

Brand Name: Kynamro ®

Generic Name: Mipomersen Sodium

Manufacturer¹: Genzyme Corp.

Drug Class^{1,2}: Apo B Synthesis Inhibitor^{1,2}

Uses:

Labeled Uses^{1,2,3,4}: Homozygous familial hypercholesterolemia

Unlabeled Uses⁴: Coronary arteriosclerosis; heterozygous familial hypercholesterolemia

Mechanism of Action^{1,2,3,4}: Mipomersen sodium is an oligonucleotide inhibitor of apo B-100 synthesis, inhibiting synthesis of apo B by sequence-specific binding to its messenger ribonucleic acid (mRNA) through enzyme-mediated pathways or disruption of mRNA function through binding alone. Its binding to apo B mRNA as a complement in the coding region of the apo B-100 mRNA allows hybridization of mipomersen to the cognate mRNA and RNase H-mediated degradation of the cognate mRNA with inhibition of translation of the apo B-100 protein resulting in decreased LDL and VLDL levels

Pharmacokinetics^{1,2,3,4}:

Absorption:

T _{max}	3-4 hours
V _d	Not reported
t _{1/2}	1-2 months
Clearance	Not reported
Protein binding	>90%
Bioavailability	54-78%

Metabolism: Mipomersen is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. Mipomersen is not a substrate for cytochrome P450 metabolism.

Elimination: The elimination of mipomersen involves metabolism in tissues and excretion primarily in the urine. Both mipomersen and putative shorter oligonucleotide metabolites were identified in human urine. Urinary recovery was limited in humans with less than 4% within the 24 hours postdose.

Efficacy:

McGowan MP, Tardif JC, Ceska R, Burgess LJ, Soran H, Gouni-Berthold I, Wagener G, Chasan-Taber S. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS One. 2012;7(11):e49006. doi: 10.1371/journal.pone.0049006. Epub 2012 Nov 13.

Study Design: Randomized, double-blind, placebo-controlled, multicenter trial.

Description of Study: *Methods:* Adult patients with severe hypercholesterolemia defined as an LDL-C > 5.1 mmol/L with known CHD or an LDL-C > 7.8 mmol/L in the absence of known CHD were studied. Patients were on a stable low fat diet, at a stable weight, on maximally tolerated lipid-lowering therapy, and met LDL-apheresis criteria but apheresis was prohibited. Exclusions included significant cardiovascular or cerebrovascular events within 24 weeks of screening, congestive heart failure, type I diabetes, poorly controlled type II diabetes, hypertension, secondary hyperlipidemia predisposition, or a history of significant renal or hepatic failure. Following 4 weeks of screening, eligible patients were randomized to 26 weeks of mipomersen 200 mg sub-q per week or placebo. The primary endpoint was percentage change in LDL-C from baseline to 2 weeks after the last dose. Secondary endpoints included percent change from baseline in apo B, non-high-density lipoprotein, and cholesterol.

Outcome Results: Fifty eight patients were randomized; 46 completed 26 weeks of treatment. The mean percent change in LDL-C was -36% (95% CI -51.3 to -15.3) in mipomersen patients compared to 12.5% (95% CI -10.8 to 35.8) in placebo patients ($p < 0.001$). This corresponds to a mean absolute change of -2.62 mmol/L and 0.38 mmol/L in mipomersen and placebo patients respectively. Changes in apo B, TC, non-HDL-C and Lp(a) mirrored those findings. A > 15% decrease in LDL-C was seen in 79% of mipomersen patients compared with 17% of placebo patients. There was a more robust LDL-C reduction in females than males in the mipomersen group, however the 27% reduction in men was statistically significant and clinically meaningful.

Limitations: Study limitations included the small study size, short-treatment period, and liver imaging applied only for cause. This small cohort may not be sufficient to evaluate the safety concerns. Potential conflicts of interest are apparent as authors had received grants from Genzyme, served as advisory board members for Genzyme, or were employees of Genzyme.

Conclusion: Mipomersen significantly lowers LDL-C and all measured ApoB-containing lipoproteins, including Lp(a) in a population at high risk for developing cardiac disease. This study supports the use of mipomersen as a potential therapeutic option for patients with severe hypercholesterolemia not adequately controlled on currently available lipid-lowering medications. Future trials with larger patient numbers will help establish the utility of mipomersen as a potential therapeutic option for the treatment of patients with severe hypercholesterolemia.

