New Drug Review

Generic Name: mipomersen
Trade Name: Kynamro®
Formulation: 200 mg injection
Manufacturer: Genzyme Corporation
FDA Approval Date: January 29, 2013

Overview/Summary

Kynamro® (mipomersen) is an oligonucleotide inhibitor of apolipoprotein B (ApoB)-100 synthesis that is Food and Drug Administration-approved as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein cholesterol, ApoB, total cholesterol, and non-high density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).[1] This agent is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for ApoB-100. Hybridization to the cognate mRNA results in inhibition of translation of the Apo B-100 protein and ultimately decreased formation of low density lipoprotein and very low density lipoprotein.[1]

Familial hypercholesterolemia is a genetically modulated clinical syndrome in which the phenotype is characterized by a high low density lipoprotein cholesterol level from birth and early onset coronary heart disease (including the absence of other risk factors). Established causes include: low density lipoprotein receptor mutations (most common), gain-of-function PCSK9 mutations (less than five percent of cases in most clinics) and familial defective ApoB (less than five percent of cases). The disorder is inherited with a gene dosing effect, in which homozygotes are more adversely affected than heterozygotes. The incidence of HoFH is rare (1 in 250,000 births) unless there is co-sanguineous union in a family with heterozygous familial hypercholesterolemia.[2] Treatment guidelines support the use of high-dose statins, low density lipoprotein apheresis and other cholesterol lowering agents (e.g., ezetimibe), often as part of combination regimens to reach cholesterol goals.[2-13] In refractory cases, liver transplant may be therapeutic options.

The safety and efficacy of mipomersen has not been established in patients with hypercholesterolemia who do not have HoFH. In addition, the effect of this agent on cardiovascular morbidity and mortality has not been established. Furthermore, the use of mipomersen as an adjunctive treatment to low density lipoprotein apheresis is not recommended. The prescribing information for mipomersen includes a Black Box Warning regarding the risk of elevations in transaminases, increases in hepatic fat content and risk of hepatotoxicity. As a result, mipomersen is only available through a restricted distribution program under a risk evaluation and mitigation strategy.[1]

Pharmacokinetics

Table 1. Pharmacokinetics[1]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Mipomersen	54 to 78	Not reported	4	None	2 to 5 hours

Clinical Trials

The safety and efficacy of Kynamro® (mipomersen) as an adjunct to lipid-lowering medications in individuals with homozygous familial hypercholesterolemia (HoFH) were evaluated in a multinational, randomized, placebo-controlled, 26-week trial (N=51). The primary efficacy endpoint was the percent change from baseline to 28 weeks in low density lipoprotein cholesterol (LDL-C). At 28 weeks, there was a significantly greater reduction from baseline with mipomersen compared to placebo with regard to LDL (-25 vs -3%; *P*=0.0003), apolipoprotein B (-27 vs -3%; *P*<0.0001), total cholesterol (-21 vs -2%; *P*<0.05), non-high density lipoprotein-cholesterol (HDL-C) (-25 vs -3%; *P*=0.0002), triglycerides (-18 vs 1%; *P*=0.013) and HDL-C (15 vs 4%; *P*<0.001). Despite the significant mean decrease from baseline in LDL-C

