PREMERA HMO

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY / MEDICAL POLICY – 5.01.558

Pharmacologic Treatment of High Cholesterol

Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 8, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

 Clicking this icon returns you to the hyperlinks menu above.

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder, which means it is passed down through families. FH is caused by a defect in a specific gene. Because of the defect, the body can't remove LDL cholesterol (the "bad cholesterol") from the blood. The result is a very high level of LDL (high cholesterol). Untreated high levels of LDL can lead to deposits of fat and cholesterol (plaque) on walls of the arteries. Plaques can narrow or block the arteries and cause heart and blood vessel disease. The first step to reduce high cholesterol is to change the diet and increase exercise. If this does not work well enough, the next step is to use standard drugs called statins. If cholesterol levels remain high after using statins, other types of cholesterol drugs may be prescribed. This policy describes when other drugs used to lower cholesterol may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug/Indication	Medical Necessity
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors	
Repatha (evolocumab)	**Repatha (evolocumab) may be considered medically necessary for the treatment of atherosclerotic cardiovascular disease (ASCVD) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Repatha (evolocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ A previous myocardial infarction or a history of an acute coronary syndrome ○ Angina (stable or unstable) ○ A past history of stroke or transient ischemic attack ○ Peripheral arterial disease (PAD) of atherosclerotic origin ○ Has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures) **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 140 mg every 2 weeks OR 420 mg every 4 weeks

Drug/Indication	Medical Necessity

	Repatha (evolocumab) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia (HeFH) when ALL the following criteria are met:
	• The individual is aged 10 years or older
	AND
	• Repatha (evolocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders
	AND
	• The individual meets one of the following:
	  ○ Has an untreated LDL-C level greater than or equal to 190 mg/dL
	  ○ Has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene
	  ○ **Dutch Lipid Network criteria** score greater than 5
	  ○ **Simon Broome criteria** met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 70 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin
	  ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation
	AND

Drug/Indication	Medical Necessity

	• The dose is limited to 140 mg every 2 weeks OR 420 mg every 4 weeks
	
	Repatha (evolocumab) may be considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) when ALL the following criteria are met:
	• The individual is aged 10 years or older
	AND
	• Repatha (evolocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders
	AND
	• The individual meets one of the following:
	  ○ Has an untreated LDL-C level greater than 400 mg/dL
	  ○ Has a treated LDL-C level greater than or equal to 300 mg/dL
	  ○ Has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 70 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin
	  ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation
	AND

Drug/Indication	Medical Necessity

	• The dose is limited to 420 mg every 2 weeks
	
	Repatha (evolocumab) may be considered medically necessary for the treatment of primary hyperlipidemia when ALL the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Repatha (evolocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders
	AND
	• The individual meets one of the following:
	  ○ Has a coronary artery calcium (CAC) or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender, and ethnicity
	  ○ Calculated 10-year ASCVD risk score of 7.5% or higher
	  ○ Has diabetes
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 100 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin
	  ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation
	AND
	• The dose is limited to 140 mg every 2 weeks OR 420 mg every 4 weeks

Praluent (alirocumab)	**Praluent (alirocumab) may be considered medically necessary for the treatment of atherosclerotic cardiovascular disease (ASCVD) when ALL the following criteria are met:**

Drug/Indication	Medical Necessity

	• The individual is aged 18 years or older
	AND
	• Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha
	AND
	• Praluent (alirocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders
	AND
	• The individual meets one of the following:
	  ○ A previous myocardial infarction or a history of an acute coronary syndrome
	  ○ Angina (stable or unstable)
	  ○ A past history of stroke or transient ischemic attack
	  ○ Peripheral arterial disease (PAD) of atherosclerotic origin
	  ○ Has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures)
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 70 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin
	  ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation
	AND
	• The dose is limited to 150 mg every 2 weeks OR 300 mg every 4 weeks

Drug/Indication	Medical Necessity

	Praluent (alirocumab) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia (HeFH) when ALL the following criteria are met:
	• The individual is aged 8 years or older
	AND
	• Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha
	AND
	• Praluent (alirocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders
	AND
	• The individual meets one of the following:
	  ○ Has an untreated LDL-C level greater than or equal to 190 mg/dL
	  ○ Has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene
	  ○ **Dutch Lipid Network criteria** score > 5
	  ○ **Simon Broome criteria** met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 70 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin

Drug/Indication	Medical Necessity
	▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 150 mg every 2 weeks OR 300 mg every 4 weeks **Praluent (alirocumab) may be considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Praluent (alirocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ Has an untreated LDL-C level > 400 mg/dL ○ Has a treated LDL-C level greater than or equal to 300 mg/dL ○ Has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR**

Drug/Indication	Medical Necessity
	○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 150 mg every 2 weeks **Praluent (alirocumab) may be considered medically necessary for the treatment of primary hyperlipidemia when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Praluent (alirocumab) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ Has a coronary artery calcium (CAC) or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender, and ethnicity ○ Calculated 10-year ASCVD risk score of 7.5% or higher ○ Has diabetes **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 100 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following:

Drug/Indication	Medical Necessity
	▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 150 mg every 2 weeks OR 300 mg every 4 weeks
Small Interfering RNA (siRNA) Directed to PCSK9 mRNA	
Leqvio (inclisiran)	**Leqvio (inclisiran) may be considered medically necessary for the treatment of atherosclerotic cardiovascular disease (ASCVD) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Leqvio (inclisiran) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ A previous myocardial infarction or a history of an acute coronary syndrome ○ Angina (stable or unstable) ○ A past history of stroke or transient ischemic attack ○ Peripheral arterial disease (PAD) of atherosclerotic origin ○ Has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures) **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL

Drug/Indication	Medical Necessity
	OR ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 284 mg at onset, 3 months later, and every 6 months thereafter **Leqvio (inclisiran) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia (HeFH) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Leqvio (inclisiran) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ Has an untreated LDL-C level greater than or equal to 190 mg/dL ○ Has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene ○ **Dutch Lipid Network criteria** score > 5 ○ **Simon Broome criteria** met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia **AND**

Drug/Indication	Medical Necessity
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 284 mg at onset, 3 months later, and every 6 months thereafter **Leqvio (inclisiran) may be considered medically necessary for the treatment of primary hyperlipidemia when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Leqvio (inclisiran) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual meets one of the following: ○ Has a coronary artery calcium (CAC) or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender, and ethnicity ○ Calculated 10-year ASCVD risk score of 7.5% or higher ○ Has diabetes **AND**

Drug/Indication	Medical Necessity
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 100 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 284 mg at onset, 3 months later, and every 6 months thereafter
Ethyl Ester of Eicosapentaenoic Acid (EPA)	
• **Vascepa (icosapent ethyl)** • **Icosapent ethyl, generic**	**Vascepa (icosapent ethyl) may be considered medically necessary to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization when the following criteria are met:** • The individual is aged 18 years or older **AND** • Triglyceride (TG) levels are greater than or equal to 150 mg/dL **AND** • Individual is on moderate-intensity or high-intensity statin therapy unless not tolerated or contraindicated (see criteria for **myalgias** and **transaminitis**) **AND** • Has established cardiovascular disease **OR** • Diabetes mellitus and 2 of the following additional risk factors for cardiovascular disease ○ Family history of premature ASCVD: ▪ Males < 55 years of age ▪ Females < 65 years of age ○ Tobacco use ○ Hypertension defined as:

Drug/Indication	Medical Necessity
	▪ BP greater than or equal to 130 mmHg systolic or greater than or equal to 80 mmHg diastolic on an antihypertensive medication ○ Renal dysfunction defined as: ▪ eGFR = 15 – 59 mL/min/1.73m^2 = CrCl< 60 mL/min with or without albuminuria **AND** • Has had a trial and treatment failure or intolerance to generic icosapent ethyl **AND** • The daily dose is 4 grams per day (taken as either four 0.5-gram capsules twice daily with food or two 1-gram capsules twice daily with food) **Vascepa (icosapent ethyl) may be considered medically necessary for the treatment of severe hypertriglyceridemia when the following criteria are met:** • The individual is aged 18 years or older **AND** • Triglyceride (TG) levels are greater than or equal to 500 mg/dL **AND** • The individual has tried and failed one of the following fibrate products: ○ Fenofibrate ○ Fenofibric acid ○ Gemfibrozil **OR** • Has tried and failed a prescription niacin extended-release product **AND** • Has had a trial and treatment failure or intolerance to generic icosapent ethyl **AND** • The daily dose is 4 grams per day (taken as either four 0.5-gram capsules twice daily with food or two 1-gram capsules twice daily with food).

Drug/Indication	Medical Necessity

	Generic icosapent ethyl may be considered medically necessary to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization when the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Triglyceride (TG) levels are greater than or equal to 150 mg/dL
	AND
	• Individual is on moderate-intensity or high-intensity statin therapy unless not tolerated or contraindicated (see criteria for **myalgias** and **transaminitis**)
	AND
	• Has established cardiovascular disease
	OR
	• Diabetes mellitus and 2 of the following additional risk factors for cardiovascular disease
	  ○ Family history of premature ASCVD:
	  ▪ Males < 55 years of age
	  ▪ Females < 65 years of age
	  ○ Tobacco use
	  ○ Hypertension defined as:
	  ▪ BP greater than or equal to 130 mmHg systolic or greater than or equal to 80 mmHg diastolic on an antihypertensive medication
	  ○ Renal dysfunction defined as:
	  ▪ eGFR = 15 – 59 mL/min/1.73m^2 = CrCl< 60 mL/min with or without albuminuria
	AND
	• The daily dose is 4 grams per day (taken as either four 0.5-gram capsules twice daily with food or two 1-gram capsules twice daily with food)
	
	Generic icosapent ethyl may be considered medically necessary for the treatment of severe hypertriglyceridemia when the following criteria are met:

Drug/Indication	Medical Necessity

	• The individual is aged 18 years or older
	AND
	• Triglyceride (TG) levels are greater than or equal to 500 mg/dL
	AND
	• The individual has tried and failed one of the following fibrate products:
	  ○ Fenofibrate
	  ○ Fenofibric acid
	  ○ Gemfibrozil
	OR
	• Has tried and failed a prescription niacin extended-release product
	AND
	• The daily dose is 4 grams per day (taken as either four 0.5-gram capsules twice daily with food or two 1-gram capsules twice daily with food).

