Therapeutic Class Overview
Homozygous Familial Hypercholesterolemia Agents

Therapeutic Class

- **Overview/Summary:** Familial hypercholesterolemia is a genetically modulated clinical syndrome in which the phenotype is characterized by a high low density lipoprotein-cholesterol (LDL-C) level from birth and early onset coronary heart disease (even in the absence of other risk factors). Established causes include: LDLR mutations (most common), gain-of-function PCSK9 mutations (<5% of cases in most clinics) and familial defective apolipoprotein B (<5% of cases). The disorder is inherited with a gene dosing effect, in which homozygotes are more adversely affected than heterozygotes. homozygous familial hypercholesterolemia is rare (1 in 250,000 births) unless there is co-sanguineous union in a family with heterozygous familial hypercholesterolemia.[1]

  Lomitapide (Juxtapid®) is microsomal triglyceride transfer protein inhibitor Food and Drug Administration (FDA)-approved as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia.[11] This agent directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apolipoprotein B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and very low density lipoprotein (VLDL) leading to reduced levels of plasma LDL-C.[11]

  Mipomersen (Kynamro®) is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis FDA-approved as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol, and non-HDL in patients with homozygous familial hypercholesterolemia.[12] This agent is an antisense oligonucleotide targeted to human messenger ribonucleic acid for apolipoprotein B-100. Hybridization to the cognate messenger ribonucleic acid results in inhibition of translation of the apolipoprotein B-100 protein and ultimately decreased formation of low density lipoprotein and VLDL.[12]

Table 1. Current Medications Available in Therapeutic Class[11-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Lomitapide (Juxtapid®)	An adjunct to a low-fat diet and other lipid-lowering treatments, including low density lipoprotein apheresis where available, to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia*		-
Mipomersen (Kynamro®)	An adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with homozygous familial hypercholesterolemia†		-

*The safety and effectiveness have not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. The effect on cardiovascular morbidity and mortality has not been determined.
†The safety and effectiveness have not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. The effect on cardiovascular morbidity and mortality has not been determined. The use as an adjunct to lipoprotein-cholesterol apheresis is not recommended.

Evidence-based Medicine

- In clinical trials, lomitapide evaluated as an adjunctive treatment, was associated with a significant decrease in low density lipoprotein-cholesterol and other secondary measures of cholesterol from

baseline.[13] However, the agent is associated with significant tolerability issues including liver toxicity, increased hepatic fat, teratogenicity, drug-drug interactions and common gastrointestinal side effects.[11]
- In clinical trials, mipomersen evaluated as an adjunctive treatment, was associated with a significant decrease in low density lipoprotein-cholesterol and other secondary measures of cholesterol from baseline.[14] However, the agent is associated with significant tolerability issues including liver toxicity and increased hepatic fat.[12]

Key Points within the Medication Class
- According to Current Clinical Guidelines:
  - Available 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.[2-10]
  - In refractory cases, liver transplant may be therapeutic options.
- Other Key Facts:
  - The safety and effectiveness of lomitapide and mipomersen has not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. In addition, the effect of this agent on cardiovascular morbidity and mortality has not been determined.[11-12]

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Therapeutic Class Review
Homozygous Familial Hypercholesterolemia Agents

Overview/Summary

Familial hypercholesterolemia is a genetically modulated clinical syndrome in which the phenotype is characterized by a high low density lipoprotein-cholesterol (LDL-C) level from birth and early onset coronary heart disease (even in the absence of other risk factors). Established causes include: LDLR mutations (most common), gain-of-function PCSK9 mutations (<5% of cases in most clinics) and familial defective apolipoprotein B (<5% of cases). The disorder is inherited with a gene dosing effect, in which homozygotes are more adversely affected than heterozygotes. homozygous familial hypercholesterolemia is rare (1 in 250,000 births) unless there is co-sanguineous union in a family with heterozygous familial hypercholesterolemia.[1] Available treatment guidelines 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.[2-10] In refractory cases, liver transplant may be therapeutic options.

