GLIN IPA

JANUARY 2024

PharmacyFactor

New and Emerging Therapies in the Management of Dyslipidemia

Drug Information Update

Question of the Month

What is the data surrounding uric acid elevations with bempedoic acid use and safety in patients with or without history of hyperuricemia?

Bempedoic acid is first-in-class lipid lowering agent. Initial studies have reported up to a 27% decrease in LDL-C when bempedoic acid is used as monotherapy, up to a 24% additional decrease in LDL-C when used with statins, and up to 48% total decrease when concurrently prescribed with ezetimibe.

Existing reports note use of bempedoic acid increases serum uric acid (SUA) and creatinine. Ray et al concluded that the use of bempedoic acid increases uric acid and gout, but increases in SUA were reversible on discontinuation of the study drug. It is known that bempedoic acid is a weak inhibitor of OAT2, leading to competition between uric acid and the bempedoic acid glucuronide metabolite for the same renal OAT2 transporter. This is likely the primary mechanism responsible for minor increases in SUA and creatinine leading to hyperuricemia or gout in some patients, but its clinical relevance is not yet determined.

In the phase 3 studies of bempedoic acid, increases in SUA occurred in 2.1% of patients treated with bempedoic acid compared with 0.5% with placebo, with hyperuricemia reported in 1.7% and 0.6% of patients treated with bempedoic acid or placebo, respectively. Development of acute gout occurred in 1.4% and 0.4% of patients, respectively. The mean increase in uric acid at 12 weeks was 0.82 mg/dL for bempedoic acid vs −0.02 mg/dL for placebo. This increase was apparent within 4 weeks of treatment and was stable over time. A history of gout also appeared to increase the risk of gout with bempedoic acid (11.0% vs 2.9%). In contrast, 0.8% of patients with no history of gout developed the condition while taking bempedoic acid (compared with 0.3% with placebo). Further studies are needed to elucidate the pathogenetic mechanisms underlying these associations and to verify the long-term safety of this treatment.

Patients who are at risk for hyperuricemia or acute gout warrant heightened vigilance and additional monitoring while they are taking bempedoic acid. Analyses of shorter-term clinical trials suggest that patients who, at baseline, have no history of gout and no elevations in uric acid have an incidence of subsequent gout similar to that of placebo. According to the prescribing information, uric acid levels should be assessed periodically as clinically indicated, patients should be monitored for signs and symptoms of hyperuricemia, and urate-lowering drugs should be initiated as appropriate. Notably, although bempedoic acid is a weak inhibitor of OAT2, significant drug-drug interactions are not anticipated.

References

Ballantyne CM, McKenney JM, MacDougall DE, et al. Effect of ETC-1002 on serum low-density lipoprotein cholesterol in hypercholesterolemic patients receiving statin therapy. Am J Cardiol. 2016;117(12):1928-1933.

Banach M, Duell PB, Gotto AM Jr, et al. Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. JAMA Cardiol. 2020:e202314.

Bays HE, Banach M, Catapano AL, et al. Bempedoic acid safety analysis: pooled data from four phase 3 clinical trials. J Clin Lipidol. 2020;14:649–659.e6.

Bay KK, Bays HE, Catapano AL, et al. CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl JMed. 2019;380(11):1022-1032.

Cicero AFG, Pontremoli R, Fogacci F, et al. Effect of bempedoic acid on serum uric acid and related outcomes: a systematic review and meta-analysis of the available phase 2 and phase 3 clinical studies. Drug Saf. 2020; 43(8): 727- 736.

