New Medicine Assessment

Colesevelam for Cardiovascular Disease (CVD) prevention in hyperlipidaemia when the patient is intolerant of all other options

Recommendation:

Amber 0 rating.

Suitable for prescribing in primary care following recommendation or initiation by a specialist.

Little or no specific monitoring required.

Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.

Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Date: September 2024

Details of Review

Name of medicine (generic & brand name)**:** Colesevelam / Cholestagel

Strength(s) and form(s): 625 mg film-coated tablets

Dose and administration: As monotherapy, the recommended starting dose of Colesevelam is 6 tablets per day taken as 3 tablets twice per day with meals or 6 tablets once per day with a meal. The maximum recommended dose is 7 tablets per day.

The recommended dose of Colesevelam for combination with a statin with or without ezetimibe is 4 to 6 tablets per day.

BNF therapeutic class / mode of action: Bile Acid Sequestrant

Colesevelam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. The LDL-C lowering mechanism of bile acid sequestrants has been previously established as follows: As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α -hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effects of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein receptors. A concomitant increase in very low density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels.

Licensed indication(s):

- Colesevelam tablets co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone.
- Colesevelam tablets as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-C in adult patients with primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated.
- Colesevelam tablets can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia

Proposed use (if different from, or in addition to, licensed indication above):

Cardiovascular Disease (CVD) prevention in hyperlipidaemia when the patient is intolerant of all other options

Course and cost:

- 180 x 625mg film coated tablets = £72.25

At a dose of 4 tablets / day = £586 / year, at a dose of 6 tablets / day = £879 / year

Current standard of care/comparator therapies:

Colestyramine 50 x 4g =£10.76, at max. dose of 6 x 4g / day = £471 / year

Colestyramine (Questran) is licensed for the Primary prevention of coronary heart disease in men between 35 and 59 years of age and with primary hypercholesterolaemia who have not responded to diet and other appropriate measures.

Relevant NICE / OTHER guidance:

SIGN 149 • Risk estimation and the prevention of cardiovascular disease –

BILE ACID SEQUESTRANTS

The effect of statins can be accentuated by combining them with agents which interfere with bile acid absorption, for example cholestyramine and colestipol. These drugs lower serum, total and LDL cholesterol and cause mild, and usually transient, elevation of triglyceride levels.

Clinical trial evidence from the 1980s demonstrates the benefit of these drugs as monotherapy in primary CHD prevention, but their side-effect profile (gastrointestinal irritation, constipation) frequently makes them unacceptable to most patients and adherence to therapy may be problematic. Nevertheless, they may be considered for the treatment of marked hypercholesterolaemia in individuals at high risk (for example, FH) where statins are contraindicated; or they may be added to maximally-tolerated statin therapy to enhance cholesterol reduction in such individuals. Whereas doubling the dose of a statin produces only a six percent further reduction in LDL cholesterol, adding a moderate dose of a bile acid sequestrant to a statin can further lower LDL cholesterol by 12–16%.

Background and context

Colesevelam acts in a similar way to cholestyramine, but it exhibits several important differences. First, colesevelam was developed to have enhanced specificity, greater affinity, and higher capacity for binding bile acids than cholestyramine. This was achieved by engineering long hydrophobic side chains to the backbone polymer, which maximize hydrophobic interactions with bile acids, adding to the effects of the ionic bonds that bind bile acids in the two first generation compounds. Thus colesevelam is at least 2 to 3 times more potent on a weight basis than cholestyramine. Hence smaller amounts of colesevelam can be used effectively, with less adverse effects, and with greater tolerability through its packaging into tablets instead of a slurry of liquefied powder. Although the usual dose requires taking 6 to 7 tablets (625 mg/tablet) per day, this is still considerably more acceptable than the ingestion of an insoluble powder several times a day. There is no need for titration of the dose of colesevelam to allow for tolerability, unlike that commonly required by first generation sequestrants.

Summary of evidence

Summary of efficacy data in proposed use:

The first indication that lowering of LDL-C through biliary diversion could successfully reduce CVD events comes from the Program on the Surgical Control of the Hyperlipidemias (POSCH).[1] In this study of 838 men and woman with hypercholesterolemia who had survived a first myocardial infarction, biliary diversion and LDL-C reduction was achieved by means of partial ileal bypass surgery. LDL-C levels were reduced by 37.7% over a 5-year period compared to that in the control group and this was accompanied by a significant 35% reduction in combined coronary heart disease (CHD) mortality and non-fatal myocardial infarction. In the modern context, this study is highly relevant because it constitutes clinical trial evidence supporting the contention that lowering of LDL-C can explain most if not all of the beneficial effect on CVD in the long term clinical trials with statins.

