OPTUMRx

Therapeutic Class Overview
Bile Acid Sequestrants

INTRODUCTION

- Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids as well as steroid hormones. The bile acid sequestrants work to modify lipids by binding to bile acids in the intestine through anion exchange, which ultimately causes an interruption of their reabsorption. This reduction leads to feedback regulation to increase the conversion of cholesterol to bile acids. The major action of these agents is to reduce low density lipoprotein cholesterol (LDL-C) specifically. The overall reduction in cholesterol causes intrahepatic cholesterol to be reduced, which in turn enhances LDL receptor expression. The receptors then bind LDL-C from the plasma causing a further reduction in blood cholesterol. Through a different mechanism, the bile acid sequestrants cause a minimal increase in high density lipoprotein cholesterol (HDL-C). The actions of bile acid sequestrants also have the potential to increase serum triglycerides (TG) *(Grundy et al 2019)*.
- There are 3 available bile acid sequestrants: cholestyramine (Prevalite, Questran, and Questran Lite), colesevelam (Welchol), and colestipol (Colestid, Flavored Colestid). Cholestyramine and colestipol are both available as powders to be mixed with water or juice, and are typically administered once or twice daily with meals. Colestipol is also available as a tablet, and the powder formulation is available in 2 flavors: tasteless and orange flavored. Colesevelam is available as a powder and tablet and is typically administered once or twice daily.
- Bile acid sequestrants are generally recommended as optional secondary agents when other second-line agents cannot be used (eg, intolerance to ezetimibe or intolerance to higher doses of statins) for further reduction of LDL-C. When administered as monotherapy, reductions in LDL-C with bile acid sequestrants have ranged from 10% to 30%, depending on the dose administered *(Grundy et al 2019)*.
- In 2018, the American College of Cardiology (ACC)/American Heart Association (AHA) and a variety of other organizations released a guideline on the management of blood cholesterol *(Grundy et al 2019)*. Statins remain the cornerstone of therapy; however, this guideline also contains very specific recommendations in a newly defined “very high risk of atherosclerotic cardiovascular disease [ASCVD]” category, which refers to patients who continue to have LDL-C levels ≥ 70 mg/dL after maximizing statin therapy. In these patients, the guideline recommends considering the addition of a non-statin medication, such as ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, to a maximally tolerated statin. Bile acid sequestrants may also be used in patients taking maximally tolerated statins (with or without ezetimibe), including patients with intermediate ASCVD risk in whom high-intensity statins are advisable but not accepted or tolerable. However, the clinical utility of bile acid sequestrants is limited due to the absence of ASCVD outcomes data when used in combination with statins. Bile acid sequestrants can increase TG levels and should therefore be avoided in patients with high TG levels or familial dysbetalipoproteinemia *(Grundy et al 2019)*.
- This review will focus on cholestyramine, colesevelam hydrochloride, and colestipol.
- Medispan class: Bile Acid Sequestrants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Colestid (colestipol hydrochloride)	✔
Questran, Questran Lite†, Prevalite* (cholestyramine)	✔
Welchol (colesevelam hydrochloride)	✔ (tablet and powder for oral suspension only)‡

* Prevalite is a branded generic of Questran/Questran Lite.

† Questran and Questran Lite were FDA-approved by a new drug application (NDA), but the products were discontinued by BMS in 2013. Par Pharmaceuticals markets both Questran and Questran Lite branded generics and cholestyramine and cholestyramine lite.

‡ The chewable bar formulation of Welchol was FDA-approved in April 2019, but is not available and is noted as discontinued by the FDA.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Cholestyramine	Colesevelam	Colestipol
Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet	✔ *		✔ †
Adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia		✔	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)		✔	
To reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification		✔	
Relief of pruritus associated with partial biliary obstruction‡	✔		

* May be useful to lower LDL-C levels in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
† For the reduction of elevated serum total cholesterol and LDL-C.
‡ Has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit elevated cholesterol as part of their disease.

(Prescribing information: Colestid & Flavored Colestid granule 2018, Colestid tablets 2017, Prevalite 2020, Questran 2016, Welchol 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trial data consistently demonstrate the superiority of the bile acid sequestrants over placebo for the management of hyperlipidemia *(Bays et al 2006, Blankenhorn et al 1987, Brown et al 1990, Davidson et al 2001, Huijgen et al 2010, Hunninghake et al 2001, Insull et al 2001, Knapp et al 2001, Stein et al 2010, Rosenson et al 2006).*
- Clinical trial data demonstrate that the addition of a bile acid sequestrant to another lipid-lowering agent has the potential to produce further reductions in lipid levels compared to monotherapy with either of the agents *(Ballantyne et al 2004, Blankenhorn et al 1987, Brown et al 1990, Davidson et al 2001, Eriksson et al 1998, Huijgen et al 2010, Hunninghake et al 2001, Knapp et al 2001).*
- The Lipid Research Clinical Coronary Primary Prevention trial (LRC-CPPT) demonstrated that compared to placebo, treatment with cholestyramine reduced the risk of coronary heart disease death and/or nonfatal myocardial infarction by 19% ($p < 0.05$) in asymptomatic males with primary hypercholesterolemia *(LRC-CPPT 1984).*
- Several clinical trials have demonstrated the safety and efficacy of colesevelam as adjunct therapy in adults with T2DM. Compared to placebo, the addition of colesevelam resulted in modest, but statistically significant reductions in glycosylated hemoglobin (HbA1c) levels *(Bays et al 2008, Fonseca et al 2008, Goldberg et al 2008, Goldberg et al 2012, Goldfine et al 2010, Jialal et al 2009, Rigby et al 2010, Rosenstock et al 2010, Zieve et al 2007).* A meta-analysis of 17 trials evaluating colesevelam and colestimide (not available in the U.S.) estimated that addition of a bile acid sequestrant lowered HbA1c levels by a mean difference of −0.55% in patients with T2DM *(Hansen et al 2017).*