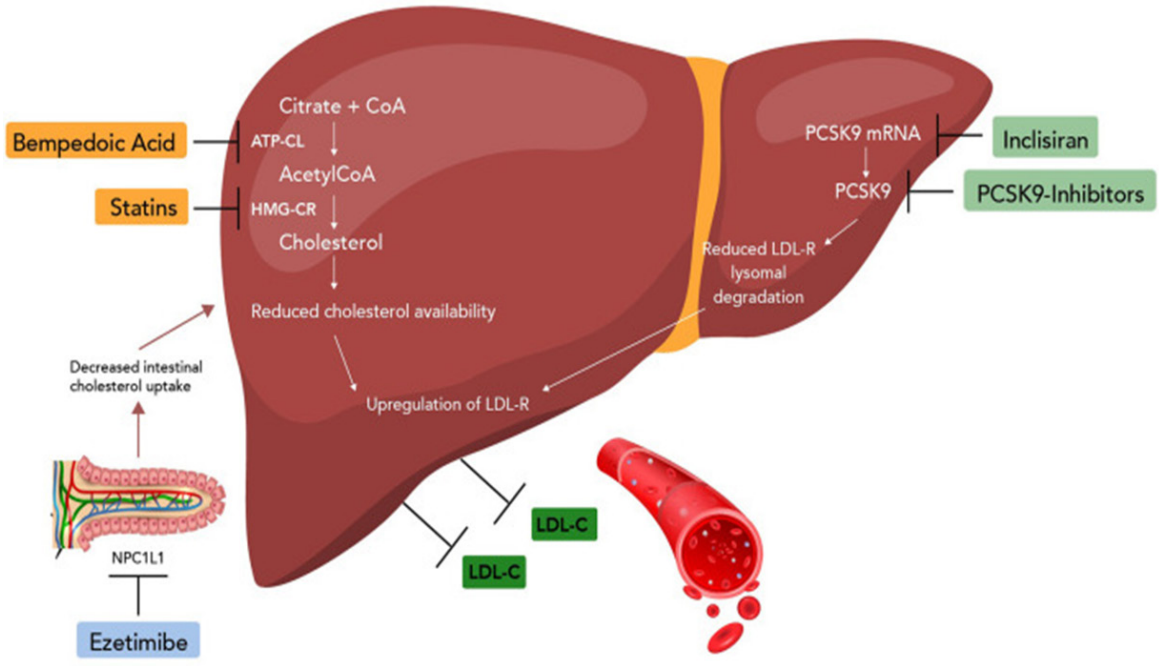
Ivanyuk A, Livio F, Biollaz J, Buclin T. Renal drug transporters and drug interactions. Clin Pharmacokinet. 2017;56:825–892.

Dyslipidemia Guideline Summary: Where We Are Now

The 2013 AHA/ACC guidelines on the treatment of blood cholesterol represented a major paradigm shift in that they focused primarily on statin benefit groups and incorporated atherosclerotic cardiovascular disease (ASCVD) risk estimation via pooled cohort equations into treatment algorithms. They differed from prior guidelines that emphasized "treat to target" by any means and rather focused on statin intensity and relative reduction in low-density lipoprotein cholesterol (LDL-C) compared to baseline.

Since 2013, additional **randomized clinical trial evidence has emerged to support the selective use of non-statin therapies as treatment adjuncts to preferred statin therapy and the use of LDL-C thresholds.** Further evidence suggests that the relationship between LDL-C and ASCVD risk tracks down to very low values of LDL-C.

The following pages cover considerations for nonstatin therapy in as supported by the 2022 ACC Nonstatin Therapy Decision Pathway **for patients already on maximally-tolerated statin therapy NOT achieving LDL-C targets and for patients with documented statin intolerance** – data is detailed separately for both primary prevention (Table 2) and secondary prevention (Table 3).



Dyslipidemia Guideline Summary: Where We Are Now (continued)

For this review, the following definitions are provided:

Major ASCVD Events: acute coronary syndrome in the past 12 months, history of myocardial infarction (MI), history of ischemic stroke, and symptomatic peripheral arterial disease.

High-Risk Conditions: age ≥ 65, heterozygous familial hypercholesterolemia (HeFH), history of prior coronary artery bypass or PCI outside of the major ASCVD event, diabetes mellitus, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C despite maximally tolerated statin therapy and ezetimibe, and a history of congestive heart failure.

Defining Statin Intolerance

Before Moving On To Nonstatin Treatment Options, in patients with clinical ASCVD, it is important to adequately trial maximally tolerated statin therapy.

True **Statin Intolerance** is defined **as the inability to tolerate at least TWO (2) statins at any dose, including a trial of 1 attempt at the lowest FDA-approved dose or using alternative dosing**.

Patients with statin-associated muscle symptoms (SAMS) should be evaluated thoroughly, and nonstatin causes and predisposing factors should be considered. Other considerations and management strategies:

- ✓ Other causes of muscle symptoms include physical activity, vitamin D deficiency, hypothyroidism, rheumatologic or musculoskeletal disease, alcohol and drug abuse, and other causes of leg cramps.
  - If vitamin D deficiency is present, the deficiency should be properly corrected prior to statin initiation or prior to the patient being classified as statin intolerant
- ✓ Consider switching to a hydrophilic statin such as pravastatin and rosuvastatin.
- ✓ Simvastatin is the most lipophilic statin and diffuses non-selectively into extrahepatic tissues such as muscles, and has the highest risk for SAMS.
- ✓ Patients experiencing mild to moderate SAMS should hold for 2-4 weeks and re-challenge at the same or lower dose if the pain resolves during the holiday.
- ✓ When using alternate dosing strategies, it is important to ensure the patient is prescribed the correct quantity and days supply reflective of the dosing frequency on their prescription.
- ✓ Every other day or weekly dosing is an option but is not preferred. Atorvastatin and rosuvastatin have the longest half-lives and would be the most appropriate in these situations.
- ✓ Myalgia is likely statin-associated if it is: 1) bilateral, 2) involves proximal muscles, 3) onset is within weeks to months after initiation of statins, and 4) resolves after statin discontinuation.
- ✓ CK (creatinine kinase) levels should be measured in patients with severe SAMS to rule out rhabdomyolysis.

Defining Statin Intolerance (continued)

In patients who cannot tolerate a statin despite an adequate trial, providers can exclude a patient from quality metrics related to statins by submitting a claim annually at the time of the provider visit by using one of the ICD-10 codes noted in Table 2. This diagnosis code list is not all-encompassing as it does not account for other exclusions and exceptions like end-stage renal disease, pregnancy/breastfeeding, or cirrhosis.

Of note, ICD-10 code T46.6X(...) which encompasses the adverse effect of antihyperlipidemic drug does NOT exclude patients from statin use metrics.

Table 1

Statin Exclusion Codes	
Condition	**ICD-10 Code**
Myalgia	M79.1, M79.10-M79.12, M79.18
Myositis	M60.80-M60.819; M60.821-M60.829; M60.831-M60.839; M60.841-M60.849; M60.851-M60.859; M60.861-M60.869; M60.871-M60.879; M60.88-M60.9
Myopathy	G72.0, G72.2, G72.9
Rhabdomyolysis	M62.82

2022 ACC ECDP on Role of Nonstatin Therapies for LDL-C Lowering

Nonstatin therapies for patients that require additional LDL-C lowering, or are statin intolerant.

Table 2

Primary Prevention			
Patient Management Group	**Adults without clinical ASCVD and with baseline LDL-C ≥ 190 mg/dL not due to secondary causes**	**Adults aged 40-75 years with diabetes and without clinical ASCVD and baseline LDL-C <190 mg/dL and 10-year ASCVD risk ≥20%, diabetes-specific risk enhancers *, or subclinical atherosclerosis**	**Adults aged 40-75 years without diabetes and 10 year ASCVD risk score ≥ 20%**
Therapy Goals	≥50% LDL-C reduction and LDL-C <100	≥50% LDL-C reduction and LDL-C <70 mg/dL	≥50% LDL-C reduction and LDL-C <70 mg/dL
First-Line Therapy	High-intensity or maximally tolerated statin therapy	Moderate-intensity or maximally tolerated statin therapy	Maximally tolerated statin therapy
Second-Line Therapy	Ezetimibe and/or PCSK9 mAb	Ezetimibe	Ezetimibe
Third-Line Therapy	Bempedoic acid or inclisiran	Bile acid sequestrants	Bile acid sequestrants
Fourth-Line Therapy	Consider evinacumab, lomitapide, and/or LDL apheresis for HoFH under care of lipid specialist	Bempedoic acid	Bempedoic acid

FH: familial hypercholesterolemia; HoHF: Homozyous familial hypercholesterolemia; RD/RDN: registered dietitian/registered dietitian nutritionist

**Diabetes risk enhancers: long duration of diabetes disease (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus), albuminuria ≥30 mcg of albumin/mg creatinine, eGFR <60 ml/min/1.73 m2, retinopathy, neuropathy, ankle-brachial index 0.9.*

Nonstatin therapies for patients that require additional LDL-C l lowering, or are statin intolerant.