Ethyl Ester of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)	
Lovaza (omega-3-acid ethyl esters)	**Lovaza (omega-3-acid ethyl esters) may be considered medically necessary for the treatment of severe hypertriglyceridemia when the following criteria are met:** • The individual is aged 18 years or older **AND** • Triglyceride (TG) levels are greater than or equal to 500 mg/dL **AND** • The individual has had a trial and treatment failure or intolerance to generic omega-3-acid ethyl esters **AND** • The daily dose is 4 grams per day (taken as a single 4-gram dose [4 capsules] or as two 2-gram doses [2 capsules given twice daily]) **Initial approval will be for 3 years.** **Re-authorization criteria:** • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal TG values specific to the individual)

Drug/Indication	Medical Necessity
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitors	
Clinical atherosclerotic cardiovascular disease (ASCVD) • **Nexletol (bempedoic acid)** • **Nexlizet (bempedoic acid and ezetimibe)**	**Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) may be considered medically necessary for the treatment of atherosclerotic cardiovascular disease (ASCVD) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Meets one of the following: ○ A previous myocardial infarction or a history of an acute coronary syndrome ○ Angina (stable or unstable) ○ A past history of stroke or transient ischemic attack ○ Peripheral arterial disease (PAD) of atherosclerotic origin ○ Has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures) **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 180 mg of bempedoic acid daily
Familial hypercholesterolemia • **Nexletol (bempedoic acid),**	**Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia (HeFH) when ALL the following criteria are met:** • The individual is aged 18 years or older

Drug/Indication	Medical Necessity

• **Nexlizet (bempedoic acid and ezetimibe)**	**AND**
	• Meets one of the following:
	  ○ Has an untreated LDL-C level greater than or equal to 190 mg/dL
	  ○ Has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene
	  ○ **Dutch Lipid Network criteria** score > 5
	  ○ **Simon Broome criteria** met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia
	AND
	• Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and:
	  ○ LDL-C remains greater than or equal to 70 mg/dL
	  OR
	  ○ Is statin intolerant as demonstrated by experiencing one of the following:
	  ▪ Rhabdomyolysis to one statin
	  ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation
	AND
	• The dose is limited to 180 mg of bempedoic acid daily

Primary hyperlipidemia • **Nexletol (bempedoic acid)** • **Nexlizet (bempedoic acid and ezetimibe)**	**Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) may be considered medically necessary for the treatment of primary hyperlipidemia when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Meets one of the following: ○ Has a coronary artery calcium (CAC) or calcification score of 100 or greater Agatston units or 75th percentile or greater for the individual's age, gender, and ethnicity

Drug/Indication	Medical Necessity
	○ Calculated 10-year ASCVD risk score of 7.5% or higher ○ Has diabetes **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 100 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 180 mg of bempedoic acid daily
Angiopoietin-like 3 Inhibitor	
Homozygous familial hypercholesterolemia • **Evkeeza (evinacumab-dgnb) IV**	**Evkeeza (evinacumab-dgnb) may be considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) when ALL the following criteria are met:** • The individual is aged 5 years or older **AND** • Evkeeza (evinacumab-dgnb) is prescribed by or in consultation with a cardiologist, endocrinologist, or a physician who focuses on the treatment of cardiovascular risk management and/or lipid disorders **AND** • The individual has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Meets one of the following: ○ Has an untreated LDL-C level > 400 mg/dL ○ Has a treated LDL-C level greater than or equal to 300 mg/dL

Drug/Indication	Medical Necessity
	○ Has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 15 mg/kg every 4 weeks
APOC-III-Directed Antisense Oligonucleotide (ASO)	
Familial chylomicronemia syndrome • **Tryngolza (olezarsen) SC**	**Tryngolza (olezarsen) may be considered medically necessary for the treatment of familial chylomicronemia syndrome (FCS) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Diagnosis of FCS is confirmed by a genetic test **AND** • History of and concurrently under a strict dietary management strategy with ≤20 g of fat per day, no sugar, and no alcohol **AND** • Confirmed fasting serum triglyceride is 880 mg/dL (9.9 mmol/L) or higher while under strict dietary management **AND** • The dose is limited to 80 mg once monthly **AND**

Drug/Indication	Medical Necessity
	• Tryngolza (olezarsen) is prescribed by or in consultation with a cardiologist, endocrinologist, gastroenterologist, lipidologist, or pancreatologist
Microsomal Triglyceride Transfer Protein Inhibitor	
Homozygous familial hypercholesterolemia • **Juxtapid (lomitapide)**	**Juxtapid (lomitapide) may be considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried Repatha (evolocumab) first and had an inadequate response or intolerance to Repatha **AND** • Meets one of the following: ○ Has an untreated LDL-C level > 400 mg/dL ○ Has a treated LDL-C level greater than or equal to 300 mg/dL ○ Has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus **AND** • Has tried one high-intensity statin therapy (e.g., atorvastatin greater than or equal to 40 mg daily or rosuvastatin greater than or equal to 20 mg daily) for at least 8 continuous weeks and: ○ LDL-C remains greater than or equal to 70 mg/dL **OR** ○ Is statin intolerant as demonstrated by experiencing one of the following: ▪ Rhabdomyolysis to one statin ▪ Skeletal-muscle related symptoms after trying both rosuvastatin and atorvastatin which resolved upon discontinuation **AND** • The dose is limited to 60 mg daily

Drug/Indication	Medical Necessity
HMG-CoA Reductase Inhibitors (statins)	
• **Altoprev (lovastatin)** • **Crestor (rosuvastatin)** • **Ezallor Sprinkle (rosuvastatin)** • **Lescol XL (fluvastatin)** • **Lipitor (atorvastatin)** • **Livalo (pitavastatin)** • **Pravachol (pravastatin)** • **Zocor (simvastatin)** • **Zypitamag (pitavastatin)**	**Altoprev (lovastatin), Crestor (rosuvastatin), Ezallor Sprinkle (rosuvastatin), Lescol XL (fluvastatin), Lipitor (atorvastatin), Livalo (pitavastatin), Pravachol (pravastatin), Zocor (simvastatin), and Zypitamag (pitavastatin) may be considered medically necessary for the treatment of hyperlipidemia when:** • The individual has had a trial and treatment failure or intolerance to TWO of the following generic drugs: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin **Initial approval will be for 3 years.** **Re-authorization criteria:** • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal LDL-C values specific to the individual)
Atorvaliq (atorvastatin oral suspension)	**Atorvaliq (atorvastatin oral suspension) may be considered medically necessary for the treatment of hyperlipidemia when the individual has documentation in the form of medical records of the following:** • At least a 3-month trial and treatment failure of 2 generic statins (atorvastatin, simvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or fluvastatin) **OR** • Documentation that liquid is clinically necessary (e.g., trouble swallowing, etc.)
• **Flolipid (simvastatin oral suspension)** • **Simvastatin oral suspension**	**Flolipid (simvastatin oral suspension) and brand simvastatin oral suspension may be considered medically necessary for the treatment of hyperlipidemia when the individual has documentation in the form of medical records of the following:** • At least a 3-month trial and treatment failure of 2 generic statins (atorvastatin, simvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or fluvastatin) **OR**

Drug/Indication	Medical Necessity
	• Documentation that liquid is clinically necessary (e.g., trouble swallowing, etc.)
• **Roszet (rosuvastatin/ ezetimibe)** • **Brand rosuvastatin/ezetimibe** • **Vytorin (simvastatin-ezetimibe)**	**Roszet (rosuvastatin/ezetimibe), brand rosuvastatin/ ezetimibe, and Vytorin (simvastatin-ezetimibe) may be considered medically necessary when the following criteria are met:** • Individual has tried generic rosuvastatin or simvastatin AND generic ezetimibe separately **AND** • There is a documented specific rationale for why the individual is not able to continue to use generic rosuvastatin or simvastatin AND generic ezetimibe separately
Fibric Acid Derivatives	
• **Antara (fenofibrate)** • **Brand fenofibrate** • **Fenoglide (fenofibrate)** • **Fibricor (fenofibric acid)** • **Lipofen (fenofibrate)** • **Lopid (gemfibrozil)** • **Tricor (fenofibrate)** • **Triglide (fenofibrate)** • **Trilipix (fenofibric acid)**	**The brand fibric acid derivatives Antara (fenofibrate), brand fenofibrate, Fenoglide (fenofibrate), Fibricor (fenofibric acid), Lipofen (fenofibrate), Lopid (gemfibrozil), Tricor (fenofibrate), Triglide (fenofibrate) and Trilipix (fenofibric acid) may be considered medically necessary for the treatment of hyperlipidemia when:** • The individual has had a trial and treatment failure or intolerance to both generic fenofibrate and generic gemfibrozil. **Initial approval will be for 3 years.** **Re-authorization criteria:** • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal LDL-C values specific to the individual)
Niacin Products	
Niacor (niacin)	**Niacor (niacin) may be considered medically necessary for the treatment of hyperlipidemia when:** • The individual has had a trial and treatment failure or intolerance to generic niacin. **Initial approval will be for 3 years.**

Drug/Indication	Medical Necessity
	Re-authorization criteria: • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal LDL-C values specific to the individual)
Niaspan (niacin extended-release)	**Niaspan (niacin extended-release) may be considered medically necessary for the treatment of hyperlipidemia when:** • The individual has had a trial and treatment failure or intolerance to generic niacin extended-release. **Initial approval will be for 3 years.** **Re-authorization criteria:** • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal LDL-C values specific to the individual)
Cholesterol Absorption Inhibitors	
Zetia (ezetimibe)	**Zetia (ezetimibe) may be considered medically necessary for the treatment of hyperlipidemia when:** • The individual has had a trial and treatment failure or intolerance to generic ezetimibe. **Initial approval will be for 3 years.** **Re-authorization criteria:** • Ongoing therapy will be approved for 3 years when chart notes document continued clinical benefit (i.e., at goal LDL-C values specific to the individual)

Symptom	Medical Necessity
Myalgias	**In addition to meeting above-stated criteria, requests involving failure of statins due to myalgias will be considered medically necessary when ALL of the following criteria have been met:** • Individual has intolerable symptoms

Symptom	Medical Necessity
	AND • Provider ruled out other potential causes for myopathy (example: concomitant use of interacting medications, hypothyroidism, reduced renal or hepatic function, steroid myopathy, vitamin D deficiency, or primary muscle disease)
Transaminitis	**In addition to meeting above-stated criteria, requests involving failure of statins due to transaminitis (e.g., elevated Liver Function Tests) will be considered medically necessary when ALL of the following criteria have been met:** • The provider ruled out other potential causes for transaminitis, such as presence of baseline elevations due to comorbid conditions, such as obesity, prediabetes, etc. **AND** • Transaminitis persists beyond the 12-week period from the start of statin therapy **AND** • Individual failed reduction of statin therapy

