Drug Use Research & Management Program
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New Drug Evaluation: mipomersen

Month/Year of Review: May 2013
End date of literature search: Week 3, March 2013 (MedLine/Scopus); 2/11/2013 (ClinicalTrials.gov)
Generic Name: mipomersen
Brand Name (Manufacturer): Kynamro™ (Genzyme)
PDL Class: Non-Statin Lipid Lowering Agents
Dossier Received: requested March 1, 2013; Received 4/30/2013

Food and Drug Administration (FDA) Approved Indication:
"KYNAMRO™ is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)."[1] There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of mipomersen outweigh the potential risk of liver injury.[1]

Potential Off-Label Indications:
- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:
- Is mipomersen more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is mipomersen safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where mipomersen is more or less effective or safe?

Conclusions:
- The three randomized placebo-controlled phase III trials were only 28weeks long and did not evaluate CHD outcomes. LDL-C goal was achieved only in the HeFH study. There is insufficient evidence to determine if mipomersen lowers the incidence of CHD events in patients with HoFH, HeFH or drug resistant hypercholesterolemia.
- The potential for liver injury secondary to chronic fat accumulation is the primary concern. However, 100% of mipomersen patients experienced adverse events (ADEs) including injection-site reactions, flu-like symptoms and proteinuria. Longer-term exposure in more patients is needed to adequately define the risks.
- There are few treatment options for HoFH. Mipomersen is a viable third-line alternative behind LDL-C apheresis.

Recommendations:
- Prior authorize mipomersen to limit use to genetically confirmed HoFH patients that have a medical contraindication to maximum lipid-lowering therapy and LDL-C apheresis, and is prescribed by or in consultation with a lipid specialist.

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.[2] Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.[2] Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.[2] Statins are not tolerated (myalgia or myostitis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Mipomersen has a new mechanism of action and reduces LDL-C levels by reducing the production of apolipoprotein B-100 (apo B-100).[1] Apo B-100 is a precursor to synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.[3] FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.[4] HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.[3] HoFH is a total LDL receptor deficiency.[3] It is very rare (estimated prevalence of 1 per 1 million people) but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.[3] LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy.[5] However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks) and is currently performed at only 35 centers in the United States. Liver transplantation is a last resort. HoFH is an orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: ClinicalTrials.gov identified 18 mipomersen randomized controlled trials. Five were Phase I trials, seven were Phase II and seven were Phase III of which four were completed and three were published. [6,7,8] Raal et al.[6] studied mipomersen in HoFH patients. Stein et al.[7] evaluated it in HeFH patients and McGowan et al.[8] in patients with drug resistant hypercholesterolemia.

Mipomersen was approved based upon a single phase III trial of 51 genetically or clinically confirmed HoFH patients.[6] Raal et al.[6] was a fair quality trial that randomized 34 patients to 200mg of subcutaneous mipomersen per week and 17 patients to a matching volume of placebo subcutaneously per week. All patients were allowed to be on maximum tolerated lipid-lowering therapy as long as the doses were stable 12 weeks. LDL-C apheresis was not allowed. Randomization and allocation concealment were well done and described. The groups were only slightly different at baseline with more children and more significant CHD history in the mipomersen group but more metabolic syndrome in the placebo group. There was no loss to follow-up but total attrition was high and uneven in the mipomersen patients due to ADE withdrawal. All mipomersen patients experienced ADEs, primarily injection site reactions. This threatened the blinding and increases the risk of performance bias. CHD outcomes were not assessed it is not likely they will be in the future given the low prevalence of HoFH. The primary outcome was percent change in LDL-C from baseline. The mean treatment time was 25 weeks and follow-up was two weeks after the last dose. There was a mean difference of 21% reduction between groups, favoring mipomersen ($p < 0.0003$) which had a 25% reduction in LDL-C. However, the LDL-C at the end of the study remained very high in both groups: mipomersen 324 mg/dL versus placebo 390mg/dL.