Visser ME, Wagener G, Baker BF, Geary RS, Donovan JM, Beuers UH, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J. 2012 May;33(9):1142-9. Epub 2012 Apr 16.

Study Design: Randomized, double-blind, placebo-controlled study.

Description of Study:

Methods: Forty-two hypercholesterolemia subjects, who were statin intolerant and at high risk for CVD events, were screened for participation; 34 were randomized. Patients were considered to be 'statin intolerant' if they were unable to tolerate at least two different statins due to side effects of any kind. Participants did not use other lipid-lowering drugs unless the dose had been stable for 8 weeks prior to screening. The primary outcome measure was percent change in LDL cholesterol from the baseline to week 28. Secondary outcome measures were percent change in apoB and lipoprotein a.

Outcome Results: Treatment with mipomersen 200 mg/week sub-q resulted in significant reductions in LDL-C of 47% ($p < 0.001$ vs. placebo) with a range of -19 to -77%. The observed reduction in LDL-C corresponded to mean apoB reductions of 46% ($p < 0.001$ vs. placebo). Mipomersen treatment also significantly lowered total cholesterol, triglycerides, and Lpa, but did not affect HDL-C and apoA1. Mipomersen differentially lowered LDL particle numbers with largest reductions in the small LDL particles when compared with the large LDL particles.

Limitations: First, determination of intrahepatic tryglyceride (IHTG) content was performed only in subjects with transaminase increases. As a consequence, baseline and highest values for IHTG content in subjects without liver transaminase increases were missing, leaving the effect of mipomersen on IHTG content incomplete. Next, conclusions based on biopsy findings were hampered by a small sample size, the short treatment duration, and the lack of pre-treatment biopsy. Potential conflicts of interest are possible within the study as Genzyme paid for the Open Access publication charges, two authors had received advisory fees from Genzyme, and two other authors were employees of Genzyme.

Conclusion: Pending long-term safety data, apoB synthesis inhibition may offer a potential therapeutic strategy for patients at high risk for CVD with statin intolerance for whom currently limited alternative options are available to effectively lower LDL-c. Future trials are needed and should have a larger sample size, longer treatment duration, and potential pretreatment biopsies. Conflicts of interest should be avoided as much as possible.

Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Mar 20;375(9719):998-1006. doi: 10.1016/S0140-6736(10)60284-X.

Study Design: Randomized, double-blind, placebo-controlled, phase 3 study.

Description of Study:

Methods: Patients were aged 12 years and older with clinical diagnosis or genetic confirmation of homozygous familial hypercholesterolaemia, who were already receiving the maximum tolerated dose of a lipid-lowering drug were randomly assigned to mipomersen 200 mg subcutaneously every week or placebo for 26 weeks. Patients had to be on a stable, low fat diet upon screening and their pre-existing maximum tolerated lipid-lowering drug with fasting LDL cholesterol concentrations of 3.4 mmol/L or greater, triglyceride concentrations less than 4.0 mmol/L, and body weight 40 kg or greater. Major exclusion criteria were significant cardiovascular events within 12 weeks of screening; unstable or inadequately treated stable angina; congestive heart failure; uncontrolled hypothyroidism or any other disorder that might predispose to secondary hyperlipidemia; serum creatine phosphokinase three times or higher the upper limit of normal (ULN); or a history of significant renal or hepatic disease. The primary outcome measure was percentage change in LDL cholesterol concentration from baseline. Prespecified secondary efficacy measures were percentage change from baseline in apolipoprotein B, total cholesterol, and non-HDL cholesterol concentrations.

Outcome Results: Forty-five patients completed the 26 week treatment period. At the primary efficacy time point, the percentage change from baseline in LDL cholesterol concentration was significantly greater with mipomersen than with placebo. The reduction in LDL cholesterol concentration with mipomersen reflected an absolute mean decrease from 11.4 mmol/L (SD 3.6, range 4.9–18.2) to 8.4 mmol/L (3.1, 1.6–15.2). The percentage change from baseline in apolipoprotein B concentration was significantly greater with mipomersen than with placebo. Mipomersen treatment resulted in a significant percentage reduction in lipoprotein(a) concentration compared with the placebo group. A significant increase from baseline in HDL cholesterol concentration was also recorded with mipomersen. The percentage reduction in the ratio of LDL to HDL cholesterol concentrations was significantly greater with mipomersen (–34.3%, 95% CI –41.7 to –27.0) than with placebo (–6.2%, –15.8 to 3.4%; $p < 0.0001$).