Drug	Investigational
• **Evkeeza (evinacumab-dgnb)** • **Generic icosapent ethyl** • **Juxtapid (lomitapide)** • **Leqvio (inclisiran)** • **Nexletol (bempedoic acid)** • **Nexlizet (bempedoic acid and ezetimibe)** • **Praluent (alirocumab)** • **Repatha (evolocumab)** • **Tryngolza (olezarsen)** • **Vascepa (icosapent ethyl)**	**All uses of Evkeeza (evinacumab-dgnb), generic icosapent ethyl, Juxtapid (lomitapide), Leqvio (inclisiran), Nexletol (bempedoic acid), Nexlizet (bempedoic acid and ezetimibe), Praluent (alirocumab), Repatha (evolocumab), Tryngolza (olezarsen), and Vascepa (icosapent ethyl) for indications not listed in the Medical Necessity sections above are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Drug	Not Medically Necessary
• **Antara (fenofibrate)**	**All uses of Antara (fenofibrate), Atorvaliq (atorvastatin oral suspension), brand fenofibrate, Ezallor Sprinkle (rosuvastatin),**

Drug	Not Medically Necessary
• Atorvaliq (atorvastatin oral suspension) • Brand fenofibrate • Ezallor Sprinkle (rosuvastatin) • Fenoglide (fenofibrate) • Fibricor (fenofibric acid) • Flolipid (simvastatin oral suspension) • Lipofen (fenofibrate) • Livalo (pitavastatin) • Lopid (gemfibrozil) • Lovaza (omega-3-acid ethyl esters) • Niacor (niacin) • Niaspan (niacin extended-release) • Rosuvastatin/ezetimibe • Roszet (rosuvastatin and ezetimibe) • Simvastatin oral suspension • Tricor (fenofibrate) • Triglide (fenofibrate) • Trilipix (fenofibric acid) • Zetia (ezetimibe) • Zypitamag (pitavastatin)	Fenoglide (fenofibrate), Fibricor (fenofibric acid), Flolipid (simvastatin oral suspension), Lipofen (fenofibrate), Livalo (pitavastatin), Lopid (gemfibrozil), Lovaza (omega-3-acid ethyl esters), Niacor (niacin), Niaspan (niacin extended-release), rosuvastatin/ezetimibe (brand), Roszet (rosuvastatin and ezetimibe), simvastatin oral suspension (brand), Tricor (fenofibrate), Triglide (fenofibrate), Trilipix (fenofibric acid), Zetia (ezetimibe), and Zypitamag (pitavastatin) not listed in the Medical Necessity sections above are considered not medically necessary.

Length of Approval	
Approval	**Criteria**
Initial authorization	Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months. All other reviews for all drugs listed in policy, unless noted otherwise for specific drugs under the medical necessity criteria, may be approved up to 12 months.
Re-authorization criteria	Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-

Length of Approval	
Approval	**Criteria**
	specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy. **All other reviews for re-authorization of all drugs listed in policy, unless noted otherwise for specific drugs under the medical necessity criteria, may be approved up to 12 months as long as the drug-specific coverage criteria are met and there is documentation of continued clinical benefit:** • At goal LDL-C or goal triglyceride (TG) values specific to the individual

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, lipid panels, and medication history

Coding

Code	Description
HCPCS	
J1305	Injection, evinacumab-dgnb, (Evkeeza) 5 mg
J1306	Injection, inclisiran, (Leqvio) 1 mg
J3490	Unclassified drugs (use to report: Tryngolza)

Related Information

Benefit Application

All drugs in this policy are managed through the pharmacy benefit except Evkeeza (evinacumab-dgnb) and Leqvio (inclisiran) which are managed through the medical benefit and Tryngolza (olezarsen) which is managed through the pharmacy and medical benefit.

Simon Broome Criteria

Simon Broome Register Diagnostic Criteria
Definite Familial Hypercholesterolemia
Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years **OR** total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years)
AND
Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle) **OR** DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation
Possible (or Probable) Familial Hypercholesterolemia
Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years **OR** total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years) AND Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative
OR
Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years **OR** total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years) AND Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

Dutch Lipid Network Criteria

Dutch Lipid Network Criteria	Score
Family History	

Dutch Lipid Network Criteria	Score
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C greater than or equal to 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA Analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total Score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

Evidence Review

Familial Hypercholesterolemia

Familial Hypercholesterolemia encompasses a group of genetic defects that causes severe elevations in LDL-C levels, as well as other lipid parameters. Heterozygous familial hypercholesterolemia (HeFH) occurs in roughly 1 in 300 to 500 individuals and is present in childhood. Total cholesterol levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels of greater than or equal to 190 mg/dL, following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with FH. Higher risk individuals may require intensification of drug therapy to achieve the more aggressive treatment goals. Intensification of medication therapy should be considered if LDL-C remains greater than or equal to 160 mg/dL, or if an initial 50% reduction in LDL-C is not achieved. HeFH is a combination of genetic mutations in either the LDL receptor, or PCSK9 genes. Alterations in any of these genes are associated with reduced clearance of LDL-C from circulation leading to hyperlipidemia, collection of cholesterol in various tissues (tendons or eyes) and marked increased risk of cardiovascular disease. Homozygous familial hypercholesterolemia (HoFH) is much less common, the estimated U.S. prevalence being 1:1,000,000. These individuals usually present with untreated LDL-C > 650 mg/dL. Over 800 mutations are known to affect PCKS9 function, and they vary in severity. At this time, genetic testing of all individuals is not standard practice, since the individual individuals' severity is indicated by the baseline untreated LDL-C.

Clinical Atherosclerotic Cardiovascular Disease

Atherosclerosis is responsible for almost all cases of coronary heart disease (CHD). Many factors are associated with an increased risk of atherosclerotic plaques in coronary arteries. Family history is an independent risk factor for CHD and is very important to be aware of, as the risk of developing CHD in the presence of positive family history can range from 15% to 100%, as has been shown in the cohort analyses done by various groups (e.g., Physician's Health Study, Women's Health Study, Reykjavik Cohort Study, Framingham Offspring Study, INTERHEART Study, Cooper Center Longitudinal Study, Danish national population database). Other risk factors include lifestyle (smoking, diet, exercise habits, etc.), as well as comorbid conditions, such as diabetes, kidney disease, thyroid disease, hypertension, etc. It is important to realize that lifestyle modifications are controllable risk factors, while positive family history is not. Atherosclerotic CV disease can manifest as coronary heart disease, carotid artery disease, peripheral arterial disease, and chronic kidney disease.

Statin-Associated Adverse Events

Statins are both effective and generally safe, however, muscle toxicity remains a concern. Muscle syndromes associated with statins include, myalgias and muscle injury, or clinical rhabdomyolysis (rare). Other statin side effects may include hepatic dysfunction (elevation of aminotransferases), renal dysfunction (proteinuria), behavioral and cognitive changes, such as memory loss (still questionable). The side effect profile of each statin may be slightly different as lipophilicity/hydrophilicity properties of statins differ and can play a role. While statin chemical properties are one of the risk factors (which can be manipulated by switching individual to a different statin), others include: drug-drug interactions (CYP 450 inhibitors), comorbid medical conditions (e.g., hypothyroidism, acute renal failure, biliary obstruction). Side effects can also be associated with dose-intensity and dosing schedule. In general, neuromuscular and skeletal adverse reactions for high-intensity statins (atorvastatin and rosuvastatin) have a 4% to 8% rate of occurrence.

Table 1. ACC/AHA Guidelines on Categorization of Statin Intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately greater than or equal to50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Text Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

Praluent and Repatha

Praluent (alirocumab) and Repatha (evolocumab) are proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors. PCSK 9 is an enzyme that acts as part of the cholesterol homeostasis process in humans. PCSK 9 binds to the epidermal growth factor-like domain of the LDL receptor on human hepatocytes. This binding forces LDL receptors to remain in the "open" confirmation, which facilitates their destruction, limiting the ability of the liver to remove LDL cholesterol from circulation. Humans with loss of function mutations in PCSK 9 have notable lower LDL-C concentrations, and somewhat lower risk of cardiovascular disease.

The recommended starting dose of alirocumab is 75 mg administered subcutaneous (SQ) once every 2 weeks since the majority of individuals achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. Measure LDL-C levels within 4 to 8 weeks of initiating or titrating alirocumab, to assess response and adjust the dose, if needed.

The recommended dosing of evolocumab for primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH is 140 mg every 2 weeks or 420 mg once monthly, administered SQ in abdomen, thigh, or upper arm. For HoFH, the dose is 420 mg once monthly. To administer 420 mg, give 3 REPATHA injections consecutively within 30 minutes.

Efficacy - Praluent and Repatha

The efficacy of alirocumab was investigated in five double-blind placebo-controlled trials that enrolled 3499 individuals: 36% were individuals with heterozygous familial hypercholesterolemia (HeFH), and 54% were non-FH individuals, who had clinical atherosclerotic cardiovascular disease. Three of the five trials were conducted exclusively on individuals with HeFH. All individuals were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies. In the trials that enrolled individuals with HeFH, the diagnosis of HeFH was made either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or WHO/Dutch Lipid Network criteria). All trials were at least 52 weeks in duration with the primary efficacy endpoint measured at week 24 (mean % change in LDL-C from baseline). Three studies used an initial dose of 75 mg every 2 weeks (Q2W), followed by criteria-based up-titration to 150 mg Q2E at week 12 for individuals who did not achieve their pre-defined target LDL-C at week 8. The majority of individuals (57% to 83%), who were treated for at least 12 weeks, did not require up-titration. Two studies used only a 150 mg Q2W dose.

Study 1 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 individuals to alirocumab 150mg Q2W and 788 individuals to placebo. All individuals were taking maximally tolerated doses of statins with or without other lipid-modifying therapy and required additional LDL-C reduction. The mean age was 61 years (range 18-89), 38% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. Overall, 69% were non-FH individuals with clinical atherosclerotic cardiovascular disease, and 18% had HeFH. The average LDL-C at baseline was 122 mg/dL. The proportion of individuals who prematurely discontinued study drug prior to 24-week endpoint was 8% among those treated with the active drug, and 8% among those treated with placebo. At week 24, the treatment difference between alirocumab and placebo in mean LDL-C % change was -58% (95% CI: -61%, -56%; p-value: <0.0001).

Study 2 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 209 individuals to alirocumab and 107 to placebo. Individuals were taking maximally tolerated doses of statins with or without other lipid-modifying therapy and required additional LDL-C reduction. The mean age was 63 years (range 39-87), 34% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Overall, 84% had clinical atherosclerotic cardiovascular disease. Mean baseline LDL-C was 102 mg/dL. The proportion of individuals who prematurely discontinued study drug prior to the 24-week endpoint was 11% among those treated with alirocumab, and 12% among those treated with placebo. At week 12, the mean % change from baseline in LDL-C was -45% with active drug compared to 1% with placebo, and the treatment difference between alirocumab 75mg Q2W and placebo in mean LDL-C % change was -46% (95% CI: -53%, -39%). At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, alirocumab was up-titrated to 150mg Q2W for the remainder of the trial. At week 24, the mean % change from baseline in LDL-C was -44% with active drug and 2% with placebo, and the treatment difference between alirocumab and placebo in mean LDL-C % change was =43% (95% CI: -50%, -35%; p-value:<0.0001). The dose was up-titrated to 150 mg Q2W in 32 (17%) of 191 individuals treated with alirocumab for at least 12 weeks.

