Bile Acid Sequestrants Step Therapy Program

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LoB: ACA

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) BCBSKC will provide coverage for brand name bile acid sequestrants when the following criteria are met. The brand name bile acid sequestrants affected are:

- Questran®, Questran® Light, Prevalite® (cholestyramine oral suspension – Par, Upsher Smith, generics)
- Colestid® (Colestipol oral suspension and micronized tablets – Pfizer, generics)
- Welchol® (colesevelam tablets and oral suspension – Sankyo Pharma)

When Policy Topic is covered
Step therapy rules have been developed to encourage the use of generic bile acid sequestrants (Step 1) prior to a brand name bile acid sequestrants (Step 2). If the step therapy rule is not met at the point of service, coverage will be determined by the criteria below.

Step 1: cholestyramine oral suspension, colestipol oral suspension, colestipol micronized tablets and Prevalite oral suspension.
Step 2: Welchol tablets, Welchol oral suspension, Questran oral suspension, Questran light oral suspension, Colestid oral suspension, and Colestid micronized tablets.

CRITERIA
1. Authorization for a Step 2 product can be made if the patient has tried one Step 1 product.

When Policy Topic is not covered
The use of bile acid sequestrants is considered investigational for all other indications.

Considerations
Bile acid sequestrants require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
Bile acid sequestrants are effective agents for the management of primary hypercholesterolemia that work by binding bile acid in the intestine to form an insoluble complex that is fecally secreted without systemic absorption. Three different agents are available in the U.S. Cholestyramine is supplied as a
powder for oral suspension, colestipol is available as a powder for oral suspension and in a tablet formulation, and Welchol is available in a tablet formulation and an oral suspension. Cholestyramine and colestipol (oral suspension packets and tablets) are available generically. The powder formulations must be mixed into a suspension with fluids or with foods. Colesipol and Welchol are dosed once to twice daily. Cholestyramine is recommended to be given twice daily, but 1 to 6 doses per day may be administered.1-4

**INDICATIONS**

Cholestyramine is indicated for use as adjunctive therapy for the lowering of serum cholesterol in patients with primary hypercholesterolemia who have not responded to diet or other measures alone. Colestipol is indicated as adjunctive therapy to diet for the reduction of elevated serum total and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet. Welchol is indicated as an adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin). Welchol should be be used for glycemic control in type 1 diabetes or for treating diabetic ketoacidosis. Welchol has not been studied in type 2 diabetes or in combination with a dipeptidyl peptidase 4 inhibitor. Welchol has not been studied in children aged < 10 years or in pre-menarchal girls. Welchol has not been studied in Fredrickson type I, III, IV and V dyslipidemias.1-4

**Rationale**

Several guidelines are available that mention bile acid sequestrant products.5-6 In 2012 the American Association of Clinical Endocrinologists’ (AACE) published a guideline for the management of dyslipidemia and prevention of atherosclerosis.6 Regarding bile acid sequestrants (cholestyramine, colestipol, Welchol), the guidelines state that these agents primarily reduce LDL-C by 15% to 25% by binding bile acids at the intestinal level. High-density lipoprotein cholesterol (HDL-C) increases by 4% to 8%; triglyceride (TG) levels may increase. In a primary prevention trial called LRC-CPPT (Lipid Research Clinics-Coronary Primary Prevention Trial), cholestyramine reduced major coronary artery disease events by 19%. In the GLOWS (Glucose-Lowering Effect of WelChol Study), Welchol significantly lowered plasma glucose among those with type 2 diabetes. Welchol decreases glucose and hemoglobin A1C (HbA1C) by approximately 0.5%.