Table 3

Secondary Prevention				
Patient Management Group	**Adults with Clinical ASCVD at very high risk**	**Adults with Clinical ASCVD who are not at very high risk**	**Adults with Clinical ASCVD and baseline LDL-C ≥ 190 without clinical or genetic diagnosis of FH**	**Adults with clinical ASCVD at very high risk and baseline LDL-C ≥190 mg/dL not due to secondary causes and with clinical diagnosis or genetic confirmation of FH**
Therapy Goals	≥50% LDL-C reduction and LDL-C <55 mg/dL	≥50% LDL-C reduction and LDL-C <70 mg/dL	≥50% LDL-C reduction and LDL-C <70 mg/dL	≥50% LDL-C reduction and LDL-C <55 mg/dL
First-Line Therapy	High-intensity or maximally tolerated statin therapy	High-intensity or maximally tolerated statin therapy	High-intensity or maximally tolerated statin therapy	High-intensity or maximally tolerated statin therapy
Second-Line Therapy	Ezetimibe and/or PCSK9 mAb	Ezetimibe	Ezetimibe or PCSK9 mAb	Ezetimibe and/or PCSK9 mAb
Third-Line Therapy	Bempedoic acid or inclisiran	Replace or add PCSK9 mAb	Bempedoic acid or inclisiran	Bempedoic acid or inclisiran
Fourth-Line Therapy	Referral to lipid specialist and/or RD/RDN	Bempedoic acid or inclisiran	Consider LDL apheresis under the care of a lipid specialist	Consider evinacumab, lomitapide, and/or LDL apheresis for HoFH under care of a lipid specialist

Review of Current Nonstatin Therapies

Below is a review of commonly prescribed generic nonstatin therapies and cardiovascular (CV) risk reduction data when addressing their role in dyslipidemia management.

Nonstatin Therapies					
Therapy	**Ezetimibe**	**Niacin (nicotinic acid)**	**Bile Acid Sequestrants (BAS)**	**Icosapent Ethyl (E-EPA)**	**Omega-3 Acid Ethyl Esters**
MOA	Inhibits NPC1L1 protein and reducing cholesterol absorption in the small intestine, leading to reductions in total cholesterol and LDL.	Partially inhibits release of free fatty acids from adipose tissue, increased lipoprotein lipase activity, and decreased rates of hepatic synthesis of VLDL and LDL.	Binds to bile acids in the intestine, preventing reabsorption.	Icosapent ethyl is an ethyl ester of eicosa-pentaenoic acid (EPA); EPA reduces hepatic VLDL TG (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles.	Reduces hepatic production and secretion of TG-rich VLDL and increase TG removal from VLDL and chylomicron particles through the upregulation of enzymes, such as lipoprotein lipase.
Indication	In combination with a statin, or alone when additional LDL lowering therapy is not possible, in primary hyperlipidemia, including HeFH, to reduce LDL.	Adjunctive therapy for severe hyper-triglyceridemia (≥ 500 mg/dL); adjunct to diet and in combination with a BAS to reduce elevated LDL-C in primary hyperlipidemia.	Adjunctive therapy to diet for the reduction of elevated cholesterol in patients with primary elevated LDL.	(1) Adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascular-ization, and unstable angina requiring hospitalization in adult patients with TG levels ≥ 150 mg/dL and either established CVD or DM with 2+ risk factors for CVD. (2) Adjunct to diet in severe hyper-triglyceridemia (≥ 500 mg/dL).	Adjunct to diet to reduce TG levels in severe hyper-triglyceridemia (≥500 mg/dL).

ACS = acute coronary syndromes; BAS = bile acid sequestrant; CVD = cardiovascular disease; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; MI = myocardial infarction; NPC1L1 = Niemann-Pick C1-Like 1; TG = triglyceride; RCT = randomized controlled trial

Nonstatin Therapies (continued)					
Therapy	**Ezetimibe**	**Niacin (nicotinic acid)**	**Bile Acid Sequestrants (BAS)**	**Icosapent Ethyl (E-EPA)**	**Omega-3 Acid Ethyl Esters**
CV Risk Reduction	IMPROVE-IT trial: a double-blind showed that when added to statin therapy after ACS, ezetimibe produced modest improvements in CV outcomes (ARR 2.0%; HR 0.936, NNT 50). While there was a 23% LDL-C reduction and reduction in incidence of MI and stroke, there was **no reduction** in all-cause or CV mortality with add-on ezetimibe.	A Cochrane Database Systemic Review published in 2017 included 23 RCTs and determined that niacin does not reduce mortality, CV mortality, the number of fatal or non-fatal MI, or the number of fatal or non-fatal strokes. The review did conclude that niacin is associated with adverse effects, and overall **CV benefit is unlikely.**	The 2022 Nonstatin guidelines have stated that BAS may be an appropriate alternative for patients with ezetimibe intolerance and triglycerides <300 mg/dL, however **CV risk reduction has not been established.**	The Reduce-IT trial investigated CV risk reduction in patients using icosapent ethyl for severe hyper-triglyceridemia (TG ≥ 500 mg/dl). It was determined that use of icosepent ethyl combined with statin in these patients **demonstrated lower risk for ischemic events and CV death.**	The STRENGTH trial demonstrated **no benefit on CV events** with omega-3 fatty acids.
Available Products and Dosing	• Zetia 10 mg tablet; generic available • Dose: 10 mg once daily	• ER tablet: 250 mg, 500 mg, 750 mg, 1000 mg • ER capsule: 250 mg, 500 mg • Tablet: 50 mg, 100 mg, 250 mg, 500 mg • Recommended maintenance dose of ER formulations: 1,000 to 2,000 mg at bedtime	Includes cholestyramine (oral powder), colestipol (oral packet or tablet), and colesevelam (oral packet or tablet)	• Vascepa® 0.5 g and 1 g capsules • Dose: 2 g twice daily with meals	• Lovaza® 1 g capsules • Dose: 4 g once daily or 2 g twice daily