Studies 3 and 4 were multicenter, double-blind, placebo-controlled trials that, combined, randomly assigned 490 individuals to alirocumab and 245 to placebo. The trials were similar with regard to both design and eligibility criteria. All individuals who had HeFH, were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction. The mean age was 52 years (range 20-87), 45% were women, 94% were Caucasian, 1% Black, and % were Hispanic/Latino. Overall, 45% of these individuals with HeFH also had clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 141 mg/dL. Considering both trials together, the proportion of individuals who prematurely discontinued study drug prior to the 24-week endpoint was 6% among those treated with active drug, and 4% among those treated with placebo. At week 12, the treatment difference between

alirocumab 75mg Q2W and placebo in mean LDL-C % change was -48% (95% CI: -52%, -44%). At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, alirocumab was up-titrated to 150mg Q2W for the remainder of the trials. At week 24, the mean treatment difference between alirocumab and placebo in mean LDL-C % change from baseline was -54% (95% CI: -59%, -50%; p-value: <0.0001). The dose was up-titrated to 150mg Q2W in 196 (42%) of 469 individuals treated with alirocumab for at least 12 weeks. The LDL-C lowering effect was sustained to week 52.

Study 5 was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 individuals to alirocumab 150mg Q2W and 35 individuals to placebo. Individuals had HeFH with a baseline LDL-C greater than or equal to 160 mg/dL, while taking a maximally tolerated dose of statin with or without other lipid-modifying therapy. The mean age was 51 years (range 18-80), 47 % were women, 88% were Caucasian, 2% were Black, and 6% were Hispanic/Latino. Overall, 50% gad clinical atherosclerotic cardiovascular disease. The average LDL-C at baseline was 198 mg/dL. The proportion of individuals who discontinued stud drug prior to the 24-week endpoint was 10% among those treated with active drug, and 0% among those treated with placebo. At week 24, the mean % change from baseline in LDL-C was -43% with alirocumab, and -7% with placebo, and the treatment difference between alirocumab and placebo in mean LDL-C % change was -36% (95%CI: -49%, -24%; p-value: <0.0001).

Evidence for the efficacy of evolocumab stems from several phase III trials that are part of the extensive PROFICIO clinical trial program. The LAPLACE-2, OSLER and RUTHERFORD-2 trials were evaluated for this analysis. LAPLACE-2 randomized 2067 individuals with hyperlipidemia to either evolocumab or ezetimibe with various strengths of statins. Evolocumab was associated with a greater reduction of LDL-C than did ezetimibe (-60% vs -23%). OSLER randomized 4465 individuals from various “parent studies” to evolocumab plus standard therapy, or standard therapy alone to evaluate long-term safety. Long-term administration of evolocumab was associated with maintained greater LDL-C reduction than did standard therapy alone (P<.001). RUTHERFORD-2 randomized 331 individuals with HeFH to either monthly evolocumab, biweekly evolocumab or placebo, in addition to statin therapy. Biweekly and monthly evolocumab were associated with greater reductions of LDL-C at 12 weeks than placebo (mean difference -59.2% and -61.3% respectively) (P<.0001). TESLA is the only study at this time evaluating evolocumab in individuals with HoFH (N=50). Participants in the evolocumab arm experienced greater percent reductions in LDL-C than did placebo (-23.1% vs 7.9%; P<.0001).

Neither drug has any evidence of long-term clinical outcomes. Specifically, as noted in the label of both products, the effect of alirocumab and evolocumab on cardiovascular morbidity and mortality has not been determined.

Cardiovascular Outcome Trials - Praluent and Repatha

Evidence of long-term cardiovascular outcomes is based on two studies:

FOURIER was a randomized trial of evolocumab (140 mg every 2 weeks or 420 mg once per month) versus placebo in 27 564 individuals with atherosclerotic disease on concurrent statin therapy. Follow up was a median of 2·2 years. 76·8% (6337 of 8256 individuals) in the evolocumab group and 76·8% (6337 of 8254 individuals) in the placebo group. The primary end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years. At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) ($P<0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 individuals [9.8%] vs. 1563 individuals [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $P<0.001$) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $P<0.001$). The results were consistent across key subgroups, including the subgroup of individuals in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%). Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that individuals with atherosclerotic cardiovascular disease benefit from lowering LDL cholesterol levels below current targets.

Outcomes evidence for alirocumab was obtained from the ODYSSEY outcomes trial presented at the American College of Cardiology's 2018 Scientific Session in March 2018. The trial was a multi-site RCT testing alirocumab versus placebo in individuals age greater than or equal to 40 years, hospitalized for ACS with MI or unstable angina 1-12 months prior to randomization. A run-in period of 2-16 weeks of high-intensity or maximally tolerated dose of atorvastatin or rosuvastatin preceded the intervention period. Following the run-in period, subjects had to meet at least one of the following: LDL-C greater than or equal to70 mg/dL, Non-HDL-C greater than or equal to100 mg/dL, or Apolipoprotein B greater than or equal to80 mg/dL.

The primary outcome was a composite of coronary heart disease death, non-fatal MI, ischemic stroke (fatal and non-fatal), and hospitalization for unstable angina. The incidence of the primary

outcome was lower in the alirocumab arm of the trial (hazard ratio (HR) 0.85, 95% CI 0.78-0.93)). There was a non-significant reduction in CHD death (HR 0.92) and cardiovascular disease death (HR 0.88) and a nominally significant reduction in all-cause mortality (HR 0.85, 95% CI (0.73-0.98)). In the subgroup of individuals with a high LDL-C level (greater than or equal to100 mg/dL) on maximally tolerated statin therapy, the HR for all-cause mortality was 0.71 and for CV mortality was 0.69. There were statistically significant reductions in the HR for the primary outcome and key secondary mortality outcomes for individuals in the high LDL-C group, as well as an improvement in clinical benefit over time in a landmark analysis.

Safety - Praluent and Repatha

The safety of alirocumab was evaluated in 9 placebo-controlled trials that included 2476 individuals treated with alirocumab, including 2135 exposed for 6 months, and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasians, 4% Black or African American, and 3% were Asians. At baseline, 37% of individuals had a diagnosis of heterozygous familial hypercholesterolemia and 66% had clinical atherosclerotic cardiovascular disease. Adverse reactions reported in at least 2% of alirocumab-treated individuals, and more frequently than in placebo-treated individuals:

Long-term evolocumab safety data is from the OSLER study in which 4465 individuals from 1 of 12 “parent” studies were randomized to either evolocumab and standard therapy, or standard therapy alone. In order to be eligible, individuals must not have had adverse events leading to study discontinuation in the “parent” study. There was no placebo in the standard therapy arm. After 4219.4 individual-years of follow-up (median follow-up 11.1 months) adverse events occurred with similar frequency in both groups. Adverse events more common in the evolocumab group included neurocognitive events (0.9% vs 0.3%), arthralgia (4.6% vs 3.2%), and injection site reaction (4.3% vs N/A).

While not expressly studied, theoretical risks of the use of PCSK9 inhibition were noted by the Pharmacy and Therapeutics Committee. The clinical relevance of rapid, drastic reductions of LDL-C are unknown. Furthermore, LDL sequestration into hepatocytes by this mechanism could increase the risk of non-alcoholic fatty liver (NAFL) or possibly lead to drug induced non-alcoholic steatohepatitis (NASH). Concern stems from the rapid introduction of LDL-C into hepatocytes while LDL clearance is unknown, combined with expert opinion that states that NAFL and NASH can develop without outward symptoms or abnormal laboratory values. Furthermore, the theoretical risk of gallstones, masses of cholesterol precipitating in the gall bladder, cannot be ruled out with given trial data.

Leqvio

Leqvio (inclisiran) is a small interfering RNA (siRNA) directed to inhibit PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA. PCSK 9 is an enzyme that acts as part of the cholesterol homeostasis process in humans. PCSK 9 binds to the epidermal growth factor-like domain of the LDL receptor on human hepatocytes. This binding forces LDL receptors to remain in the "open" confirmation, which facilitates their destruction, limiting the ability of the liver to remove LDL cholesterol from circulation. Humans with loss of function mutations in PCSK 9 have notable lower LDL-C concentrations, and somewhat lower risk of cardiovascular disease.

The recommended dosage of inclisiran, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months. Assess LDL-C when clinically indicated. The LDL-lowering effect of LEQVIO may be measured as early as 30 days after initiation and anytime thereafter without regard to timing of the dose.

Efficacy- Leqvio

The efficacy of inclisiran was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3457 adults with HeFH or clinical ASCVD, who were taking maximally tolerated statin therapy and who required additional LDL-C lowering. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials.

Study 1, ORION-10, was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1561 individuals with ASCVD were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 781) or placebo (n = 780) on Day 1, Day 90, Day 270, and at Day 450. Individuals were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. Individuals were stratified by current use of statins or other lipid-modifying therapies. Individuals taking PCSK9 inhibitors were excluded from the trial. The mean age at baseline was 66 years (range: 35 to 90 years), 60% were greater than or equal to 65 years old, 31% were women, 86% were White, 13% were Black, 1% were Asian and 14% identified as Hispanic or Latino ethnicity. Forty five percent (45%) of individuals had diabetes at baseline. The mean baseline LDL-C was 105 mg/dL. At the time of randomization, 89% of individuals were receiving statin therapy and 69% were receiving high-intensity statin therapy. The primary efficacy outcome measure in Study 1 was the percent change from baseline to Day 510 in LDL-C. The difference between the LEQVIO and placebo

groups in mean percentage change in LDL-C from baseline to Day 510 was -52% (95% CI: -56%, -49%; p < 0.0001).

Study 2, ORION-11, was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1414 adults with ASCVD were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 712) or placebo (n = 702) on Day 1, Day 90, Day 270, and Day 450. Individuals were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. Individuals were stratified by country and by current use of statins or other lipid-modifying therapies. Individuals taking PCSK9 inhibitors were excluded from the trial. The mean age at baseline was 65 years (range: 35 to 88 years), 56% were greater than or equal to 65 years old, 25% were women, 98% were White, 1% were Black, < 1% were Asian, and 1% identified as Hispanic or Latino ethnicity. Thirty one percent (31%) of individuals had diabetes at baseline. The mean baseline LDL-C was 101 mg/dL. At the time of randomization, 96% of individuals were receiving statin therapy and 80% were receiving high-intensity statin therapy. The primary efficacy outcome measure in Study 2 was the percent change from baseline to Day 510 in LDL-C. The difference between the LEQVIO and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -51% (95% CI: -54%, -47%; p < 0.0001).