Limitations: Therapeutic lifestyle changes as recommended by the National Cholesterol Education Program Adult Treatment Panel III were advised and encouraged for the duration of the study, which may convolute the true results of the study. Another limitation was that hepatic fat was not routinely measured on treatment, but was measured only in patients whose aminotransferase values increased by more than three times the upper limit of normal. Also, only one dose of mipomersen was used in this study. While they had mentioned that high baseline LDL concentrations were present, they failed to include higher or more frequent doses that may have shown benefit in some patients. Conflicts of interest may be present as multiple authors have served on advisory boards, received payment, performed research, or own stock in Genzyme Corporation.

Conclusion: Mipomersen could be a valuable addition to the drugs used in the management of homozygous familial hypercholesterolemia and should prove useful in the management of other forms of severe refractory hypercholesterolemia.

Contraindications^{1,2,3,4}:

Moderate or Severe Hepatic Impairment: Child-Pugh B or C, or active liver disease, including unexplained persistent elevations of serum transaminases.

Patients with a known hypersensitivity to any component of this drug.

Precautions^{1,2,3,4}:

Risk of Hepatotoxicity: Mipomersen can cause elevations in transaminases and hepatic steatosis. To what extent mipomersen-associated hepatic steatosis promotes the elevations in transaminases is unknown. There is concern that mipomersen could induce steatohepatitis, which can progress to cirrhosis over several years.

Elevation of transaminases: Mipomersen can cause increases in serum transaminases (ALT and/or AST). In the clinical trial, 12% of subjects treated with mipomersen compared with 0% of subjects treated with placebo had an elevation in ALT at least $3 \times$ ULN, and 9% of those treated with mipomersen compared with 0% treated with placebo had at least 1 elevation in ALT at least $5 \times$ ULN. If transaminase elevations are accompanied by clinical symptoms of liver injury (eg, nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin at least $2 \times$ ULN, or active liver disease, discontinue treatment and identify the probable cause

Hepatic Stenosis: Mipomersen 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. The long-term consequences of hepatic steatosis associated with mipomersen are unknown. During the clinical trials in patients with heterozygous familial hypercholesterolemia and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by MRI.

Injection-site reactions: Injection-site reactions have been reported in 84% of patients receiving mipomersen and typically consist of 1 or more of the following: erythema, pain, tenderness, pruritus, and local swelling.

Flu-like symptoms: Flu-like symptoms have been reported in 30% and include 1 or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise, and fatigue. Flu-like symptoms, which typically occur within 2 days after an injection.

Immunogenicity: Thirty-eight percent of mipomersen-treated patients tested positive for anti-mipomersen antibodies during the 6-month trials. Efficacy results in patients who tested positive for anti-mipomersen 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 mipomersen tested positive for anti-mipomersen antibodies (35% with titers more than 3,200). The incidence of flu-like symptoms and the incidence of discontinuation of mipomersen were higher in antibody-positive patients. Antibodies to mipomersen were associated with higher trough levels for the drug.

Renal function impairment: Mipomersen is not recommended in patients with severe renal impairment, with clinically significant proteinuria, or undergoing renal dialysis.

Hepatic function impairment: Mipomersen is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) or active liver disease, including unexplained persistent elevations of transaminases.

Children: Safety and effectiveness have not been established in pediatric patients.

Elderly: Patients 65 years and older had a higher incidence of hypertension and peripheral edema. Hepatic steatosis was also reported with greater frequency in the 65 years and older group (13.6%) compared with the younger than 65 years group (10.4%).