Lomitapide (Juxtapid®) is microsomal triglyceride transfer protein inhibitor Food and Drug Administration (FDA)-approved as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia.[11] This agent directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apolipoprotein B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and very low density lipoprotein (VLDL) leading to reduced levels of plasma LDL-C.[11]

Mipomersen (Kynamro®) is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis FDA-approved as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol, and non-HDL in patients with homozygous familial hypercholesterolemia.[12] This agent is an antisense oligonucleotide targeted to human messenger ribonucleic acid for apolipoprotein B-100. Hybridization to the cognate messenger ribonucleic acid results in inhibition of translation of the apolipoprotein B-100 protein and ultimately decreased formation of low density lipoprotein and VLDL.[12]

The safety and effectiveness of lomitapide and mipomersen has not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. In addition, the effect of this agent on cardiovascular morbidity and mortality has not been determined.[11-12]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Lomitapide (Juxtapid®)	Microsomal triglyceride transfer protein inhibitor	-
Mipomersen (Kynamro®)	Oligonucleotide inhibitor of apolipoprotein B-100 synthesis	-

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications[11-12]

Indication(s)	Lomitapide	Mipomersen
An adjunct to a low-fat diet and other lipid-lowering treatments, including low density lipoprotein apheresis where available, to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia*	✔	

Indication(s)	Lomitapide	Mipomersen
An adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with homozygous familial hypercholesterolemia†		✔

*The safety and effectiveness have not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. The effect on cardiovascular morbidity and mortality has not been determined.
†The safety and effectiveness have not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia. The effect on cardiovascular morbidity and mortality has not been determined. The use as an adjunct to lipoprotein-cholesterol apheresis is not recommended.

Pharmacokinetics

Table 3. Pharmacokinetics[11-12]

Generic Name	Bioa-vailability (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Lomitapide	7	Oxidation, glucuronide conjugation, Cytochrome P-450 3A4	M1, M3	Renal (59.5) Feces (33.4)	39.7
Mipomersen	54 to 78	Tissue Endonucleases	None	Renal (4)	1 to 2 months

Clinical Trials

The safety and effectiveness of lomitapide and mipomersen is outlined In Table 4. As these agents have not been established in patients with hypercholesterolemia who do not have homozygous familial hypercholesterolemia, only trials for the treatment of homozygous familial hypercholesterolemia have been included in this review.[11-12]

The safety and efficacy of lomitapide in treating elevated cholesterol has been evaluated in an open-label, phase III, non-randomized, dose-escalating study, 29 patients with homozygous familial hypercholesterolemia over the age of 18. Study participants were treated with lomitapide at a median dose of 40 mg daily. Most patients received a high-dose statin and 18 patients underwent regular low density lipoprotein (LDL)-apheresis. After 26 weeks of therapy, low density lipoprotein-cholesterol (LDL-C) was reduced by approximately 50% from baseline (from 336 to 166 mg/dL; *P*<0.0001). Percent changes from baseline for key secondary endpoints (total cholesterol [TC] [-46%; *P*<0.0001], apolipoprotein B [ApoB] [-49%; *P*<0.0001] and triglycerides [TG] [-45%; *P*<0.0001]) were consistent with those for LDL-C.[13]