in the mipomersen arm, there was wide inter-patient variability ranging from an increase of 2% to an 82% decrease.[1,14]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Raal et al[14] Mipomersen 200 mg SC weekly vs placebo Patients were maintained on maximum tolerated prior lipid lowering drugs (high-dose statins, cholesterol absorption inhibitors, bile acid sequestrants or nicotinic acid) throughout the study.	DB, MC, PC, PG Patients ≥12 years of age with genetically or clinically determined HoFH with a fasting LDL-C >3.5 mmol/L, triglycerides <4 mmol/L and bodyweight >40 kg	N=51 26 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in ApoB, total cholesterol and non-HDL-C from baseline and safety evaluations	Primary: At week-28, there was a significantly greater improvement from baseline in LDL-C for patients treated with mipomersen compared to patients treated with placebo (-25 vs -3%; *P*=0.0003). Secondary: At week-28, there was a significantly greater improvement from baseline in ApoB for patients treated with mipomersen compared to patients receiving placebo (-27 vs -3%; *P*<0.0001), TC (-21 vs -2%; *P*<0.05), non-HDL-C (-25 vs -3%; *P*=0.0002), triglycerides (-18 vs 1%; *P*=0.013) and HDL-C (15 vs 4%; *P*<0.001). The most common adverse event was injection-site reaction, which was three-times more common in the mipomersen group than in the placebo group. Three serious adverse events were reported. One patient in the placebo group had nephrolithiasis. In the mipomersen group, one patient had an acute coronary syndrome and one fractured an ankle. None of these adverse events was considered to be related to the study drug.

Drug regimen and study abbreviations: ApoB=apolipoprotein B, DB=double blind, HDL-C=high density lipoprotein cholesterol, HoFH=homozygous familial hypercholesterolemia, LDL-C=low density lipoprotein cholesterol, MC=multicenter, PC=placebo controlled, PG=parallel group, SC=subcutaneous, TC=total cholesterol

Special Populations

Table 3. Special Populations[1]

Population	Precaution
Elderly	In pooled clinical trials including elderly patients (without homozygous familial hypercholesterolemia), mipomersen was associated with a higher rate of hypertension and peripheral edema compared to placebo-treated patients.
Renal Dysfunction	Safety in renal dysfunction has not been established. This agent is not recommended in patients with severe renal impairment, clinically significant proteinuria or in those on dialysis.
Hepatic Dysfunction	Mipomersen is contraindicated in patients with clinically significant hepatic dysfunction, which may include persistent elevations of transaminases.
Pregnancy/Nursing	Category: B Percent excretion through breast milk is not known.
Children	Safety and efficacy in children have not been established.
Age Restrictions	FDA-approved for use in patients ages ≥18 years.

Adverse Drug Events

Kynamro® (mipomersen) safety data is based upon pooled results from four Phase III, randomized, double-blind, placebo-controlled trials (N=390, including 41 with homozygous familial hypercholesterolemia). Adverse reactions occurring in ≥5% of patients receiving active treatment in clinical trials are summarized in Table 4.

Table 4. Adverse Events[1]

Adverse Event	Kynamro® (mipomersen) 200 mg weekly, %, N=261	Placebo %, N=129
Gastrointestinal Disorders		
Nausea	14	8
General Disorders and Administration Site Conditions		
Chills	6	1
Edema, peripheral	5	2
Fatigue	15	8
Influenza-like illness	13	3
Injection site reactions	84	33
Pyrexia	8	3
Hepatobiliary disorders		
Hepatic steatosis	7	2
Investigations		
Alanine aminotransferase increased	10	1
Aspartate aminotransferase increased	6	2
Liver function test abnormal	5	1
Musculoskeletal Disorders		
Pain in extremity	7	3
Nervous System Disorder		
Headache	12	9
Vascular Disorders		
Hypertension	7	3

Contraindications/Precautions

Black Box Warning for Kynamro® (mipomersen)[1]

WARNING
Kynamro® (mipomersen) can cause elevations in transaminases. 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 mipomersen if the ALT or AST is ≥3 times the upper limit of normal (ULN). Discontinue mipomersen for clinically significant liver toxicity. Mipomersen increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Hepatic steatosis associated with mipomersen may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Because of the risk of hepatotoxicity, mipomersen is available only through a restricted program called the Kynamro® REMS.