Adverse Effects:

Occurring in >10% of patients

Gastrointestinal

Nausea (14%)

Vomiting (5% to 17%)

General Disorders and Administration Site Conditions

Injection Site Reactions (84%)

Fatigue (15%)

Influenza-like illness (13%)

Nervous System Disorders

Headache (12%)

Other

Alanine aminotransferase increased (10%)

Occurring in >1% to <10% of patients

Cardiac

Angina Pectoris (4%)

Palpitations (3%)

Gastrointestinal

Vomiting (4%)

Abdominal Pain (3%)

General Disorders and Administration Site Conditions

Pyrexia (8%)

Chills (6%)

Peripheral Edema (5%)

Hepatobiliary Disorders

Hepatic Steatosis (7%)

Musculoskeletal and Connective Tissue Disorders

Pain in extremity (7%)

Musculoskeletal Pain (4%)

Psychiatric Disorders

Insomnia (3%)

Vascular Disorders

Hypertension (7%)

Other

Aspartate aminotransferase increased (6%)

Liver function test abnormal (5%)

Hepatic enzyme increased (3%)

Drug Interactions^{1,2,3,4}:

Alcohol and other hepatotoxic agents (eg, amiodarone, high doses of acetaminophen, isotretinoin, methotrexate, tamoxifen, tetracyclines): Alcohol and some other LDL-lowering agents can increase levels of hepatic fat, similar to mipomersen. Coadministration with other LDL-lowering agents that can increase levels of hepatic fat is not recommended; limit consumption of alcoholic drinks to no more than 1 per day.

Coadminister with other hepatotoxic agents with caution and frequently monitor liver-related tests.

No clinically relevant pharmacokinetic interactions were reported between mipomersen and warfarin or between mipomersen and simvastatin or ezetimibe. Additionally, coadministration of mipomersen with warfarin did not result in a pharmacodynamics interaction as determined by INR, aPTT, and PT.

Dosing/Administration^{1,2,3,4.}

Adult Dosing

200 mg SC once weekly. Administer the injection on the same day every week. If a dose is missed, the injection should be given at least 3 days from the next weekly dose. Measure transaminases (ALT, AST), alkaline phosphatase, and total bilirubin prior to initiation of therapy. Monitor lipid levels at least every 3—4 months for the first year. Maximal reduction of LDL-C may be seen after approximately 6 months. Assess the patient's LDL-C level after 6 months to determine if the LDL-C reduction achieved is sufficient to warrant the potential risk of liver toxicity. Geriatric patients are at increased risk for hypertension, peripheral edema, and hepatic steatosis compared to younger patients during mipomersen therapy and should be closely monitored

Pediatrics (≥4 years of age)

Safety and effectiveness have not been established in pediatric patients.

Elderly

Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Of the 261 patients who received mipomersen in the pooled Phase 3 trials, 59 (22.6%) were ≥ 65 years old and 10 (3.8%) were ≥75 years old. In the pooled Phase 3 trials, patients ≥ 65 years of age treated with mipomersen had a higher incidence of hypertension and peripheral edema compared to placebo patients in this age group, as well as compared to the younger mipomersen-treated age group. Hepatic steatosis was also reported with greater frequency in the ≥ 65 group (13.6%) compared to the <65 group (10.4%)

Renal impairment

Specific guidelines for dosage adjustments in renal impairment are not available. Due to the lack of clinical data and the renal safety profile of mipomersen, the drug is not recommended in patients with severe renal impairment or clinically significant proteinuria.

Hepatic impairment

Safety and efficacy in patients with known hepatic impairment have not been established. Further, use is contraindicated in patients with clinically significant hepatic dysfunction, which may include persistent elevations of transaminases.

Use in special circumstances:

Overdosage:¹ There have been no reports of overdose with mipomersen treatment. In clinical trials, patients receiving higher doses of mipomersen (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.

Conclusion:

Mipomersen may have clinical utility in patients who have exhausted other LDL lowering options such as statins. Most studies have reported positive outcomes in reaching their primary endpoints, however they have also had potential conflicts of interest present. Further genetic studies and clinical trials are needed to fully establish a place in therapy and develop more comprehensive safety and efficacy data for mipomersen.

Recommended References:

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5. Visser ME, Wagener G, Baker BF, Geary RS, Donovan JM, Beuers UH, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. *Eur Heart J*. 2012 May;33(9):1142-9. Epub 2012 Apr 16.
6. Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010 Mar 20;375(9719):998-1006. doi: 10.1016/S0140-6736(10)60284-X.
7. McGowan MP, Tardif JC, Ceska R, Burgess LJ, Soran H, Gouni-Berthold I, Wagener G, Chasan-Taber S. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. *PLoS One*. 2012;7(11):e49006. doi: 10.1371/journal.pone.0049006. Epub 2012 Nov 13.