

FDA Withdraws Approval of Niaspan ER and Fenofibric Acid DR in Combination with Statins

On April 18th 2016, the FDA announced retraction of prior approvals related to combinations of statins with niacin extended release (ER) and statins with fenofibric acid delayed release (DR).¹ The decision to remove these indications was prompted by evidence from three large published trials, which failed to show reductions in important cardiovascular events when either niacin ER or fenofibric acid DR was added to statin therapy in the populations studied.²⁻⁴ The FDA has concluded that existing evidence does not support that reducing triglycerides or raising of high-density lipoprotein cholesterol (HDL) with any drug, including fenofibric acid or niacin, improves cardiovascular risk in patients on statins and therefore, the benefit of either combination with statins no longer exceeds the potential risk. The VA Pharmacy Benefits Management (PBM), Medical Advisory Panel (MAP) and VISN Pharmacist Executives' (VPEs) position on statin-niacin and statin-fibrate combination therapies are consistent with the recent FDA ruling and with the 2014 VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction.

In August 2014, the Department of Veterans Affairs Pharmacy Benefits Management (PBM), Medical Advisory Panel (MAP), VISN Pharmacist Executives (VPEs), Office of National Program Director for Cardiology and the Center for Medication Safety (VA MedSAFE) released a bulletin detailing the results of two of the three trials which pertained to niacin. Based upon the evidence from those trials, provider considerations and recommendations for managing patients on statin-niacin combinations were provided (See below).⁶

PROVIDER CONSIDERATIONS/RECOMMENDATIONS (From Bulletin)

1. *Review and discuss the use of niacin with your patients who are currently receiving niacin or being considered for niacin at their next visit.*
 - a. *Niacin should not be routinely used or combined with statins. Evidence supports statin monotherapy as the having the best evidence for cardiovascular risk reduction.*
 - b. *If niacin was added solely for the purpose of increasing HDL-C in a patient receiving at least a moderate dose statin, PBM recommends discontinuing the niacin. A recent meta-analysis of lipid therapies (niacin, fibrates or cholesterol ester transfer protein [CETP] inhibitors) added to statins to increase HDL-C were not shown to improve cardiovascular outcomes.*
 - c. *Niacin may be recommended for initiation or continued as monotherapy in selected patients not able to tolerate statins, as clinically appropriate. However, providers should discuss the risks (as observed in HPS2-THRIVE) of niacin therapy (including the use of over the counter niacin products) with their patients if the decision is made to initiate or to continue niacin therapy.*
2. *Assess statin choice and dosage at the time of discontinuation of niacin. If appropriate, consider increasing the dose of the particular statin and/or changing to a higher potency statin at recommended dosing for the underlying condition or cardiac risk profile.*
 - a. *If the patient is not receiving at least a moderate dose statin, increase the dose of statin as tolerated to moderate (reduces baseline LDL-C 30 to <50%) or high dose (reduces baseline LDL-C >50%), as clinically indicated and discontinue niacin.*
 - b. *If the statin dose has been maximized but the desired percent reduction in baseline LDL-C has not been achieved (30 to >50%), consider switching to an alternate high potency statin (e.g., atorvastatin or rosuvastatin).*
3. *If, despite the potential risks and lack of outcomes evidence with statin combination therapy, a clinician and patient choose combination therapy for further reducing LDL-C, consider continuation of niacin or alternatively, replacement of niacin with ezetimibe or bile acid sequestrants (e.g., colestipol, cholestyramine). However, it is important to recognize, and for patients to be aware, that the addition of other lipid lowering drugs (e.g., niacin, fibrates, ezetimibe*, bile acid sequestrants) to statin based therapy for the purpose of lowering LDL-C levels has not been proven to reduce cardiovascular events and*

therefore, these combinations should not be routinely used.

4. In patients who are on statins and have severely elevated triglyceride levels (>500 mg/dL), despite life-style modification and management of secondary causes of hypertriglyceridemia, formulary fish oil should be used rather than niacin. If fish oils inadequately reduced triglycerides or if the patient cannot tolerate fish oils, the best option for combination therapy is unclear given the potential for interaction/harm and the lack of evidence for benefit in reducing cardiovascular events or for preventing pancreatitis when a statin is combined with either a fibrate or niacin for reducing triglyceride levels. Therefore, caution should be used when considering combining a statin with either a fibrate or niacin in these patients.

*Ezetimibe improved nonfatal events in a study of >18,000 patients with acute coronary syndrome when added to moderate dose statins over a period of 6 years.⁶ This trial was published in 2015, after the bulletin had been released.

The VA PBM, MAP and VPEs have not previously advocated for combining statins with fibrates, including fenofibrate or fenofibric acid. Therefore recommendations for avoiding routine combinations of statins with fibrates remain.⁷⁻⁹

The VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction was finalized in December 2014. The guideline recommends against routine combination therapy with statins and other lipid lowering therapies for reducing cardiovascular risk due to the lack of evidence.¹⁰⁻¹¹

In light of the available evidence and the recent FDA withdrawal of approved indications for combination therapy, VA providers are encouraged to individually reconsider the appropriateness of combination therapy with niacin or fibrates in their patients on statin therapy.

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