Study 3, ORION-9, was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 482 individuals with HeFH were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 242) or placebo (n = 240) on Day 1, Day 90, Day 270, and at Day 450. Individuals with HeFH were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria using either the Simon Broome or WHO/Dutch Lipid Network criteria. Individuals were stratified by country and by current use of statins or other lipid-modifying therapies. Individuals taking PCSK9 inhibitors were excluded from the trial. The mean age at baseline was 55 years (range: 21 to 80 years), 22% were greater than or equal to 65 years old, 53% were women, 94% were White, 3% were Black, 3% were Asian and 3% identified as Hispanic or Latino ethnicity. Ten percent (10%) of individuals had diabetes at baseline. The mean baseline LDL-C was 153 mg/dL. At the time of randomization, 90% of individuals were receiving statin therapy and 74% were receiving high-intensity statin therapy. Fifty-two percent (52%) of individuals were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin. The primary efficacy outcome measure in Study 3 was the percent change from baseline to Day 510 in LDL-C. The difference between the LEQVIO and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -48% (95% CI: -54%, -42%; p < 0.0001).

Safety- Leqvio

The safety of inclisiran was evaluated in 3 placebo-controlled trials that included 1833 individuals, including 1682 individuals exposed for 18 months (median treatment duration of 77 weeks). The mean age of the population was 64 years, 32% of the population were women, 92% were White, 6% were Black, 1% were Asian, and < 1% were other races. At baseline, 12% of individuals had a diagnosis of heterozygous familial hypercholesterolemia and 85% had clinical atherosclerotic cardiovascular disease. Adverse reactions that occurred more frequently in the inclisiran treated arm versus placebo include injection site reaction (8.2% vs 1.8%), arthralgia (5% vs 4%), urinary tract infection (4.4% vs 3.6%), and bronchitis (2.7% vs 4.3%). Adverse reactions led to discontinuation of treatment in 2.5% of individuals treated with inclisiran and 1.9% of individuals treated with placebo. The most common adverse reactions leading to treatment discontinuation in individuals treated with inclisiran were injection site reactions (0.2% versus 0% for inclisiran and placebo, respectively).

Vascepa

Vascepa (icosapent ethyl) forms an active metabolite, eicosapentaeonic acid (EPA), which is subsequently absorbed in the small intestine. Studies suggest that EPA reduces hepatic very-low-density lipoprotein cholesterol (VLDL-C) and triglyceride synthesis and/or secretion as well as increases triglyceride clearance from circulating VLDL particles. Although the exact mechanism of action is unknown, potential mechanisms include increased beta-oxidation, acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT) inhibition, decreased hepatic lipogenesis, and increased plasma lipoprotein lipase activity.

Efficacy - Vascepa

MARINE study was a multicenter, randomized, double-blinded, placebo-controlled Phase III study that was conducted in subjects globally. The population of interest was adult individuals with severe hypertriglyceridemia (HTG) with fasting triglyceride (TG) levels greater than or equal to500 and ≤2000 mg/dL. The study was conducted over 12 weeks after a 4 - 6-week lead-in period to washout individuals of previous lipid-altering or statin therapy followed by a 2–3-week qualifying period that measured fasting TG level. Subjects of this study included men and women > 18 years old that were willing to maintain a stable diet and physical activity throughout the study. Individuals (n=610) were screened and the 229 individuals that qualified for the study were randomized into 3 treatment groups: AMR101 4 g/day (n=77), AMR101

2g/day (n= 76), and placebo (n=76). Some subjects from each group discontinued the study: 3, 6, and 5, respectively. The primary endpoint of this study was the placebo-corrected median percent change in TG from baseline to week 12 in both treatment groups. The secondary and exploratory endpoints evaluated the percent change from baseline of the following variables: very-low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (Apo B), phospholipase A2 ($Lp\text{-}PLA_2$), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), VLDL-TG, and non-HDL-C.

AMR101 showed superiority in efficacy in:

- 4g/day treatment group:
    - significant median percent reduction from baseline in TG, VLDL-C, Apo B, $Lp\text{-}PLA_2$, and non-HDL-C levels by 33%, 29%, 9%, 14%, and 18%, respectively, compared to that of the placebo group ($P<0.01$)
    - significant median percent reduction in TG levels in individuals with >750 mg/dL compared to that of the placebo group
    - significant additive TG lowering effect in individuals on concurrent statin therapy by 65%
    - lack of increase in LDL-C levels
- 2g/day treatment group:
    - significant median percent reduction from baseline in the placebo-corrected TG levels by 20% and compared to that of the placebo group ($P<0.01$)
    - no significant effect on the change from baseline in HDL-C levels
    - significant additive TG lowering effect in individuals on concurrent statin therapy by 41%
    - lack of increase in LDL-C levels

ANCHOR was a phase III, multicenter, placebo-controlled, double-blinded, randomized 12-week clinical trial. The population of interest was adult individuals at high risk for CVD. Entry criteria includes TG-qualifying values. Eligible individuals were randomized to AMR101 4g/day, AMR101 2g/day, or placebo. The Primary endpoint was median placebo-adjusted percent change in TG levels from baseline to week 12. Secondary endpoints were prespecified and included median placebo-adjusted percent change in TC, HDL-C, LDL-C, apo B, VLDL, and $Lp\text{-}PLA_2$.

AMR101 showed superiority in efficacy in:

- 4g/day treatment group:

- significant median percent reduction vs placebo from baseline in primary endpoint TG by -21.5%.
- significant median percent reduction vs placebo from baseline in secondary endpoints LDL, non-HDL, VLDL, Lipoprotein associated phospholipase A2, and Apo B by levels of -6.2%, -13.6%, -24.4%, -19.0%, -9.3%, respectively.

- 2g/day treatment group:
  - significant median percent reduction vs placebo from baseline in primary endpoint TG by -10.1%.
  - significant median percent reduction vs placebo from baseline in secondary endpoints LDL-C, non-HDL-C, VLDL, Lp-PLA_2, and ApoB by levels of -3.6%, -5.5%, -10.5%, -8.0%, -3.8%, respectively.

REDUCE-IT was a randomized, double-blinded, placebo-controlled Phase III study conducted on subjects globally. The population of interest was adults greater than or equal to45 years with established CVD or age greater than or equal to50 years with DM and 1 added CV risk factor. Additional inclusion criteria were fasting LDL-C levels >40 and ≤ 100 mg/dL, and fasting TG levels greater than or equal to135 and <500 mg/dL (*2013 amendment fasting TG levels greater than or equal to200 and < 500 mg/dL). The study was event-driven and continued until 1,612 primary endpoint events had occurred. The median follow up duration was 58 months (4.9 years). The sample size was based on a hazard ratio assumption of 0.85 with 90% power and a 1-sided α-level of 2.5% to produce a target sample size of 7,990. Individuals (n=8,129) were randomized and followed with ITT analysis. Subjects were randomized into treatment (n= 4,089) or placebo (n=4040) group with a 1:1 ratio. The primary outcome of the study was a composite of CV mortality, nonfatal MI, nonfatal stroke, coronary revascularization, and UA. Additional secondary, tertiary, and exploratory outcomes included incidence of CV events, lipid and lipoprotein levels and subgroup analyses.

Icosapent ethyl showed superiority in efficacy in:

- 4g/day treatment group:
  - 25% risk reduction versus placebo in 5-point MACE
  - 26% risk reduction versus placebo in 3-point MACE
  - significant reductions in TG and LDL-C levels

Safety - Vascepa

In the ANCHOR and MARINE study, reported adverse events for AMR101 4g, AMR101 2g, and placebo were comparable. In the REDUCE-IT study, reported adverse events for icosapent ethyl and placebo were also comparable. Most treatment adverse events were mild or moderate in severity and deemed unrelated to the study drug. The most common treatment-emergent adverse events were gastrointestinal disorders, which also occurred at a larger percentage in the placebo group. Due to the similarity of incidence in adverse effects of icosapent ethyl and placebo, we conclude that icosapent ethyl has an adequate safety profile. Although adverse effects did occur, they were similar to the placebo group.

In the ANCHOR study, a total of 18 SAE were reported. Seven individuals in AMR101 4g group, 6 in AMR101 2g, and 5 in the placebo group. In the MARINE study, 2 SAEs occurred, including coronary artery disease in AMR101 4g group and noncardiac chest pain in AMR101 2g group. The most frequently occurring AE in the REDUCE-IT study was pneumonia, with higher incidence in the placebo group (2.6% in icosapent ethyl versus 2.9% in placebo). The incidence of serious TEAE was comparable between placebo and icosapent ethyl (30.7% placebo versus 30.6% icosapent ethyl). However, neither SAE was determined to be correlated to treatment drug.

Nexletol and Nexlizet

Nexletol (bempedoic acid) is a first-in-class oral prodrug that inhibits ATP-citrate lyase (ACL). Bempedoic acid is activated to its active metabolite in the liver by bempedoyl-CoA. ACL acts upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Inhibiting ACL leads to upregulation of LDL receptors and increase LDL cholesterol clearance without activation in the skeletal muscle.

Efficacy - Nexletol and Nexlizet

Four phase III trials assessed the efficacy and safety of bempedoic acid with a 2:1 randomization of bempedoic acid 180 mg to placebo. The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Harmony and Wisdom recruited individuals with high CV risk with either diagnosed ASCVD and/or HeFH whose LDL levels are not adequately controlled on other lipid modifying therapies including statins. CLEAR Serenity recruited individuals with a history of intolerance of at least two statins, but who are currently taking other lipid modifying therapies.

CLEAR Tranquility looked at individuals with a history of statin intolerance who are currently taking ezetimibe and possibly other lipid modifying therapies.

Although CLEAR Harmony individuals have a history of ASCVD and/or HeFH, the mean (±SD) LDL cholesterol level at baseline was only slightly high at 103.2 ± 29.4 mg/dL. Individuals were followed for 52 weeks with lipid panels done at week 4, 8, 12, 24, 36 and 52. Results from CLEAR Harmony indicate that when added to maximally tolerated statins, bempedoic acid shows statistically significant reduction in secondary endpoints of LDL cholesterol, non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12. There was also favorable lipid lowering effects for these endpoints up to 52 weeks, but the favorable lipid effects were greatest at week 12 for all endpoints.