Stein et al.[7] was a fair quality trial that randomized 83 patients to self-administered subcutaneous mipomersen 200mg and 41 patients to an un-described, but self-administered placebo. Both were given weekly for 26 weeks. All patients were genetically or clinically confirmed with HeFH on a stable, maximally tolerated lipid-lowering drug regimen for 12 weeks. LDL-C apheresis was not allowed. There was slightly more patients with cardiovascular history and who smoked in the mipomersen group. Risks for selection, performance and attrition biases were identified. There was inadequate description of randomization, allocation concealment and blinding. Three mipomersen patients were lost to follow-up and nine mipomersen patients withdrew due to ADEs. Again CHD

outcomes were not assessed and the percent change from baseline to 28 weeks in LDL-C was the primary outcome. The mean difference in LDL-C between groups was a decrease of 33% favoring mipomersen (p <0.001) to final LDL-C levels of: mipomersen 104 mg/dL and placebo 143 mg/dL.

McGowan et al.[8] was a good quality trial that randomized 39 patients to self-administered mipomersen 200mg subcutaneously per week to and 19 patients to a self-administered similarly appearing placebo for 26 weeks. It included adults with severe hypercholesterolemia on maximum lipid-lowering therapy and excluded from apheresis. There was a good description of randomization, allocation concealment and blinding. The groups differed in that there was more alcohol use and metabolic syndrome in the mipomersen group but more tobacco use in the placebo group. The mipomersen group experienced more loss to follow-up (13%) and total attrition (36%) than the placebo group (5% and 16% respectively). Blinding may have been broken due to all mipomersen patients experiencing an ADE, most of which were injection site reactions. CHD outcomes were not assessed. The mean difference in the primary outcome, percent change in LDL-C at 28 weeks, was 48% favoring mipomersen (0.001). The final LDL-C for both groups remained high: mipomersen 174mg/dL versus placebo 263mg/dL.

Another trial[9] was identified in the dossier but was not available for review except in abstract form.[10]

Clinical Safety:

According to the FDA Summary Review[11] the primary safety concern with mipomersen is the potential liver injury secondary to chronic fat accumulation. Other safety issues include injection-site reactions, flu-like symptoms and proteinuria. The FDA safety assessment was derived from four phase III trials involving 390 patients that were randomized to mipomersen 2: placebo 1 for 6 months.[9] Table 1 summarizes the FDA Summary Review data.[9]

Table 1- Summary of FDA Summary Review Safety Data

Endpoint	Placebo Percent of Patients	Mipomersen Percent of Patients
Percent fat content change from baseline ≥ 5%	8.3%	61.8%
ALT ≥ 3x Upper Limits of Normal (ULN)	1.0%	16.0%
AST ≥ 3x ULN	0.0%	4.2%
Injection-site reactions	33.0%	84.0%
Flu-like symptoms	16.0%	30.0%
Antibody Response at Week 50	0.0%	33.0%
Proteinuria	0.8%	2.3%
Cardiovascular Events reported as ADE	6.0%	9.0%
Neoplasms	0.5%	1.2%
Withdrawals due to ADE	2.3%	18.0%

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CHD events
2) Withdrawals due to ADEs
3) Serious ADEs

Primary Study Endpoints:

1) Percent change in LDL-C from baseline to 28 weeks
2) Withdrawals due to ADEs
3) Serious ADEs

Ref./ Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Raal et al.[6] RCT PC DB MC	M: Mipomersen 200mg/week SQ; mean treatment period 159 days. P: Matching SQ placebo /week; mean treatment period 176 days. f/u 28 weeks	Patients with HoFH already on lipid-lowering treatment. Demographics: Mean age: 31.3 years SD 12.4; 7 patients <18 Female: M: 56%, P:59% Group comparison at baseline: Group differences include: more children and significant CV history in control; more metabolic syndrome in mipomersen. Inclusion: ≥12 years old Genetically confirms homozygous FH OR Untreated LDL-C >500mg/dl + xanthoma before 10 yrs. or + both parental heterozygous FH Stable low-fat diet Maximum tolerant lipid-lowering therapy with fasting LDL-C 130mg/dL & weight of ≥40kg. Exclusion: LDL apheresis within 8 weeks CV event within 12 weeks Angina CHF Secondary hyperlipidemia predisposition SCr > 3x ULN Hx of renal or hepatic disease	ITT: M:34 P:17 Total attrition: M: 6 (17.6%) P: 0 (0.0%) Loss to f/u: M: 5 (14.7%) P: 0 (0.0%)	Primary Outcome: % Δ in LDL-C @ baseline to 2 weeks after last dose. M: -24.7% (-31.6%, 17.7%) to 324mg/dL P: -3.3% (-12.1%, 5.5%) to 390mg/dL MD: -21.3% 95% CI (-32.9%, -9.8%) P <0.0003	NA / NA	Total withdrawals due to AE: M: 5 (14.7%) P: 0 (0.00%) RR: NA 95% CI NA p-value NA SAE: M: 2 (7.1%) [ACS, ankle fx] P: 1 (5.9%) [nephrolithiasis] RR: 1.21 95% CI (0.12, 12.40) p-value NA	14.7% / NA 1.3% / 79	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - Adequate description of randomization and allocation concealment. Stratified by weight (<50kg, ≥50kg). Though baseline group comparison of prognostic factors has small differences. No effect. Performance: MOD- Good description of blinding of patients, caregivers, investigators and outcomes assessors, but all mipomersen patients experienced ADE. Possible bias away from null. Detection: LOW - Good description of blinding of patients, caregivers, investigators and outcomes assessor, but all mipomersen patients experienced ADE. Objective outcome likely not affected. Attrition: HIGH – small sample size, >10% difference between groups in total attrition and loss to follow-up. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics: Study results apply to HoFH patients only Setting: Lipid clinics in 7 countries (United States, Brazil, Canada, Singapore, South Africa, Taiwan, and United Kingdom). 9/6/2007 – 3/25/2009. Outcomes: LDL-C surrogate, short duration and did not get close to LDL-C goal. Low Power: 80% to detect 20% difference.