Kynamro® (mipomersen) is contraindicated in patients with a known hypersensitivity to any component of the product. The agent is also contraindicated in moderate to severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases.[1]

Due to the concerns of liver toxicity, a full liver panel should be obtained prior to initiating treatment. Causes of abnormal liver enzyme elevations should be identified and resolved before treatment, if possible. During the first year, liver tests should be conducted monthly and least every three months thereafter. If symptoms of liver toxicity are present, treatment should be discontinued immediately. In addition, caution should be exercised when using this agent with other medications known to cause hepatotoxicity or increases in hepatic fat and patients should not consume greater than one alcoholic drink per day.[1]

Mipomersen has also been associated with injection site reactions (consisting of erythema, pain, pruritus and local swelling). Proper injection technique should be followed to minimize the risk of these events.[1] In addition, mipomersen has been associated with flu-like symptoms usually within two days of an injection.

Drug Interactions

No clinically relevant pharmacokinetic interactions were reported between mipomersen and warfarin, or between mipomersen and simvastatin or ezetimibe.[1]

Dosage and Administration

Kynamro® (mipomersen) should be injected into the abdomen, thigh region or outer area of the upper arm avoiding areas affected by active skin disease, tattoos, scarring or injury (e.g., sunburn, inflammation).

Table 5. Dosing and Administration[1]

Adult Dose	Pediatric Dose	Availability
Homozygous familial hypercholesterolemia: Injection: initial, maximum and maintenance, 200 mg injected SC weekly	Safety and efficacy in children have not been established.	Injection: 200 mg/mL (in 1 mL vials or prefilled syringes; packaged as single dose or a carton containing four doses)

Drug regimen abbreviations: SC=subcutaneously

Clinical Guidelines

Table 6. Clinical Guidelines

Clinical Guideline	Recommendations
The Third Report of the National Cholesterol Education Program (NCEP): **Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001)[3]** **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[4]**	• Low-density lipoprotein cholesterol (LDL-C) is identified as the primary target of cholesterol-lowering therapy. • Therapeutic lifestyle changes remain an essential modality in clinical management. • In high-risk patients, the recommended LDL-C goal is <100 mg/dL; however, when risk is very high, an LDL-C goal of <70 mg/dL is a therapeutic option. • When a high-risk patient has high triglycerides (TG) or low high-density lipoprotein cholesterol (HDL-C), consideration can be given to combining a fibrate or nicotinic acid within an LDL-lowering drug. • For moderately high-risk patients, the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal <100 mg/dL is a therapeutic option. • When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30 to 40% reduction in LDL-C levels. • With lower-risk patients, the recommended LDL-C goal is <160 mg/dL. • Initial LDL-lowering treatment is typically with a moderate-dose statin but alternatives are a bile acid sequestrant or nicotinic acid. • If after six weeks the goal of therapy has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant, nicotinic acid, or fibric acid derivative. • For patients with familial hypercholesterolemia, management with high-dose statins, nicotinic acid or LDL-apheresis should be considered to reduce coronary heart disease risk.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)[5]**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non-high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): Healthcare Guideline: **Lipid Management in Adults (2011)[6]**	• For monotherapy, statins are the drugs of choice for lowering LDL. These agents should be initiated in patients with coronary heart disease (CHD) or CHD equivalents. • If a patient is intolerant to a statin, other statins should be tried or the dose should be decreased before attempting alternate therapies. • If patients are unable to take statins, then bile acid sequestrants, niacin, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it.