- At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg/dL. This meant a placebo corrected least-squares (LS) mean difference of -18.1% (95% CI, -20.0 to -16.1; P <0.001) when comparing bempedoic acid to placebo.
- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
    - Non-HDL cholesterol levels: -13.3% (95% CI, -15.1 to -11.6; P <0.001)
    - Total cholesterol levels: -11.1% (95% CI, -12.5 to -9.8; P <0.001)
    - ApoB levels: -11.9% (95% CI, -13.6 to -10.2; P <0.001)
    - hCRP levels: -21.5% (95% CI, -27.0 to -16.0; P <0.001)
- At week 12, there was no statistically significant placebo corrected LS mean difference in LDL cholesterol levels for individuals on a low/moderate statin compared to a high intensity statin (P= 0.18):
    - Individuals on low/moderate intensity statin: -20.0% (95% CI, -22.8 to -17.3)
    - Individuals on high intensity statin -17.5% (95% CI, -20.2 to -14.7)

CLEAR Wisdom individuals have a history of ASCVD and/or HeFH with current hyperlipidemia despite current statin usage. The mean (±SD) LDL cholesterol level at baseline was 120.4 ± 37.9 mg/dL. Individuals were followed for 52 weeks with lipid panels done at week 4, 12, 24, and 52. Results from CLEAR Wisdom indicate that when added to the maximally tolerated statins, bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and in secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12 and LDL cholesterol at week 24.

- At week 12, bempedoic acid reduced the mean LDL cholesterol level by 22.8 mg/dL. This meant a placebo corrected LS mean difference of -17.4% (95% CI, -21.0 to -13.9; P <0.001) when comparing bempedoic acid to placebo.
- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
    - Non-HDL cholesterol levels: -13.0% (95% CI, -16.3 to -9.8; P <0.001)
    - Total cholesterol levels: -11.2% (95% CI, -13.6 to -8.8; P <0.001)
    - ApoB levels: -13.0% (95% CI, -16.1 to -9.9; P <0.001)
    - hCRP levels -8.7% (95% CI, -17.2 to -0.4; P= 0.04)
- At week 24, the placebo corrected LS mean difference for bempedoic acid follows:
    - LDL cholesterol levels: -14.8% (95% CI, -19.5 to -10.0; P <0.001)

CLEAR Serenity individuals have a history of intolerance to at least two statins and still require additional lipid-lowering for primary or secondary prevention of CV events. The mean (±SD) LDL cholesterol level at baseline was 157.6 ± 39.9 mg/dL. Individuals were followed for 24 weeks with lipid panels done at week 4, 12, and 24. Many individuals (58.%) were not receiving any concomitant lipid-modifying therapy, while one-third of individuals were on non-statin therapy (the most common agents were ezetimibe and fish oil). Results from CLEAR Serenity indicate that bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12 and LDL cholesterol at week 24.

- At week 12, bempedoic acid reduced the mean LDL cholesterol level by 39.3 mg/dL. This meant a placebo corrected LS mean difference of -21.4% (95% CI, -25.1 to -17.7; P <0.001) when comparing bempedoic acid to placebo.
- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
    - Non-HDL cholesterol levels: -17.9% (95% CI, -21.1 to -14.8; P <0.001)
    - Total cholesterol levels: -14.8% (95% CI, -17.3 to -12.2; P <0.001)
    - ApoB levels: -15.0% (95% CI, -18.1 to -11.9; P <0.001)
    - hCRP levels -24.3% (95% CI, -35.9 to -12.7; P <0.001)
- At week 24, the placebo corrected LS mean difference for bempedoic acid follows:

- LDL cholesterol levels: -17.0% (95% CI, -20.5 to -13.7; P <0.001)

CLEAR Tranquility individuals have a history of statin intolerance and currently are on ezetimibe 10 mg daily, but still require additional LDL cholesterol lowering therapies. 57.6% of individuals had a baseline LDL cholesterol less than 130 mg/dL. Individuals were followed for 12 weeks with lipid panels done at week 4, 8, and 12. Results from CLEAR Tranquility indicate that bempedoic acid shows statistically significant reduction in the primary endpoint of LDL cholesterol at week 12 and secondary endpoints of non-HDL cholesterol, total cholesterol, ApoB, and hsCRP at week 12.

- At week 12, the was a placebo corrected mean difference of LDL cholesterol was -28.5% (95% CI, -34.4 to -25.5; P <0.001) when comparing bempedoic acid to placebo.
- At week 12, the placebo corrected LS mean difference for bempedoic acid follows:
  - Non-HDL cholesterol levels: -23.6% (95% CI, -26.4 to -20.8; P <0.001)
  - Total cholesterol levels: -18.0% (95% CI, -20.0 to -16.0; P <0.001)
  - ApoB levels: -19.3% (95% CI, -21.6 to -17.0; P <0.001)
  - hCRP levels -34.6% (P <0.001)

Safety - Nexletol and Nexlizet

Bempedoic acid was generally well tolerated with three treatment related non-fatal SAEs compared to placebo. Urinary tract infection, hyperuricemia and hypertension incidence rates were higher in the bempedoic acid group compared to placebo. Safety data is limited to two RCTs that assessed adverse events up to 52 weeks, one RCT with a time horizon of 24 weeks, and one RCT with a time horizon of 12 weeks. The most common adverse events for bempedoic acid (incidence greater than 4%) include nasopharyngitis, myalgia, arthralgia, dizziness, muscle spasms, diarrhea, hyperuricemia, and headache, which occurred in similar incidence rates as the placebo groups. Muscular disorders, gout, urinary tract infection, hypertension, and liver function test increases were reported more frequently in the bempedoic acid group than in the placebo group.

In CLEAR Harmony, SAEs occurred in 216 (14.5%) of 1487 bempedoic acid treated individuals (including 13 deaths) and in 104 (14.0%) of 742 placebo treated individuals (including 2 deaths). All 15 deaths were judged by the trial site investigator to not be related to study treatment.

In CLEAR Wisdom, SAEs occurred in 106 (20.3%) of 522 bempedoic acid treated individuals (including 6 fatal treatment-emergent AE) and in 48 (18.7%) of 257 placebo treated individuals (including 2 fatal treatment-emergent AE). All fatal treatment emergent adverse events were found to be unrelated to study drug. Three non-fatal SAEs that occurred were considered to be at least possibly related to study treatment: ulcerative colitis and ischemic stroke in bempedoic acid group and upper abdominal pain in the placebo group.

In CLEAR Serenity, SAEs occurred in 14 (6.0%) of 234 bempedoic acid treated individuals and in 4 (3.6%) of 111 placebo treated individuals, none of which were considered by the investigator to be related to study treatment.

In CLEAR Tranquility, SAEs occurred in 5 (2.8%) of 181 bempedoic acid treated individuals and in 3 (3.4%) of 87 placebo treated individuals, none of which were considered by the investigator to be related to study treatment. No fatal SAEs occurred during the study.

Evkeeza

Evkeeza (evinacumab-dgnb) is an angiopoietin-like 3 (ANGPTL3) inhibitor. Genetic studies have shown that humans with sequence variations in ANGPTL3 have reduced plasma lipid levels. Individuals who have mutations in both ANGPTL3 alleles have pan-hypolipidemia with low plasma TG, LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C) levels and increased plasma LPL activity. ANGPTL3 is secreted from the liver. Because the adult liver expresses little to no LPL, it is presumed that ANGPTL3 functions as a circulating inhibitor of LPL. ANGPTL3 inhibits LPL activity in vitro and in vivo, and mice deficient in ANGPTL3 have increased LPL activity and low plasma TG levels. ANGPTL3 inhibits LPL activity by inducing a conformational change in LPL, resulting in increased susceptibility to cleavage by proprotein convertases, dissociation of LPL from the cell surface, and inhibition of its catalytic activity. In addition to inhibiting LPL, ANGPTL3 also inhibits the activity of endothelial lipase (EL), which hydrolyzes HDL phospholipids.

Efficacy - Evkeeza

Two clinical trials assessed the efficacy and safety of evinacumab in different targeted populations. The phase III trial published 8/19/2020, ELIPSE HoFH, showed evinacumab administered as an IV infusion is superior to placebo in reducing LDL-C by ~50% in individuals with HoFH in conjunction with maximal tolerated lipid-lowering therapy over 24 weeks. In a phase II trial, evinacumab in SQ and IV administrations proved to be superior to placebo in

reducing LDL-C among individuals with refractory hypercholesterolemia on GDMT over 16 weeks. Both studies demonstrated widely positive results in LDL reduction compared to placebo

Study ELIPSE-HoFH was a multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of evinacumab compared to placebo in 65 individuals with HoFH. During the 24-week, double-blind treatment period, 43 individuals were randomized to receive evinacumab 15 mg/kg IV every 4 weeks and 22 individuals to receive placebo. After the double-blind treatment period, 64 of 65 individuals entered a 24-week open-label extension period in which all individuals received evinacumab 15 mg/kg IV every 4 weeks.

Principal findings showed evinacumab IV infusions every 4 weeks is superior to placebo in reducing LDL. At week 24, individuals in the evinacumab group had a 47.1% reduction from baseline in the LDL cholesterol level, as compared with a 1.9% increase in the placebo group, for a between-group least-squares mean difference of –49.0 percentage points (95% confidence interval [CI], –65.0 to –33.1; P<0.001). The percent changes in LDL cholesterol levels from baseline to week 24 were consistent across the range of background therapies, including statins, ezetimibe, lomitapide, PCSK9 inhibitors, and apheresis

Secondary outcomes support principal findings and provide impressive leads for further research. Individuals in the evinacumab group had significantly lower levels of apolipoprotein B, non-HDL cholesterol, and total cholesterol from baseline to week 24 than those in the placebo group (P<0.001 for all comparisons). Individuals with a >30% reduction from baseline LDL were 84% in the evinacumab group compared to 18% in placebo. Individuals with a >50% reduction from baseline LDL were 56% in the evinacumab group compared to 5% in placebo. Absolute change from baseline in calculated LDL was -134.7±12.4 in the evinacumab treated group and -2.6±17.6 for the placebo group. 15 (28%) of evinacumab treated individuals had an LDL <70 mg/dl by week 24 compared to 1 (5%) placebo treated individual. ELIPSE HoFH also noted HDL cholesterol level reductions 29.6% in the evinacumab group, compared with an increase of 0.8% in the placebo group.

Safety - Evkeeza

Evinacumab was generally well tolerated with common adverse reactions (greater than or equal to 5%) being nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea. There are warnings and precautions regarding serious hypersensitive reactions noting that these have occurred in clinical trials and if a serious hypersensitivity reaction occurs to discontinue treatment and following standard-of-care and monitor until signs and symptoms resolve. A second warning and precaution is regarding potential embryo-fetal toxicity with the prescribing

information noting that evinacumab may cause fetal harm based on animal studies. Individuals should consider obtaining a pregnancy test prior to initiating treatment with evinacumab and for individuals who may become pregnant they should use contraception during treatment and for at least 5 months following the last dose.