The safety and efficacy of mipomersen as an adjunct to lipid-lowering medications in individuals with homozygous familial hypercholesterolemia were evaluated in a multinational, randomized, placebo-controlled, 26-week trial (N=51). The primary efficacy endpoint was percent change in LDL from baseline to week 28. At week 28, there was a significantly greater improvement from baseline with mipomersen compared to placebo in LDL (-25 vs -3%, respectively; *P*=0.0003), ApoB (-27 vs -3%, respectively; *P*<0.0001), TC (-21 vs -2%, respectively; *P*<0.05), non-HDL (-25 vs -3%, respectively; *P*=0.0002), TG (-18 vs 1%, respectively; *P*=0.013) and HDL (15 vs 4%, respectively; *P*<0.001). Despite the significant mean decrease from baseline in LDL in the mipomersen arm, there was wide inter-patient variability ranging from an increase of 2 to an 82% decrease.[14]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cuchel et al[13] Lomitapide 5 mg QD for 2 weeks then 10, 20, 40, and 60 mg QD at 4 week intervals or until a maximum dose was reached based on tolerability All patients entered a minimum of a 6-week run in period during which concomitant LDL lowering therapies (including apheresis and other lipid lowering agents, vitamin E and fatty acid supplementation and low fat diet) were stabilized. Patients remained on these therapies during the 26 week efficacy phase. These therapies could be modified during the 52 week safety phase.	MC, OL Patients with HoFH	N=29 26 week efficacy phase followed by a 52 week safety phase; completers of both phases could enter a separate long term study bringing the total duration of treatment to 84 weeks in duration	Primary: Percent change from baseline in concentration of LDL-C at the maximum tolerated dose after 26 weeks of treatment Secondary: Percent changes in other lipid parameters, long term safety and changes in hepatic-fat content	Primary: Mean LDL-C significantly decreased by 50% from baseline to the end of the efficacy phase (*P*<0.0001). Overall, 19 of 23 patients (with data at week 26) had decreased concentrations of LDL-C >25% with 12 patients having >50% reduction. In addition, on the basis of LDL-C response, three patients permanently discontinued LDL apheresis and three permanently increased the time interval between apheresis treatments at some point during the safety phase. Secondary: Percent changes from baseline for key secondary endpoints (TC [-46%; *P*<0.0001], ApoB [-49%; *P*<0.0001] and TG [-45%; *P*<0.0001]) were consistent with those for LDL-C at week 26. However, concentrations of HDL-C were significantly reduced at week 26 (-12%; *P*<0.0001) and remained reduced at 78 weeks (-5%; *P*<0.0001). Most patients had at least one adverse event during both the efficacy (27 of 29 patients) and safety (21 of 23) phases, most of which were mild to moderate in intensity and gastrointestinal in nature. Ten patients had elevated levels of ALT, AST, or both ≥3x upper limit of normal at least once during the study. No patient discontinued treatment permanently because of elevations in liver-function-test parameters and all elevations were managed either by dose reduction or temporary interruption of lomitapide. Mean hepatic fat in the 20 patients with evaluable NMRS scans was 1% (range 0 to 5%) at baseline, 8.6% (0 to 33.6%) at week 26, 5.8% (0 to 16.5%) at week 56 and 8.3% (0 to 19%) at week 78.
Raal et al[14] Mipomersen 200 mg SQ weekly	DB, MC, PC, PG Patients ≥12 years of age with genetically or	N=51 26 weeks	Primary: Percent change in LDL-C from baseline Secondary:	Primary: At Week 28, there was a significantly greater improvement from baseline with mipomersen compared to placebo in LDL (-25 vs -3%, respectively; *P*=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	clinically determined HoFH with a fasting LDL >3.5 mmol/L, TG <4 mmol/L and bodyweight >40 kg		Percent change from baseline in ApoB, TC and non-HDL-C from baseline and safety evaluations	Secondary: At Week 28, there was a significantly greater improvement from baseline with mipomersen compared to placebo in ApoB (-27 vs -3%, respectively; *P*<0.0001), TC (-21 vs -2%, respectively), non-HDL-C (-25 vs -3%, respectively; *P*=0.0002), TG (-18 vs 1%, respectively; *P*=0.013) and HDL (15 vs 4%, respectively; *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.
McGowan et al[15] Mipomersen 200 mg SQ weekly vs placebo	DB, MC, PC Adults patients with severe hyper-cholesterolemia; patients were on a stable low fat diet, at a stable weight, on maximally tolerated lipid-lowering therapy, met LDL-apheresis criteria but apheresis was prohibited	N=58 26 weeks	Primary: Percent change in LDL-C from baseline to two weeks after last dose Secondary: Percent change from baseline in ApoB, non-HDL-C, and TC, percent change in TG, Lipoprotein (a), very low-density lipoprotein cholesterol, apolipoprotein A1, HDL-C, and LDL/HDL ratio	Primary: Mipomersen reduced LDL-C by 36%, from a baseline of 7.2 mmol/L, for a mean absolute reduction of 2.6 mmol/L. Conversely, mean LDL-C increased 13% in placebo from a baseline of 6.5 mmol/L (mipomersen vs placebo; *P*=0.001). Secondary: Mipomersen produced statistically significant (*P*=0.001) reductions in ApoB and lipoprotein(a), with no change in HDL-C. Mild-to-moderate injection site reactions were the most frequently reported adverse events with mipomersen. Mild-to-moderate flu-like symptoms were reported more often with mipomersen. ALT, AST, and hepatic steatosis occurred in 21, 13 and 13% of mipomersen treated patients, respectively. Adverse events by category for the placebo and mipomersen groups respectively were: total adverse events, 16(84.2%), 39(100%); serious adverse events, 0(0%), 6(15.4%); discontinuations due to adverse events, 1(5.3%), 8(20.5%) and cardiac adverse events, 1(5.3%), 5(12.8%).