- One meta-analysis evaluated the effects of bile acid sequestrants (colesevelam, colestimide, and cholestyramine) on lipid and blood glucose profiles *(Mazidi et al 2017)*. Based on data from 15 clinical trials (as pooled estimates [weighted mean difference]), bile acid sequestrants were reported to increase serum TG levels by 0.54 mg/dL, with total cholesterol reduced by 1.18 mg/dL and LDL-C by 0.24 mg/dL vs placebo. The reduction in HbA1c was 0.83%.

CLINICAL GUIDELINES

- In general, statins are recommended first-line for the reduction of LDL-C; if the target goal is not achieved, the addition of ezetimibe, or bile acid sequestrants in select patients, should be considered. If further LDL-C reduction is needed to achieve target LDL-C goals in select patients, PCSK9 inhibitors may be considered (*American Diabetes Association 2021, Cosentino et al 2020, Grundy et al 2019, Handelsman et al 2020, Knuuti et al 2020, Mach et al 2020, Newman et al 2020, Rosenzweig et al 2019*).
  - Statin intolerance: In patients with mild statin-associated adverse effects, rechallenge with a statin should be considered to achieve a maximal LDL-C lowering by using a modified dosing regimen, an alternate statin, or in combination with nonstatin therapy. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use randomized controlled trial-proven nonstatin therapy that is likely to provide net clinical benefit.
- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guideline recommends LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary therapy to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. In statin-intolerant patients, an alternate statin, lower statin dose or frequency, or addition of a nonstatin LDL-C therapy such as ezetimibe, colesevelam, bempedoic acid, or PCSK9 inhibitor should be considered. Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk (*Garber et al 2020, Handelsman et al 2020*).

- **American Heart Association (AHA)/American College of Cardiology (ACC): Guideline on the Management of Blood Cholesterol** *(Grundy et al 2019)*
  - Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions.
  - Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.
    - Ezetimibe is the most commonly used non-statin agent. It lowers LDL-C levels by 13% to 20% and has a low incidence of adverse effects.
    - Bile acid sequestrants reduce LDL-C levels by 15% to 30% depending on the dose. Bile acid sequestrants are not absorbed and do not cause systemic adverse effects, but they are associated with gastrointestinal complaints (eg, constipation) and can cause severe hypertriglyceridemia when fasting TGs are ≥ 300 mg/dL.
    - PCSK9 inhibitors are powerful LDL-lowering drugs. They generally are well tolerated, but long-term safety remains to be proven.
  - When administered to patients with severe hypercholesterolemia who are taking maximally tolerated statins with or without ezetimibe, bile acid sequestrants have demonstrated LDL-C lowering efficacy. However, the clinical utility of bile acid sequestrants is limited by the absence of ASCVD outcomes data when used in combination with statins, as well as twice-daily dosing, high pill burden, the absence of well-tolerated generic formulations, drug interactions, and the potential for TG elevation. Nonetheless, in patients with very severe hypercholesterolemia, adding bile acid sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor may be considered.

- **American Heart Association (AHA): Cardiovascular Risk Reduction in High-Risk Pediatric Patients** *(de Ferranti et al 2019)*
  - Treatment for HeFH should include statins, a low-saturated-fat diet high in fiber, adequate physical activity, and a smoke-free environment.
  - If a 50% reduction of LDL-C is not achieved or if there are adverse effects to multiple statins (rare), then ezetimibe or a bile acid binding resin can be added as a second-line agent.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE): Consensus Statement on the Comprehensive T2DM Management Algorithm** *(Garber et al 2020)*

- For glycemic control, colesevelam is among the second-line agents that may be utilized after metformin. However, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl-peptidase 4 inhibitors (DPP-4i), thiazolidinediones, and basal insulin are preferred over colesevelam in the suggested hierarchy of usage.
- Colesevelam lowers glucose modestly, does not cause hypoglycemia, and decreases LDL-C. A perceived modest efficacy for both HbA1c and LDL-C lowering as well as gastrointestinal intolerance (constipation and dyspepsia, which occurs in 10% of users), may contribute to limited use. In addition, colesevelam can increase TG levels in individuals with pre-existing TG elevations, but this is somewhat preventable by concomitant statin use.
- For T2DM patients with dyslipidemia, lifestyle modifications are followed by first-line therapy with statins. If the desirable LDL-C goal is not reached with a statin, second-line options to lower LDL-C include statin intensification or the addition of ezetimibe, a PCSK9 inhibitor, colesevelam, or niacin.