ACS = acute coronary syndromes; BAS = bile acid sequestrant; CVD = cardiovascular disease; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; MI = myocardial infarction; NPC1L1 = Niemann-Pick C1-Like 1; TG = triglyceride; RCT = randomized controlled trial

Review of Novel Nonstatin Therapies

Below novel nonstatin therapies and cardiovascular (CV) risk reduction data for those therapies is reviewed when addressing their role in dyslipidemia management.

Therapy	Nexletol® (bempedoic acid)	Leqvio®(inclisiran)	Evkeeza™	Juxtapid® (lomitapide)
Mechanism of Action	Prodrug activated by acyl-coA synthetase-1, which is found in liver cells, that inhibits ATP-citrate lyase. ATP-citrate lyase is an enzyme found upstream from HMG-CoA reductase and inhibition causes up-regulation of the LDL receptor, resulting in increased LDL clearance.	Double-stranded small interfering ribonucleic acid that prevents PCSK9 translation in the liver, increasing LDL-C receptor recycling and expression on the hepatocyte.	Recombinant human monoclonal antibody that inhibits ANGPTL3, a liver expressed protein and inhibitor of lipoprotein lipase, two main enzymes in lipoprotein metabolism	Binds and inhibits MTP in the lumen of the endoplasmic reticulum. Prevents the assembly of apoB containing lipoproteins in enterocytes and hepatocytes, inhibiting the synthesis of chylomicrons and VLDL. Decreased VLDL results in reduced levels of plasma LDL-C.
Indication	Treatment of HeFH or established atherosclerosis to reduce LDL-C	Treatment of HeFH or established atherosclerosis to reduce LDL-C	Use as adjunct to other LDL-C lowering therapies in the treatment of HoFH	Treatment of HoFH as an adjunct to low-fat diet and other lipid-lowering treatments
CV Risk Reduction	The CLEAR Outcomes Trial demonstrated that CV events were significantly lower in statin-intolerant patients treated with bempedoic acid*	The effect of inclisiran on cardiovascular morbidity and mortality has not been determined	The effect of evinacumab on cardiovascular morbidity and mortality has not been determined	The effect of lomitapide on cardiovascular morbidity and mortality has not been determined
LDL Lowering Potential	Monotherapy: 24.5% When combined with maximally tolerated statin therapy, additional lowering of 15-17.8%. When added to ezetimibe, LDL lowering of 38% from baseline.	Up to 52% lowering when combined with maximally tolerated statin therapy.	Average LDL-C lowering from baseline was 49%. Of note, a total of 63% of the patients were taking at least three lipid-modifying drugs.^	Average LDL-C lowering from baseline was 40% in HoFH with statins, with or without LDL-C apheresis.
Clinical Pearls	Increased risk for gout and cholelithiasis Does not penetrate skeletal muscle, may be better tolerated in patients with statin intolerance	Subcutaneous injection given by a healthcare provider**	Administered as an IV infusion	Available through a lomitapide REMS program due to risk for hepatotoxicity. Triglycerides were reduced by 35-65%.
Available Products & Dosing	Nexletol 180mg tablets Nexlizet 180mg-10mg Dosing: 180mg by mouth once daily with maximally tolerated statin therapy	Leqvio 284mg/1.5mL solution for injection Dose: 284mg subcutaneously every three (3) months for two (2) doses, then every six (6) months thereafter	Evkeeza 1200mg/8mL solution Evkeeza 345mg/2.3mL solution Dosing: 15mg/kg/dose administered IV over 60 minutes every four (4) weeks	Juxtapid capsule: 5mg, 10mg, 20mg, 30mg, 40mg, 60mg Dosing: 5mg by mouth once daily, may titrate to 10mg once daily after 2 weeks, 20mg once daily after 4 weeks, and then 60mg once daily after at least four (4) weeks