Drug regimen and study abbreviations: ALT=alanine aminotransferase, ApoB=apolipoprotein B, AST=aspartate aminotransferase, DB=double blind, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, MC=multicenter, NMRS=nuclear magnetic resonance spectroscopy, PC=placebo controlled, PG=parallel group, OL=open-label, QD=once daily, SQ=subcutaneous, TC=total cholesterol, TG=triglycerides

Special Populations

Table 5. Special Populations[11-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Lomitapide	Clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients; in general, dosing for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Safety and effectiveness have not been established in pediatric patients.	Patients with end-stage renal disease receiving dialysis should not exceed 40 mg daily. There are no data available to guide dosing in other patients with renal impairment.	Patients with mild hepatic impairment (Child-Pugh A) should not exceed 40 mg daily. Treatment is generally contraindicated in patients with moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases.	X	Percent excretion through breast milk is not known.
Mipomersen	In pooled clinical trials including elderly patients there was a higher rate of hypertension and peripheral edema compared to placebo-treated patients. Safety and effectiveness have not been established in pediatric patients.	The safety and efficacy in patients with known renal impairment or in patients undergoing renal dialysis have not been established. Due to the lack of clinical data and the safety profile, it is not recommended in patients with severe renal	The safety and efficacy in patients with known hepatic impairment have not been established. Contra-indicated in patients with clinically significant hepatic dysfunction, which may include persistent	B	Percent excretion through breast milk is not known.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		impairment, clinically significant proteinuria, or on renal dialysis.	elevations of trans-aminases.		

Adverse Drug Events

Table 6. Adverse Drug Events (%) Associated With Lomitapide[11]

Adverse Event	Reported Frequency; N=29
Gastrointestinal Disorders	
Diarrhea	23 (79)
Nausea	19 (65)
Increase in hepatic fat from baseline	18 (78)
Dyspepsia	11 (38)
Vomiting	10 (34)
Abdominal pain	10 (34)
Abdominal discomfort	6 (21)
Abdominal distension	6 (21)
Constipation	6 (21)
Flatulence	6 (21)
Gastroesophageal reflux disease	3 (10)
Defecation urgency	3 (10)
Rectal tenesmus	3 (10)
Infections	
Influenza	6 (21)
Nasopharyngitis	5 (17)
Gastroenteritis	4 (14)
Investigations	
Increased alanine transaminase/aspartate aminotransferase ≥3x upper limit of normal	10 (34)
Decreased weight	7 (24)
Increased alanine transaminase	5 (17)
General Disorder	
Chest pain	7 (24)
Fatigue	5 (17)
Fever	3 (10)
Musculoskeletal Disorders	
Back pain	4 (14)
Nervous System Disorder	
Headache	3 (10)
Dizziness	3 (10)
Respiratory Disorders	
Pharyngolaryngeal pain	4 (14)
Nasal congestion	
Cardiac Disorders	
Angina pectoris	3 (10)
Palpitations	3 (10)

Table 7. Adverse Drug Events (%) Associated With Mipomersen[12]

Adverse Event	Mipomersen 200 mg weekly; N=261	Placebo; N=129
Gastrointestinal Disorders		
Nausea	14	8
General Disorders and Administration Site Conditions		
Injection site reactions	84	33
Fatigue	15	8
Influenza-like illness	13	3
Pyrexia	8	3
Chills	6	1
Edema, peripheral	5	2
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