Clinical Guideline	Recommendations
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[7]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies: **European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[8]	• Total plasma cholesterol should be <5 mmol/L (<190 mg/dL), and LDL-C should be <3 mmol/L (<115 mg/dL). • Statins are considered first-line drugs for lowering LDL-C. • Non-statin treatment o Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C concentrations. o Bile acid sequestrants also decrease total and LDL-C but tend to increase triglyceride concentrations. o Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for triglyceride lowering. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels. • All patients with familial hypercholesterolemia must be recognized as high-risk patients and be treated with lipid-lowering therapy. o Rare patients with severe hypercholesterolemia, especially homozygous familial hypercholesterolemia, require specialist evaluation of the need for LDL apheresis.
National Heart Lung and Blood Institute: **Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk (2011)**[9]	Specific recommendations regarding the management of familial hypercholesterolemia include: • Children with homozygous familial hypercholesterolemia and extremely elevated LDL-C levels (>500 mg/dL) have undergone effective LDL-C lowering therapy with biweekly LDL apheresis under the care of lipid specialists in academic medical centers. • Statins have been shown to reduce LDL-C in children and adolescents with marked LDL-C elevation or familial hypercholesterolemia. • Plant sterol esters and/or plant stanol esters up to 2 g/day as replacement for usual fat sources can be used after two years of age in children with familial hypercholesterolemia
National Institute for Health and Clinical Excellence (NICE): **Identification and Management of Familial Hypercholesterolemia (2008)**[10]	• Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Healthcare professionals should offer treatment with a statin with a low acquisition cost for adults with familial hypercholesterolemia in whom the diagnosis is made after the 60 years of age and who do not have

Clinical Guideline	Recommendations
	coronary heart disease. • Prescribing of drug therapy for adults with homozygous familial hypercholesterolemia should be undertaken within a specialist center. • Healthcare professionals should offer adults with familial hypercholesterolemia a referral to a specialist with expertise in familial hypercholesterolemia if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. • Adults with familial hypercholesterolemia with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in familial hypercholesterolemia for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce their LDL-C concentration. • Lipid-modifying drug therapy for a child or young person with familial hypercholesterolemia should usually be considered by 10 years of age. Statins should be considered as initial treatment.
National Lipid Association (NLA): Management of Familial Hypercholesterolemia in Adult Patients: **Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia (2011)**[11]	• For adult familial hypercholesterolemia patients, initial treatment is the use of moderate to high doses of high-potency statins titrated to achieve an LDL-C reduction ≥50% from baseline. Low potency statins are generally inadequate for familial hypercholesterolemia patients. • If the initial statin is not tolerated, consider changing to an alternative statin, or every-other-day statin therapy. • If initial statin therapy is contraindicated or poorly tolerated, ezetimibe, a bile acid sequestrant (colesevelam) or niacin may be considered. • For patients who cannot use a statin, most will require combination drug therapy. • If the patient is not at LDL-C treatment goal with the maximum available and tolerable dose of statin, then combine with ezetimibe, niacin, or a bile acid sequestrant (colesevelam preferred). • Decisions regarding selection of additional drug combinations should be based on concomitant risk factors for myopathy, concomitant medications, and the presence of other disease conditions and lipid abnormalities. • In patients who, after six months, do not have an adequate response to maximum tolerated drug therapy, LDL apheresis is indicated according to these guidelines: o Functional homozygous familial hypercholesterolemia patients with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL). o Functional heterozygous familial hypercholesterolemia patients with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and one or fewer risk factors. o Functional heterozygous familial hypercholesterolemia patients with LDL-C ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high risk characteristics such as two or more risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay. o Functional heterozygotes with LDL-C ≥160 mg/dL (or non-HDL-C ≥190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease, or diabetes).

Conclusions

Kynamro® (mipomersen) is an oligonucleotide inhibitor of apolipoprotein B (ApoB)-100 synthesis that is approved as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein cholesterol

(LDL-C), ApoB, total cholesterol, and non-high density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).[1] Available treatment guidelines for this condition support the use of high-dose statins, LDL apheresis and other cholesterol lowering agents (e.g., ezetimibe), often as part of combination regimens to reach cholesterol goals.[2-13]

In clinical trials, mipomersen was evaluated as an adjunctive treatment and was associated with a significant decrease from baseline in LDL-C and other secondary measures of cholesterol.[14] Mipomersen is associated with significant tolerability issues including liver toxicity and increased hepatic fat. Moreover, the effects of mipomersen on cardiovascular outcomes in patients with HoFH have not been established.[1]

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