HeFH: heterozygous familial hypercholesterolemia; HoHF: Homozyous familial hypercholesterolemia; MTP: microsomal triglyceride transfer protein
* refer to the GLIN PharmacyPRN previously released in May 2023 for a summary of the trial and results
** refer to the GLIN PharmacyPRN previously released in July 2022 for more information
^ 94% of the trial patients were receiving a statin (77% high-intensity statin); a PCSK9 inhibitor was being administered in 77% of the patients, ezetimibe in 75%, and lomitapide in 25%; 34% of the patients were undergoing apheresis

Pipeline Nonstatin Therapies for Dyslipidemia

Pelacarsen

Pelacasen is an investigational medication that was designed to inhibit and directly lower the production of apolipoprotein(a) within the liver, which has been linked to genetic causes of cardiovascular disease.

Ionis Pharmaceuticals announced the **enrollment completion of pelacarsen into a Phase 3 Lp(a) HORIZON study to determine cardiovascular benefit**, with expected trial completion in 2025.

Oral PSCK9 Inhibitor

Merck & Co recently announced plans for a **Phase 3 pivotal study of their investigational product, MK-0616, which is an oral PCSK9 inhibitor.** In a phase 2b clinical trial, Ballantyne et al. randomized participants with clinical ASCVD plus LDL-C 70-160 mg/dL, intermediate or higher risk for ASCVD, and borderline risk for ASCVD to placebo or one of four doses of MK-0616 (6 mg, 12 mg, 18 mg or 30 mg). About 60% were taking a statin at study entry, with about a quarter receiving high-intensity statin therapy. **The trial demonstrated significant LDL-C lowering at all doses of oral PCSK9i versus placebo at eight (8) weeks (range 41.2%-60.9%, p<0.001 for all doses), with excellent patient tolerability.**

Obicetrapib

Obicetrapib is an investigational cholesteryl ester transfer protein (CETP) inhibitor that is currently in a Phase 3 study to investigate safety and efficacy in patients with HeFH; **PREVAIL is currently recruiting participants to evaluate the cardiovascular outcomes of obicetrapib** (https://clinicaltrials.gov/ct2/show/NCT05202509). Data for this trial is anticipated to be released in 2026.

Pemafibrate

Introduced by Kowa Pharmaceuticals, pemafibrate is a selective PPARα (peroxisome proliferator-activated receptor, subtype alpha; SPPARMα) modulator intended to treat both dyslipidemia and primary biliary cholangitis. PPARα activation leads to changes in the activity of multiple different genes within the nucleus, leading to a range of metabolic changes in the body. The main effect of pemafibrate is reduction of blood triglycerides.

The PROMINENT clinical trial studied patients with type 2 diabetes, mild-moderate hypertriglyceridemia, and low HDL and LDL levels, and determined that **the incidence of CV events was not decreased in those who took pemafibrate** compared with placebo. While studies have ceased on pemefibrate, it is anticipated that addition SPPARMα trials will be forthcoming given superior benefit-risk balance compared to conventional fibrates for triglyceride reduction and HDL-C elevation, and can be used for patients for whom it was difficult to use existing fibrates, including those who are taking statins and those with renal dysfunction. Pemafibrate has been approved for use in Japan, under the brand name Parmodia®, for the indication of lowering blood triglycerides.

Information regarding the trial and study termination (due to futility based on efficacy, not safety analysis) can be reviewed at: https://clinicaltrials.gov/ct2/show/results/NCT03071692.

Gemcabene

Gemcabene was introduced by NeuroBo Pharmaceuticals and, similarly to pemafibrate, lowers lipid levels through activation of PPARα. Gemcabene was in a Phase 2 randomized, double-blind, placebo-controlled study to assess efficacy and safety parameters, however research is currently on a partial clinical hold, as NeuroBo is investing additional indications for the drug.

With the expansion of the GLIN IPA Pharmacy Team in 2023, our pharmacists will be available to assist in improving these outlined quality metrics. Our pharmacists will provide payer quality reports as done in previous years OR provide patient specific messages within your electronic medical record with recommendations AND patient follow-up if agreeable by your providers.

Pharmacy Phone Number
(716) 800-CARE (2273)

Pharmacy Email
pharmacy@glin.com

For additional questions, please reach out to your assigned Practice Transformation Consultant.

GLIN.COM