Stein et al.[7] RCT PC DB MC	M: mipomersen 200mg / week self-administered SQ x 26 weeks P: placebo un-described self-administered SQ x26 weeks f/u 28 weeks	Patients with HeFH and CAD on maximally tolerated lipid-lowering therapies. Demographics: Mean Age: M- 56.2, P-55.9 Female: M-39.8%, P-31.7% White: M-97.6%, P-92.7% Baseline: More in CV history and smoking in mipomersen group generally Inclusion: ≥ 18 years old HeFH (genetic confirmation)OR HeFH defined as untreated LDL-C >2.9mmol/L [190mg/dL] + Simon Broome Register criteria for HeFH + documented stable CAD LDL-C ≥ 100mg/dL ;TG <2.26 200mg/dL Stable max. tolerated dose of lipid-lowering therapy x 12 wks. Exclusion: LDL apheresis within 8 wks. Unstable angina CHF – Class II or IV DM Condition causing 2° hyperlipidemia ALT >1.5x upper limit of normal (ULN) CK ≥ 3x ULN Significant renal or hepatic disease	ITT: M:83 P:41 Total Attrition: M: 10 (12%) P: 0 (0%) Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.	Primary outcome: % Δ LDL-C from baseline to 2 weeks after the last dose M: -28.0% (-34, -22.1) to 104 mg/dL P: 5.2% (-0.5, 10.9) to 143 mg/dL MD: -33.2 95% CI: NA p-value: <0.001	NA / NA	Total withdrawals due to AE: M: 9 (10.8%) P: 0 (0.0%) RR: NA 95% CI: NA p-value: NA SAE: M: 6 (7.2%) [basal cell CA, angina, AMI, PE, non-cardiac chest pain] P: 2 (4.9%) [CAD & SVT] RR: 1.5 95% CI: 0.32, 7.11 p-value: NA	10.8% / NA 2.44% / 41	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - No description of randomization or allocation concealment though baseline group comparison of prognostic factors is fairly even. No effect. Performance: MOD- All mipomersen patients experienced ADE; Possible bias away from null. Detection: LOW - No description of placebo only the assurance that "Patients and study personnel were blinded to treatment assignment and to lipid data." In addition, the hepatic fat assessor was said to be blinded to allocation. Objective outcomes at lower risk from lack of blinding. Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics: Study results apply to HeFH patients only Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration but mipomersen group did get close to LDL-C goal in primary. Low Power: 90% power to detect 20% difference.