**Type 2 Diabetes – Improving Glycemic Control**

Of the bile acid sequestrants, Welchol has the most robust data and is indicated to improve glycemic control in adults with type 2 diabetes mellitus.1,7-11 Welchol has been studied in combination with metformin, sulfonylureas, and insulin in those with type 2 diabetes. The expected reduction in HbA1C with Welchol is generally described as modest and is approximately 0.5% to 1.0%.1,5,12-14 Data are available but are limited with the other bile acid sequestrants regarding improvement in glycemic control in those with type 2 diabetes.5,7,15-16 Many other agents are used in the management of type 2 diabetes and Welchol is an option in selected populations.5,12,14,17-18

**Pediatric Data**

Welchol is indicated for use in children aged 10 to 17 years1 and data are available.24-25 Although not indicated, some data are available with other bile acid sequestrants in children (e.g., cholestyramine, colestipol), although the data are from older studies.19-22 Bile acid sequestrants mainly decrease LDL-C and total cholesterol. The AACE guidelines for the management of dyslipidemia and the prevention of atherosclerosis state that Welchol is indicated in children but notes that cholestyramine has also been used in children.6 Studies with bile acid sequestrants in the pediatric population have noted a 15% to 20% reduction in LDL-C with relatively low doses. Therefore, initiate therapy at low doses (< 8 grams daily of cholestyramine or < 10 grams daily of colestipol) regardless of body weight. Do not use bile acid sequestrants in children with elevated TG levels. Because bile acid sequestrants are not absorbed, they have limited systemic side effects.
Adverse Effects (AEs)
In non-comparative trials, Welchol was relatively well tolerated and had minimal AEs.1 The prescribing information for Welchol lists the rates of constipation and dyspepsia (placebo) as 11% (7%) and 8.3% (3.5%), respectively, in the treatment of primary hyperlipidemia. In patients treated with type 2 diabetes mellitus, 6.7% of patients given Welchol vs. 3.2% in the placebo group discontinued from the diabetes trials due to AEs, with the difference mainly being driven by gastrointestinal (GI) AEs such as abdominal pain and constipation. The rates of constipation and dyspepsia with Welchol (placebo) were 8.7% (2.0%) and 3.9% (1.4%), respectively.1 In contrast, at the end of the first year of the LRC-CPPT trial cholestyramine therapy led to a high rate of patients reporting constipation (39%), abdominal gas (32%), and heartburn (27%).27 In addition to the intolerable GI AEs (e.g., constipation, dyspepsia, flatulence, bloating) often associated with these agents, some patients find the powder for suspension preparations unpalatable due to their sandy, gritty taste. Studies performed prior to the approval of Welchol suggest that compliance with bile acid sequestrants is poor and only about 50% of patients continue therapy for longer than one year. Direct comparative studies between products are needed to fully ascertain differences in tolerability and compliance. The 2012 guidelines for the management of dyslipidemia and prevention of atherosclerosis from AACE state that bile acid sequestrants have high discontinuation rates due to GI AEs.6 Welchol appears to be better tolerated.

Drug-Drug Interactions
Drug interactions among the agents differ. Although colesevelam is similar to the other bile acid sequestrants in its mechanism of action, it differs in its biochemical structure, which may reduce its potential for drug interactions compared with the other bile acid sequestrants.14

Pregnancy Category
Colesevelam is in Pregnancy Category B.1 Cholestyramine is in Pregnancy Category C.4 The colestipol product labeling does not note a pregnancy category but emphasizes low systemic absorption which suggests little harm in pregnancy. A standard reference that evaluates medications used in pregnancy notes colestipol to be assigned a pregnancy risk category of B, but recommends that the agent be halted during gestation due to the potential reduction in the absorption of fat-soluble vitamins.26

References:


**Other References Utilized**

Billing Coding/Physician Documentation Information
N/A The bile acid sequestrants are considered a pharmacy benefit.

Additional Policy Key Words
Policy Number: 5.01.594

Policy Implementation/Update Information
07/2014 New Policy titled Bile Acid Sequestrants Step Therapy Program
07/2015 Annual Revision – no changes made
07/2016 Annual Revision- no changes to policy statement
07/2017 Annual Revision- no changes to policy statement
07/2018 Annual review – no changes made

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