Table 8. Contraindications[11-12]

Contraindications	Lomitapide	Mipomersen
Concomitant administration with moderate or strong CYP3A4 inhibitors.	✔	
Known hypersensitivity to any component of this product.		✔
Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases.		✔
Moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases.	✔	
Pregnancy.	✔	

Black Box Warning for Juxtapid® (lomitapide)[11]

WARNING: RISK OF HEPATOTOXICITY

Juxtapid® (lomitapide) can cause elevations in transaminases. In the clinical trial, 10 (34%) of the 29 patients treated with Juxtapid® (lomitapide) had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

Juxtapid® (lomitapide) also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with Juxtapid® (lomitapide) treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

WARNING: RISK OF HEPATOTOXICITY
Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose of Juxtapid® (lomitapide) if the ALT or AST are ≥3x ULN. Discontinue Juxtapid® (lomitapide) for clinically significant liver toxicity. Because of the risk of hepatotoxicity, Juxtapid® (lomitapide) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Juxtapid® (lomitapide) REMS program.

Black Box Warning for Kynamro® (mipomersen)[12]

WARNING: RISK OF HEAPTOTOXIICITY
Kynamro® (mipomersen) can cause elevations in transaminases. In the Kynamro® (mipomersen) clinical trial in patients with homozygous familial hypercholesterolemia, four (12%) of the 34 patients treated with Kynamro® (mipomersen) compared to 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). Kynamro® (mipomersen) also increases hepatic fat, with or without concomitant increases in transaminases. In the 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 magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease; including steatohepatitis and cirrhosis. Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of Kynamro® (mipomersen) if the ALT or AST are ≥3 x ULN. Discontinue Kynamro® (mipomersen) for clinically significant liver toxicity. Because of the risk of hepatotoxicity, Kynamro® (mipomersen) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kynamro® (mipomersen) REMS.

Warnings and Precautions

Table 9. Warnings and Precautions[111-12]

Warnings/Precautions	Lomitapide	Mipomersen
Elevation of Transaminases	✔	✔
Hepatic Steatosis	✔	✔
Hepatotoxicity	✔	✔

Drug Interactions

Table 10. Drug-Drug Interactions[16]

Drug(s)	Interaction	Mechanism
Lomitapide	Azole antifungal agents (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Hepatitis C virus protease inhibitors (boceprevir, telaprevir)	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is

Drug(s)	Interaction	Mechanism
		contraindicated.
Lomitapide	Macrolide and related antibiotics (clarithromycin, erythromycin, telithromycin)	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Protease inhibitors (atazanavir, darunavir/ritonavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Aprepitant	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Conivaptan	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Crizotinib	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Diltiazem	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Ginkgo biloba	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. If concurrent use cannot be avoided, do not exceed a dosage of lomitapide 30 mg daily.
Lomitapide	Goldenseal	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. If concurrent use cannot be avoided, do not exceed a dosage of lomitapide 30 mg daily.
Lomitapide	Grapefruit Juice	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Imatinib	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.
Lomitapide	Nefazodone	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity. Coadministration is contraindicated.

Dosage and Administration

Table 11. Dosing and Administration[11-12]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Lomitapide	Homozygous familial hypercholesterolemia: Capsule: initial, 5 mg once daily; maintenance, titrate dose based on safety/tolerability; increase to 10 mg once daily after two weeks and then at four week intervals to 20 mg, 40 mg and the maximum dose of 60 mg once daily; maximum, 60 mg once daily*	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg 20 mg
Mipomersen	Homozygous familial hypercholesterolemia: Injection: initial, maximum and maintenance, 200 mg once weekly as a subcutaneous injection	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)

*Liver transaminases should be monitored prior to any increase in dose. Dose adjustments may be required for patients taking concomitant CYP 3A4 inhibitors, renal impairment, baseline hepatic impairment or any increase in transaminase levels ≥3X the upper limit of normal.