McGowan et al.[8] RCT PC DB MC	M: Mipomersen 200mg / week P: Placebo = 9mg NaCl + 0.0004mg riboflavin / week Both are 1 ml self-administered SQ injections, similar in appearance and administration. f/u 28 weeks.	Adults with sever e hypercholesterolemia on maximum lipid-lowering therapy and excluded from apheresis. Demographics: Mean Age: 50.5 (18-77) Male: 25 (43.1%) White: 49 (84.5%) Baseline comparison: More current alcohol use and metabolic syndrome in mipomersen group; More tobacco use in the placebo group Inclusion: ≥ 18 years old LDL-C ≥5.1 197 mg/dL + CHD OR LDL-C ≥ 301 mg/dL with no CHD Stable low-fat diet with stable weight Maximum tolerated lipid lowering therapy Met LDL-apheresis criteria but was prohibited Exclusion: Significant CVD or cerebrovascular event within 24 weeks CHF DM-I or poorly controlled DM-II HTN Secondary hyperlipidemia predisposition Hx of renal or hepatic disease	ITT: M: 39 P: 19 Total attrition: M: 12 (30.8%) P: 1 (5.2%) Loss to F/U: M: 5 (12.8%) P: 1 (5.3%) There were significant differences between groups in protocol deviations: M: 16 (41%) P: 2 (11%)	Primary Outcome: % Δ in LDL-C @ baseline to 2 weeks after last dose. M: -35.9% 95% CI (-51.3, -15.3) to 174mg/dL P: 12.5% 95% CI (-10.7, 35.8) to 263 mg/dL MD: -48.4% 95% CI NA p-value < 0.001	 NA / NA	Withdrawals due to ADE: M: 8 (20.5%) C: 1 (5.3%) RR 3.90 95% CI (0.52, 28.95) p-value NA SAE: M: 5 (20.0%) [liver toxicity, CVA] P: 1 (6.3%) [MI] RR 3.20 95% CI (0.41, 24.94) p-value NA	 15.3% / 7 13.8% / 7	**Quality Rating: GOOD** **Internal Validity: RoB** Selection: LOW - Good description of adequate randomization & allocation concealment though baseline group comparison of prognostic factors is uneven. No effect. Performance: MOD- Blinding of patients, caregivers, investigators and outcomes assessor is adequate and well described but all mipomersen patients experienced ADE; Possible bias away from null. Detection: LOW - Blinding of patients, caregivers, investigators and outcomes assessor is adequate and well described but all mipomersen patients experienced ADE ; Objective outcomes at lower risk from lack of blinding. Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics Population studied is limited to adults with severe disease as add-on therapy. Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration and LDL-C goal not achieved. Low Power: 80% power to detect 20% difference.

AMI = acute myocardial infarction;
CA = cancer;
CAD = coronary artery disease
CHD = cardiac heart disease;
CHF = congestive heart failure;
CVA = cardiovascular accident;
DB = Double-Blind;
DM = diabetes mellitus;
f/u = Follow-up;
fx = fracture
Hx = history of;
HTN = hypertension;
LDL-C = low-density lipoprotein cholesterol;
M=mipomersen group;
MC = Multi-Center;
NA = not available or applicable;
P=placebo group;
PC = Placebo Controlled;
PE = pulmonary embolism;
RCT = Randomized Controlled Trial;
SCr = serum creatinine
SQ = subcutaneous;
SVT = supraventricular tachycardia;

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Mipomersen is an antisense oligonucleotide that reduces the genetic production of apo-B 100 which is the principle apolipoprotein of LDL. Thus, LDL is not produced.[1]

PHARMACOKINETICS[1]

Parameter	Result
SQ Bioavailability	54 – 78%
Protein Binding	≥ 90%
Elimination	< 4% recovered in the urine
Half-Life	1 – 2 months
Metabolism	Metabolized in tissues by endonucleases

INTERACTIONS[1]

Drug interactions are not anticipated via the cytochrome P450 enzymes or via the P-glycoprotein transporter mechanism.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
200 mg / 1 ml	SQ	Weekly	NA	Withhold dose x 1 week if ALT or AST is ≥ 3 ULN. Resume when ≤ 3 ULN and monitor weekly. If ≥ 5 ULN; withhold and obtain additional liver tests	NA (only 7 patient < 18 were included in the trials)	NA (only 22.6% of patients in trial were ≥ 65 years old)	May cause fetal harm; Pregnancy category B

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Mipomersen is only available through a restricted REMS program. Only certified providers may prescribe and pharmacies may distribute it. Further information is available at www.KynamroREMS.com or by telephone at 1-877-KYNAMRO (1-877-596-2676).[1]

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. 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."[1]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Misoprostil
Miconazole
Kalydeco

Appendix 2: Suggested PA Criteria

Mipomersen (Kynamro®) and Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Has the patient failed or are they not appropriate for LDL-C apheresis OR Is LDL-C apheresis not available to them?	**Yes:** Approve for 6 months.	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Mipomersen and lomitapide are approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. Both are proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen in patients with lower CHD risk.[1, 2]

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.

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