- **National Lipid Association (NLA) for Patient-Centered Management of Dyslipidemia Part 1** (*Jacobson et al 2015*)
  - The NLA guideline recommends non-statin drug therapy (cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid) may be considered for patients with contraindications for, or intolerance to, statin therapy. Combination drug therapy with a statin plus a second (or third) agent that further lowers non-HDL-C and LDL-C may be considered for patients who have not attained their treatment goals for atherogenic cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy.

- **American Association for the Study of Liver Diseases (AASLD): Primary Biliary Cholangitis Practice Guidance** *(Lindor et al 2018)*
  - Ursodeoxycholic acid (UDCA) is recommended for patients with primary biliary cholangitis who have abnormal liver enzyme values regardless of histologic stage.
  - For patients requiring bile acid sequestrants, UDCA should be given at least 1 hour before or 4 hours after the bile acid sequestrant.
  - Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
  - Colestipol and colesevelam are available as pills and are preferred by some patients over the powder preparation of cholestyramine.
  - Colesevelam was not effective in a single placebo-controlled trial that enrolled patients with cholestatic pruritus who had already failed other resins.

SAFETY SUMMARY

- Contraindications
  - Cholestyramine is contraindicated in patients with complete biliary obstruction.
  - Colesevelam is contraindicated in patients with serum TG concentrations > 500 mg/dL, a history of hypertriglyceridemia-induced pancreatitis, or a history of bowel obstruction.
- Warnings and precautions
  - Bile acid sequestrants have been reported to increase serum TG concentrations and should be used with caution in patients with hypertriglyceridemia.
  - Bile acid sequestrants may produce or severely worsen pre-existing constipation. Use is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction.
  - Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K.
    - Chronic use of colestipol may be associated with an increased bleeding tendency due to hypoprothrombinemia from vitamin K deficiency.
  - Bile acid sequestrants may reduce the absorption of other drugs. It is generally advised that other medications be taken at least 1 hour before or 4 to 6 hours after the administration of bile acid sequestrants.
  - Powder formulations of bile acid sequestrants contain phenylalanine, which may be harmful to patients with phenylketonuria.

- Colestipol hydrochloride is a chloride form of an anion exchange resin; thus, prolonged use may lead to the development of hyperchloremia acidosis.

- Adverse effects
  - Bile acid sequestrants are not well absorbed from the gut; they are generally regarded as safe with limited systemic side effects. However, they may cause problems in the gastrointestinal tract, such as constipation, diarrhea, and flatulence.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
cholestyramine (Prevalite, Questran)	Powder	Oral	Twice daily	Powder should be mixed with fluids prior to administration May be administered in 1 to 6 doses per day
colesevelam (Welchol)	Powder Tablet	Oral	Powder: Once daily Tablets: Once or twice daily	Powder should be mixed with fluids prior to administration Take with a meal
colestipol (Colestid)	Granules Tablet	Oral	Once or twice daily	Granules should be mixed with fluids prior to administration

See the current prescribing information for full details

CONCLUSION

- The major function of the bile acid sequestrants class of medications is to decrease LDL-C levels. In general, these agents work by binding to bile acids in the intestine through anion exchange causing an interruption of the reabsorption of bile acids. This reduction in bile acids leads to feedback regulation on the conversion of cholesterol to bile acids. Currently, there are 3 bile acid sequestrants available: cholestyramine, colesevelam, and colestipol. All agents are typically administered once or twice daily, and are available generically.
- The bile acid sequestrants are all FDA-approved for adjunctive treatment in patients with hypercholesterolemia. Cholestyramine is also FDA-approved for relief of pruritus associated with partial biliary obstruction. In addition, colesevelam is FDA-approved as monotherapy in children 10 to 17 years of age for the treatment of HeFH and as adjunct therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Clinical trial data consistently demonstrate the superiority of the bile acid sequestrants over placebo for the management of hyperlipidemia.
- The addition of a bile acid sequestrant to another lipid-lowering agent has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents.
- In the LRC-CPPT trial, treatment with cholestyramine demonstrated a mortality benefit in reducing the risk of coronary heart disease death and/or nonfatal myocardial infarction in asymptomatic males with primary hypercholesterolemia.
- Trials have also demonstrated that as add-on therapy to existing antidiabetic regimens, colesevelam achieved modest reductions in HbA1c compared to placebo.
- Lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When pharmacologic therapy to lower LDL-C is required, initial treatment with a statin is recommended.
- The 2018 AHA/ACC guidelines recommend that cholesterol absorption inhibitors, bile acid sequestrants, and PCSK9 inhibitors are all options in patients who do not achieve therapeutic goals with statins alone *(Grundy et al 2019)*.

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