Tryngolza

Tryngolza (olezarsen) is FDA approved as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). Olezarsen is an antisense oligonucleotide-GalNAc3 conjugate that binds to apolipoprotein C-III (apoC-III) mRNA leading to mRNA degradation and resulting in a reduction of serum apoC-III protein. Reduction of apoC-III protein leads to increased clearance of plasma triglycerides and very low-density lipoprotein.

Efficacy - Tryngolza

There is one good quality Phase III clinical trial evaluating the efficacy and safety of olezarsen in patients with FCS (BALANCE). Adults with a fasting triglyceride (TG) greater than or equal to880 mg/dL and suspected FCS were enrolled and the diagnosis was confirmed through genetic testing. Patients with confirmed FCS were randomized 1:1:1 to olezarsen 50 mg, olezarsen 80 mg, or placebo SC every four weeks for 49 weeks. The coprimary study endpoints (in order of hierarchy) were the difference in % change in fasting TG level from baseline to 6 months for a) 80 mg olezarsen vs placebo and b) 50 mg olezarsen vs placebo. Secondary study endpoints included % change in fasting TG level from baseline to 12 months; % change in fasting APO3C levels, APOB-48, and non-HDL cholesterol from baseline to 6 months and 12 months; reduction in fasting TG level greater than or equal to40% and greater than or equal to70% from baseline to 6 months; independently adjudicated acute pancreatitis events weeks 1-53 and 13-53 among patients with a history of pancreatitis in the last 10 years, among all patients, and among greater than or equal to2 events in the last 5 years; fasting TG level ≤880 mg/dL and ≤500 mg/dL (5.6 mmol/L) at 6 months, and safety.

Results from the Phase III BALANCE trial documented:

- The difference in least squares mean % change from baseline to 6 months in fasting TG level was statistically significant for the 80 mg olezarsen dose vs placebo (-43.5%; 95% CI -69.1, -17.9; P<0.001) but was not for the hierarchical coprimary endpoint of the 50 mg dose vs placebo.

- After 12-months of treatment in the 80 mg olezarsen dose group, the difference in least squares mean fasting TG level vs placebo was -59.4% (95% CI -90.7, -28.1).
- The frequency of acute pancreatitis episodes at week 53 was 1/22 patients in the 80 mg olezarsen arm, 1/21 patients in the 50 mg olezarsen arm, and 11/7 patients in the placebo arm. The mean rate ratio for the pooled olezarsen groups vs placebo was 0.12 (95% CI 0.02, 0.66). Despite this was a secondary endpoint for which statistical significance could not be established given a lack of significance with the second coprimary endpoint, the effect size favoring olezarsen is very large.

Safety - Tryngolza

In the Phase III BALANCE trial, serious adverse events (SAEs) occurred in 3 (14%) olezarsen 80 mg patients, 4 (19%) olezarsen 50 mg patients, and 9 (39%) placebo patients. No SAEs were attributed to the study treatment. Overall, most adverse events were mild or moderate in severity. No statistically significant or clinically meaningful change in platelet laboratories was reported. The most common adverse events (incidence >5% of olezarsen-treated patients and >3% higher frequency than placebo) were injection site reactions, decreased platelet count, and arthralgia.

Livalo (pitavastatin)

Many studies have assessed the efficacy of Livalo (pitavastatin) in reducing LDL-C, and influencing lipid parameters and reducing cardiovascular risk, especially to assess pitavastatin versus other HMG-CoA reductase inhibitors. Although head-to-head studies are still lacking, a meta-analyses reported that pitavastatin has similar cumulative probability of reducing the risk of CHD mortality as rosuvastatin and all-cause mortality as atorvastatin and simvastatin. Specific data in Japanese individuals are available. Although pitavastatin shares the same side effects as other agents in its class, there is evidence of fewer drug interactions than some others, due to its being mainly metabolized through glucuronidation. Pitavastatin is available by brand only, suggesting a higher cost over all the other commonly used agents within the same class. There is no evidence of clinical superiority in the majority of individuals.

2018 Update

A literature search was conducted from 1/1/17 to 10/31/18. Outcomes evidence from the FOURIER and ODYSSEY Outcomes trials was added; however, there is no change to the medical necessity criteria, as the results of these trials confirm and do not alter earlier projections based on initial short-term studies.

2019 Update

Reviewed Praluent (alirocumab) and Repatha (evolocumab) prescribing information and conducted a literature search from July 1, 2018, through August 15, 2019. No new evidence was found that would change this policy.

2020 Update

Reviewed all FDA-approved indications for drugs in policy. No new evidence was found that would change policy criteria.

2021 Update

Reviewed all FDA-approved indications for drugs in policy and performed a literature search on the management of hyperlipidemia and product availability. Removed Nikita (pitavastatin) from policy as product has been discontinued and is no longer available in the United States. Added coverage criteria for Roszet (rosuvastatin and ezetimibe) for the treatment of hyperlipidemia. Roszet is a combination of rosuvastatin, an HMG CoA-reductase inhibitor (statin), and ezetimibe, a dietary cholesterol absorption inhibitor, that can lower LDL-C up to 72%.

2022 Update

Reviewed all FDA-approved indications for drugs in policy and performed a literature search on the management of hyperlipidemia and product availability. Added coverage criteria for Leqvio (inclisiran) for the treatment of hyperlipidemia. Leqvio is a small interfering RNA directed to inhibit PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA. Added coverage criteria for

brand rosuvastatin/ezetimibe for the treatment of hyperlipidemia. Brand rosuvastatin/ezetimibe is an authorized generic of Roszet (rosuvastatin and ezetimibe).

2023 Update

Reviewed all FDA-approved indications for drugs in policy and performed a literature search on the management of hyperlipidemia and product availability. Updated coverage criteria for Vascepa to require trial and failure with generic icosapent ethyl. Added Altoprev (lovastatin), Crestor (rosuvastatin), Lescol (fluvastatin), Lescol XL (fluvastatin), Lipitor (atorvastatin), Pravachol (pravastatin), and Zocor (simvastatin) to the Brand Statin criteria requiring trial and treatment failure or intolerance to two generic statins. Added Vytorin (simvastatin-ezetimibe) to the Brand Statin and Ezetimibe Combination criteria requiring that the individual has tried the generic options in combination.

2024 Update

Reviewed all FDA-approved indications for drugs in policy and performed a literature search on the management of hyperlipidemia and familial hypercholesterolemia. Updated coverage criteria for Leqvio (inclisiran), Repatha (evolocumab), Praluent (alirocumab), Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) to include treatment of certain adults with primary hyperlipidemia. Added generic pitavastatin as a preferred alternative option in the HMG-CoA Reductase Inhibitors (statins) coverage criteria. Updated Evkeeza (evinacumab-dgnb) coverage criteria age requirement from 12 years to 5 years of age and older. Updated Evkeeza (evinacumab-dgnb) and Juxtapid (lomitapide) coverage criteria step therapy requirement from Praluent (alirocumab) and Repatha (evolocumab) to Repatha only. Updated Repatha (evolocumab) coverage criteria age requirement to 10 years of age and older for heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH). Updated Praluent (alirocumab) HeFH coverage criteria age requirement from 18 years to 8 years of age and older. Updated the diagnostic criteria for heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) across the policy in the coverage criteria of Leqvio (inclisiran), Repatha (evolocumab), Praluent (alirocumab), Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Nexletol (bempedoic acid), and Nexlizet (bempedoic acid-ezetimibe). Updated Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) coverage criteria to include a quantity limit and added an age requirement to the ASCVD criteria. Removed initial authorization requirement to use in combination with a high-intensity statin from Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Nexletol (bempedoic

acid), and Nexlizet (bempedoic acid and ezetimibe). Removed indication requirement from Roszet (rosuvastatin-ezetimibe), brand rosuvastatin-ezetimibe, and Vytorin (simvastatin-ezetimibe) coverage criteria. Removed re-authorization requirement to continue using a maximum tolerated statin from Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Leqvio (inclisiran), Nexletol (bempedoic acid), Nexlizet (bempedoic acid and ezetimibe), Praluent (alirocumab), and Repatha (evolocumab).

2025 Update

Reviewed all FDA-approved indications for drugs in policy. Added coverage criteria for Tryngolza (olezarsen) for the treatment of familial chylomicronemia syndrome. Removed Lescol (fluvastatin) from policy as product has been discontinued and is no longer available in the United States. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

1. Praluent (alirocumab) [package insert]. Bridgewater, NJ and Terrytown, NY: Sanofi-Aventis and Regeneron Pharmaceuticals. Updated March 2024.
2. American College of Cardiology/American Heart Association Prevention Guideline: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Published June 24th, 2014. Vol. 129, No. 25, Suppl: 2 S1-S45. Available at: **http://www.onlinejacc.org/content/63/25_Part_B/2889** Accessed January 29, 2025.
3. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-excecutive summary. J Clin Lipidol. 2014;8:473-488. Available at: **http://www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf**. Accessed January 29, 2025.
4. Repatha (evolocumab) [package insert]. Amgen Pharmaceuticals, Thousand Oaks, CA. Updated November 2024.
5. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA (2014) PMID: 24825642.
6. Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med (2015) PMID: 25773607.
7. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet (2015) PMID: 25282519
8. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet (2015) PMID: 25282520.

9. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology (2012) PMID: 22656328.

10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722. doi: 10.1056/NEJMoa1615664. Epub 2017 Mar 17.

11. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. NEJM, November 7. 2018 [ePub ahead of print]

12. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. New England Journal of Medicine [Internet]. 2019 [cited 2019 Dec 4];380(11):1022–32.

13. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease. JAMA [Internet]. 2019 Dec [cited 2019 Dec 4];322(18):1780.

14. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. Journal of the American Heart Association [Internet]. 2019 Feb [cited 2019 Dec 4];8(7).

15. Ballantyne CM, Banach M, Mancini GJ, Lepor NE, Hanselman JC, Zhao X, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis [Internet]. 2018 Jun 5 [cited 2019 Dec 4];277:195–203.

16. Bilen O, Ballantyne CM. Bempedoic Acid (ETC-1002): an Investigational Inhibitor of ATP Citrate Lyase [Internet]. Current atherosclerosis reports. Springer US; 2016 [cited 2019 Dec 13].Clinical Trials [Internet]. ESPERION. [cited 2019 Dec 13].

