu-like symptoms), an increase in bilirubin $\geq 2xULN$ or active liver disease, mipomersen should be stopped and the cause identified.
- If LFTs become abnormal, follow the recommended steps for dose adjustment and monitoring:

ALT or AST Elevation	Recommendation
<p>$\geq 3x ULN$ and $< 5 x ULN^*$</p> <p>*Based upon an ULN of approximately 30-40 IU/L</p>	<ul style="list-style-type: none"> • Confirm elevation with repeat measurement in 1 week. • In confirmed, withhold dosing, obtain additional LFTs if not already measured (e.g., total bilirubin, alkaline phosphatase and international normalized ratio [INR]). • If resuming mipomersen after transaminases resolve to $<3xULN$, consider monitoring LFTs more often.
<p>$\geq 5x ULN^*$</p> <p>*Based upon an ULN of approximately 30-40 IU/L</p>	<ul style="list-style-type: none"> • Withhold dosing, obtain additional LFTs if not already measured (e.g., total bilirubin, alkaline phosphatase and international normalized ratio [INR]) and investigate to identify the probable cause • If resuming mipomersen after transaminases resolve to $<3xULN$, consider monitoring LFTs more often.

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+Table adapted from prescribing information

LFTs=liver function tests, INR=international normalized ratio, ULN=upper limit of normal

- After initiation of mipomersen, lipid levels should be monitored at least every 3 months for the first year. Maximal LDL reduction is observed after 6 months of therapy. Providers should assess the LDL reduction achieved with mipomersen to determine if the LDL reduction is sufficient to warrant continuation of mipomersen in light of the potential risk of liver toxicity.

Issues for Consideration

- **BECAUSE OF THE POTENTIAL RISK FOR LIVER INJURY, USE OF MIPOMERSEN IS RESTRICTED TO ONLY THOSE PATIENTS DIAGNOSED WITH HOFH. THERE ARE MULTIPLE WAYS THE DIAGNOSIS OF HOFH CAN BE MADE, INCLUDING:**
 - Confirmed with generic testing
 - Extremely high LDL (e.g., untreated LDL >500 mg/dL OR maximally treated LDL of >300 mg/dL [on lipid lowering therapy including statins] and physical findings including tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.
- Mipomersen has been studied in very few patients with HoFH for a short duration. It is possible that uncommon, severe adverse events were not identified during the completed trials because of the small numbers of patients.
- Mipomersen can increase liver transaminases and increase hepatic steatosis. Although there have not been reported cases of liver impairment or liver failure in patients taking mipomersen that has been considered related to treatment, there is concern that steatohepatitis could develop in association with mipomersen and gradually progress to cirrhosis. Because of the risk for liver injury developing in patients receiving mipomersen, the FDA has instituted a Risk Evaluation and Mitigation Strategy (REMS) program restricting its prescribing and distribution to only certified providers and pharmacies. The goals of the REMS are as follows:
 - To educate providers of the risk of hepatotoxicity with mipomersen and reinforce the need to monitor patients as instructed in the approved labeling.
 - To restrict access to patients who have a clinical or laboratory diagnosis consistent with HoFH.
- Patients should have baseline LFTs (ALT, AST, alkaline phosphatase and total bilirubin) performed prior to initiation of mipomersen. ALT and AST, at a minimum, should be measured monthly for the first year. After the first year, ALT and AST should be measured every 3 months. (*See the Monitoring section for recommendations for patients with transaminase elevation during mipomersen therapy*)
- Lipids should be monitored every 3 months for the first year.
 - Maximal LDL reduction should be observed after 6 months of therapy.
 - If after 6 months the reduction in LDL is not considered sufficient, providers must determine whether continued therapy with mipomersen is justified in light of the potential risk for liver toxicity.
- Patients should be instructed to limit alcohol-containing beverages to no more than one per day. In the clinical trial, those consuming more alcohol than recommended had a higher risk for transaminase elevation.
- Mipomersen should not be used in patients with severe hypercholesterolemia or statin intolerant patients who do not have HoFH. The risk/benefit profile is unfavorable in these patients because of the potential for liver injury.
- Patients receiving LDL apheresis were excluded from all trials involving mipomersen. Therefore the combination of mipomersen with LDL apheresis is not recommended.
- Injection site reactions and flu-like syndrome are common adverse events associated with mipomersen.
- Caution should be used when mipomersen is combined with other drugs that may cause liver injury (e.g., isotretinoin, amiodarone, excessive doses of acetaminophen, methotrexate, tetracyclines and tamoxifen) since the effect of concomitant use with mipomersen is unknown. More frequent monitoring of LFTs may be indicated.
- The effect of combining mipomersen with other drugs known to increase hepatic fat is unknown and therefore these combinations are not advised.

Renewal Criteria

- Patient is tolerating mipomersen and is adherent to therapy
- Meaningful reduction in LDL (>30% reduction)
- LFT monitoring is being conducted as recommended

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