Clinical Guidelines

Current guidelines are summarized in Table 12. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[2]**	General recommendations • With regards to therapeutic lifestyle changes (TLC), higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low density lipoprotein (LDL) lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve low density lipoprotein cholesterol (LDL-C) treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Clinical Guideline	Recommendation(s)
	Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high triglycerides (TG) to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.

Clinical Guideline	Recommendation(s)
American Association of Clinical Endocrinologists: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2012)**[3]	• Aggressive lipid-modifying therapy is recommended to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk. • An LDL-C goal <70 mg/dL is recommended as an appropriate goal for *all* patients with established CAD. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective. • Patients for whom aggressive therapy is recommended: o Patients undergoing coronary artery bypass graft. o Patients with acute coronary syndrome. o Certain healthy and functional older patients at high risk. • Statins are the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. • Fibrates are recommended for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL). Adjunct use of 2 to 4 g of omega 3 acids can be used, if necessary, to achieve satisfactory triglyceride lowering. • Niacin is recommended for reducing triglycerides, increasing high density lipoprotein cholesterol (HDL-C), and reducing LDL-C. Adjunct use of 2 to 4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering. • Bile acid sequestrants are recommended for reducing LDL-C and apolipoprotein B (apo B) and modestly increasing HDL-C, but they may increase triglycerides. Bile acid sequestrants have a glucose-lowering effect; colesevelam is now also approved for treatment of type 2 diabetes. Available agents in this drug class are cholestyramine, colestipol, and colesevelam. • Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. Combination therapy with statins is recommended because current research indicates that this enhances these benefits and further improves the beneficial effects of statins on triglycerides and HDL-C. It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events. • Combination therapy be considered in the following circumstances: o When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal. o When mixed dyslipidemia is present. o Niacin or fibrates in combination with statins may be appropriate options for many patients with hypertriglyceridemia and associated low HDL-C. o To reduce the risk of dosage-related adverse effects. • Recommendations for lipid management in children include: o Colesevelam has been approved for patients older than eight years. o Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older. • Cholestyramine may also be used in children.
American Heart Association/American	Lipid management • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of

Clinical Guideline	Recommendation(s)
College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)**[4]	<100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2011)**[5]	<u>Clinical highlights</u> • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease (CAD), non-cardiac atherosclerosis, or CAD equivalent. <u>Ongoing drug therapy</u> • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in

Clinical Guideline	Recommendation(s)
	CHD events. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, total cholesterol (TC) is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a

Clinical Guideline	Recommendation(s)
	statin. • Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after. Combination therapy • It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe. o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy. o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events. o The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints. • Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. • Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. • There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. • No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. Lifestyle modifications • Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. • Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment**	• TLC remain an essential modality in clinical management. • When LDL-C lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants,

Clinical Guideline	Recommendation(s)
Panel III Guidelines (2004)[6]	ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-apheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apo B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
American Heart Association: **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. • Niacin is rarely used to treat the pediatric population.

Clinical Guideline	Recommendation(s)
	• Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[8]	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification (2010)**[9]	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative

Clinical Guideline	Recommendation(s)
	preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with ACS should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a TC <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2011)**[10]	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, and medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.

Conclusions

Lomitapide (Juxtapid®) is microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments in patients with homozygous familial hypercholesterolemia, a genetically modulated clinical syndrome characterized by a high low density lipoprotein cholesterol (LDL-C) level from birth and early onset coronary heart disease.[11] 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.[2-10]

Mipomersen (Kynamro®) is an oligonucleotide inhibitor of APOb-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol, and non high density lipoprotein cholesterol (HDL-C) in patients with homozygous familial hypercholesterolemia.[12] 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.[2-10]

In clinical trials, lomitapide evaluated as an adjunctive treatment, was associated with a significant decrease in LDL and other secondary measures of cholesterol from baseline.[13] However, the agent is associated with significant tolerability issues including liver toxicity, increased hepatic fat, teratogenicity, drug-drug interactions and common gastrointestinal side effects.[11]

In clinical trials, mipomersen evaluated as an adjunctive treatment, was associated with a significant decrease in LDL and other secondary measures of cholesterol from baseline.[14] However, the agent is associated with significant tolerability issues including liver toxicity and increased hepatic fat.[12]

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