17. Ballantyne C, Bays H, Kastelein J et al. Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides (from the ANCHOR Study). Am J Cardiol. 2012;110(7):984-992. doi:10.1016/j.amjcard.2012.05.031

18. Bays H, Ballantyne C, Kastelein J, Isaacsohn J, Braeckman R, Soni P. Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] Trial). Am J Cardiol. 2011;108(5):682-690. doi:10.1016/j.amjcard.2011.04.015

19. Bhatt D, Steg P, Brinton E et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. Clin Cardiol. 2017;40(3):138-148. doi:10.1002/clc.22692

20. Fan W, Philip S, Granowitz C, Toth P, Wong N. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. J Clin Lipidol. 2019;13(1):100-108. doi:10.1016/j.jacl.2018.11.008

21. Ollendorf D, McQueen R, Fazioli K, Synnott P, Campbell J, Quinlan T, Zaim R, Pearson S, Rind D. Additive Therapies for Cardiovascular Disease: Effectiveness and Value. Institute for Clinical and Economic Review, October 17, 2019. http://icer-review.org/material/cvd-final-evidence-report/ (ICER REPORT)

22. Nichols G, Arondekar B, Garrison L. Patient Characteristics and Medical Care Costs Associated With Hypertriglyceridemia. Am J Cardiol. 2011;107(2):225-229. doi:10.1016/j.amjcard.2010.09.010

23. Wall H, Ritchey M, Gillespie C, Omura J, Jamal A, George M. Vital Signs: Prevalence of Key Cardiovascular Disease Risk Factors for Million Hearts 2022 — United States, 2011–2016. MMWR Morb Mortal Wkly Rep. 2018;67(35):983-991. doi:10.15585/mmwr.mm6735a4.

24. Raal, Frederick J., et al. "Evinacumab for homozygous familial hypercholesterolemia." New England Journal of Medicine 383.8 (2020): 711-720.

25. Gusarova, Viktoria, et al. "ANGPTL3 blockade with a human monoclonal antibody reduces plasma lipids in dyslipidemic mice and monkeys." Journal of lipid research 56.7 (2015): 1308-1317.

26. Leqvio (inclisiran) [package insert]. Cambridge, MA: Novartis Pharmaceuticals. Updated July 2023.

27. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–19.

28. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation*. 2015;132(22):2167-2192.

29. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2012;23:282-289.

30. Tryngolza (olezarsen) [package insert]. Ionis Pharmaceuticals, Inc. Carlsbad, CA. Updated December 2024.

31. Ionis presents positive results from phase 3 Balance study of olezarsen for familial chylomicronemia syndrome. News release. Ionis Pharmaceuticals, Inc.; April 7, 2024. **https://ir.ionis.com/news-releases/news-release-details/ionis-presents-positive-results-phase-3-balance-study-olezarsen**. Accessed January 29, 2025.

32. Ionis announces olezarsen FCS new drug application accepted for priority review and enrollment in phase 3 sHTG program completed. News release. Ionis Pharmaceuticals, Inc.; June 25, 2024. **https://ir.ionis.com/news-releases/news-release-details/ionis-announces-olezarsen-fcs-new-drug-application-accepted**. Accessed January 29, 2025.

33. Stroes ESG, et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. N Engl J Med. 2024;390(19):1781–1792. doi:10.1056/NEJMoa2400201

History

Date	Comments
08/05/15	New policy, add to Pharmacy subsection. Considered medically necessary as an adjunct to diet and maximally tolerated statin therapy treatment for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD when criteria are met.
9/14/15	Interim update. Policy updated with recently FDA-approved drug, evolocumab (Repatha). Heterozygous removed from policy statement; criteria numbered for improved clarity. References 8-14 added. "Inhibitors" added to policy title.
03/01/16	Interim update, approved February 18, 2016. Policy updated with guidelines around management of statin-induced myopathy, as well as statin-induced transaminitis.
09/13/16	Policy moved into new format; no change to policy statements. Corrected formatting to show that criteria for myalgias and transaminitis apply to both FH and ASCVD.
07/01/17	Annual Review, approved June 13, 2017. Updated ASCVD diagnoses criteria to exclude angina. Created two sections for FH, homozygous and heterozygous. Specified when a PCSK9 inhibitor might be used for primary vs. secondary prevention.
05/01/18	Interim Review, approved April 3, 2018. Medical Necessity criteria language revised for clear intent; no clinical criteria changes made. Note regarding "effect of alirocumab or evolovumab on cardiovascular morbidity and mortality has not been determined" was removed.

Date	Comments
12/01/18	Annual Review, approved November 21, 2018. Literature search 1/1/17-10/31/18. Summary of Fourier and Odyssey Outcomes trials added. No change to criteria.
04/01/19	Interim Review, approved March 12, 2019. Updated and simplified diagnostic criteria for familial hypercholesterolemia, changed LDL-c target from 100mg/dL to 70, removed CK testing requirement for myalgia and eliminated specialty prescribing requirement. Approved by P&T February 26, 2019.
10/01/19	Annual Review, approved September 5, 2019. Updated criteria to only require maximum tolerated doses of atorvastatin or rosuvastatin. Added peripheral arterial disease and stable or unstable angina as qualifying conditions for ASCVD.
04/01/20	Interim Review, approved March 10, 2020. Renamed policy from "Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors" to "Pharmacologic Treatment of High Cholesterol". Added criteria for Vascepa (icosapent ethyl) for established cardiovascular disease and severe hypertriglyceridemia. Added criteria for Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) for treatment of familial hypercholesterolemia and ASCVD. Moved Ezallor Sprinkle (rosuvastatin), Flolipid (simvastatin liquid), Livalo (pitavastatin), Nikita (pitavastatin), and Zypitamag (pitavastatin) from policy 5.01.605 with identical coverage criteria.
05/01/20	Interim Review, approved April 14, 2020. Moved Juxtapid (lomitapide) from policy 5.01.605. Kynamro has been withdrawn from the market and no criteria were added to policy for Kynamro. Added criteria to Juxtapid for homozygous familial hypercholesterolemia with requirement to try Praluent or Repatha first. Added criteria for brand simvastatin oral suspension with same criteria as Flolipid. Updated Vascepa (icosapent ethyl) criteria with a daily dose requirement.
08/01/20	Annual Review, approved July 23, 2020. Added to Juxtapid (lomitapide) a daily dose limit of 60 mg.
01/01/21	Interim Review, approved December 8, 2020. Updated coverage criteria for Repatha (evolocumab) and Praluent (alirocumab) for the management of ASCVD and HoFH. Updated criteria for Praluent also requires trial with Repatha first.
05/01/21	Interim Review, approved April 13, 2021. Added generic icosapent ethyl to policy with identical coverage criteria as Vascepa (icosapent ethyl). Added coverage criteria for Evkeeza (evinacumab-dgnb) for the treatment homozygous familial hypercholesterolemia. Added HCPCS code J3590.
07/01/21	07/01/21 Coding update, Added HCPCS code C9079.
08/01/21	Annual Review, approved July 22, 2021. Removed Nikita (pitavastatin) from policy as product has been discontinued. Updated re-authorization length of approval to 3-years for Ezallor Sprinkle (rosuvastatin), Livalo (pitavastatin), and Zypitamag (pitavastatin). Added coverage criteria for Roszet (rosuvastatin and ezetimibe) for the treatment of hyperlipidemia.
10/01/21	Coding update, Added HCPCS code J1305 and removed J3590.

Date	Comments
03/01/22	Annual Review, approved February 8, 2022. Added coverage criteria for Leqvio (inclisiran) for the treatment of ASCVD. Added coverage for brand rosuvastatin/ezetimibe for the treatment of hyperlipidemia. Added HCPCS code J3490 for Leqvio.
07/01/22	Coding update. Added HCPCS code J1306. Removed HCPCS code J3490.
02/01/23	Interim Review, approved January 10, 2023. Added coverage for Lovaza (omega-3-acid ethyl esters) for the treatment of severe hypertriglyceridemia. Added coverage for Antara (fenofibrate), brand fenofibrate, Fenoglide (fenofibrate), Fibricor (fenofibric acid), Lipofen (fenofibrate), Lopid (gemfibrozil), Niacor (niacin), Niaspan (niacin extended-release), Tricor (fenofibrate), Triglide (fenofibrate), Trilipix (fenofibric acid), and Zetia (ezetimibe) for the treatment of hyperlipidemia. Changed the wording from "patient" to "individual" throughout the policy for standardization. Removed termed HCPC code C9079 and removed effective date from HCPC code J1305.
05/01/23	Annual Review, approved April 24, 2023. Updated coverage criteria for Vascepa to require trial and failure with generic icosapent ethyl. Added Altoprev (lovastatin), Crestor (rosuvastatin), Lescol (fluvastatin), Lescol XL (fluvastatin), Lipitor (atorvastatin), Pravachol (pravastatin), and Zocor (simvastatin) to the Brand Statin criteria requiring trial and treatment failure or intolerance to two generic statins. Added Vytorin (simvastatin-ezetimibe) to the Brand Statin and Ezetimibe Combination criteria requiring that the individual has tried the generic options in combination.
07/01/24	Annual Review, approved June 11, 2024. Updated coverage criteria for Leqvio (inclisiran), Repatha (evolocumab), Praluent (alirocumab), Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) to include treatment of certain adults with primary hyperlipidemia. Added generic pitavastatin as a preferred alternative option in the HMG-CoA Reductase Inhibitors (statins) coverage criteria. Updated Evkeeza (evinacumab-dgnb) coverage criteria age requirement from 12 years to 5 years of age and older. Updated Evkeeza (evinacumab-dgnb) and Juxtapid (lomitapide) coverage criteria step therapy requirement from Praluent (alirocumab) and Repatha (evolocumab) to Repatha only. Updated Repatha (evolocumab) coverage criteria age requirement to 10 years of age and older for heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH). Updated Praluent (alirocumab) HeFH coverage criteria age requirement from 18 years to 8 years of age and older. Updated the diagnostic criteria for heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) across the policy in the coverage criteria of Leqvio (inclisiran), Repatha (evolocumab), Praluent (alirocumab), Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Nexletol (bempedoic acid), and Nexlizet (bempedoic acid-ezetimibe). Updated Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) coverage criteria to include a quantity limit and added an age requirement to the ASCVD criteria. Removed initial authorization requirement to use in combination with a high-intensity statin from Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Nexletol (bempedoic acid), and Nexlizet (bempedoic acid and ezetimibe). Removed indication requirement from Roszet (rosuvastatin-ezetimibe), brand rosuvastatin-ezetimibe, and Vytorin

Date	Comments
	(simvastatin-ezetimibe) coverage criteria. Removed re-authorization requirement to continue using a maximum tolerated statin from Evkeeza (evinacumab-dgnb), Juxtapid (lomitapide), Leqvio (inclisiran), Nexletol (bempedoic acid), Nexlizet (bempedoic acid and ezetimibe), Praluent (alirocumab), and Repatha (evolocumab).
03/01/25	Annual Review, approved February 11, 2025. Added coverage criteria for Tryngolza (olezarsen) for the treatment of familial chylomicronemia syndrome. Removed Lescol (fluvastatin) from policy as product has been discontinued. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. HCPC code J3490 added back to policy to report Tryngolza.
05/01/25	Interim Review, approved April 8, 2025. Added coverage of Atorvaliq (atorvastatin oral suspension) for the treatment of hyperlipidemia.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.