The strongest evidence that the effects of surgically induced biliary diversion are mirrored by sequestrant-induced biliary depletion comes from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and the NHLBI Type II Coronary Intervention Study. In the CPPT, one of the first large studies to definitively associate a drug-induced reduction in LDLC with a reduction in CHD risk, 3806 men were randomized to cholestyramine or placebo for a mean of 7.4 years; the cholestyramine group had a 19% reduction in CHD risk ($p < 0.05$) that was associated with a 13% decrease in LDL-C levels. The NHLBI Type II Coronary Intervention Study evaluated the effects of cholestyramine versus placebo on the progression of coronary angiographic lesions after 5 years of treatment in 116 patients.[2] LDL-C levels were reduced by 26% in the cholestyramine and 5% in the placebo groups ($p < 0.001$) and coronary lesions progressed in 49% of placebo treated patients versus 32% of cholestyramine-treated patients ($p < 0.05$). There have also been several secondary intervention trials using bile acid sequestrants in combination with niacin, statins and/or fibrates which were uniformly and in some cases dramatically positive, but in which it was not possible to tease out the effect of the bile acid sequestrants from the other agents used. Finally a meta-analysis of 8 bile acid sequestrant studies found that monotherapy significantly reduced cardiac mortality. While there have been no such intervention trials with colesevelam, the evidence to date supports the notion that lowering of LDL-C through bile acid depletion is associated with beneficial effects on CHD.[3 4]

Ye et al[5] conducted study to examine adherence to colesevelam amongst newly treated patients with hyperlipidaemia and/or type 2 diabetes mellitus and relationship to the risk of major cardiovascular events; with adherence calculated as the number of days covered by prescription claims in the 1-year period after colesevelam treatment was initiated. A total of 42,549 patients with hyperlipidaemia and/or type 2 diabetes mellitus were assigned to cohorts based on their adherence, with the primary outcome as time to hospitalisation for acute myocardial infarction (AMI) or stroke. Of the included 42,549 patients in this analysis, 7968 (18.7%) were adherent to treatment with 6197 (14.6%) were deemed partially adherent and 28,384 (66.7%) were not adherent. After adjustments for patient demographics and clinical characteristics, patients in the adherent cohort were ~ 43% less likely to experience hospitalisation due to AMI or stroke (0.57, 95% CI 0.44–0.73, $p<0.0001$ compared to the non-adherent cohort).

Schwab et al[6] performed a similar retrospective analysis of data derived from healthcare insurance claims, with the aim of evaluating composite cardiovascular and acrovascular complication events over a period of 12 months. Six hundred and seventy nine patients with hypercholesterolaemia initiated on treatment with colesevelam were compared with 1388 treated with ezetimibe. Lower odds of composite cardiovascular events (odds ratio [OR] 0.54, 95 % confidence interval [CI] 0.30-0.97) within 12 months for patients treated with colesevelam compared with ezetimibe. Unadjusted OR was lower (0.52, 95 % CI 0.30-0.90) and there was no statistically significant OR for macrovascular complications (0.821, 95 % CI 0.49-1.35) identified between the two cohorts.

Ross et al[7] conducted a systematic review and meta-analysis of randomized controlled trials to assess the effect of cholestyramine and colesevelam on reducing the risk of coronary artery disease (CAD). Nineteen randomized controlled trials with a total of 7021 study participants were included. Cholestyramine 24 g/d was associated with a reduction in LDL-C of 23.5 mg/dL (95% confidence interval [CI] −26.8,−20.2; N=3806) and a trend toward reduced risk of CAD (odds ratio 0.81, 95% CI 0.70–1.02; P=0.07; N=3806), whereas colesevelam 3.75 g/d was associated with a reduction in LDL-C of 22.7 mg/dL (95% CI −28.3, −17.2; N=759). They estimated that cholestyramine was associated with an odds ratio for CAD of 0.63 (95% CI 0.52–0.77; P=6.3×10−6) and colesevelam with an odds ratio of 0.64 (95% CI 0.52–0.79,

P=4.3×10−5), which were not statistically different from bile acid sequestrants (BAS) clinical trials (P>0.05).

Conclusions—The cholesterol lowering effect of bile acid sequestrants may translate into a clinically relevant reduction in coronary artery disease.

Summary of safety data:

The most frequently occurring adverse reactions are flatulence and constipation, found within the gastrointestinal disorders system organ class.

Nervous system disorders
Common: Headache
Gastrointestinal disorders
Very common: Flatulence, constipation
Common: Vomiting, diarrhoea*, dyspepsia*, abdominal pain, abnormal stools, nausea, abdominal distension
Uncommon: Dysphagia
Very rare: Pancreatitis
Not known: Intestinal obstruction
Musculoskeletal and connective tissue disorders
Uncommon: Myalgia
Investigations
Common: Serum triglycerides increased
Uncommon :Serum transaminases increased

very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Strengths and limitations of the evidence:

Strengths – Large number of trials showing colesevelam reduces LDL-C and that lower LDL-C is associated with a reduced risk of CVD / CAD.

Limitations – No studies have been conducted that directly demonstrate whether treatment with Colesevelam as monotherapy or combination therapy has any effect on cardiovascular morbidity or mortality.

Summary of evidence on cost effectiveness:

180 x 625mg film coated tablets = £72.25

At a dose of 4 tablets / day = £586 / year, at a dose of 6 tablets / day = £879 / year.

Treatment is more expensive than statins +/- ezetimibe and colestyramine.

However, patient compliance is greater with colesevelam than colestyramine, with less side effects.

Prescribing and risk management issues:

Prescribing should only be initiated when the patient is intolerant of all other options

References

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