

NEW DRUG EVALUATION

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COLESEVELAM

Colesevelam is a bile acid sequestrant licensed as monotherapy and in combination with a statin to reduce low density lipoprotein cholesterol. Clinical efficacy is modest with reductions of about 15% when used as monotherapy and additional reductions of about 10% in combination. There are no long-term clinical outcome data, and it has not been compared with similar drugs such as colestyramine. It appears to be well tolerated with adverse effects limited to the gastrointestinal system, but there is an absence of long-term safety data. Colesevelam with or without a statin is not recommended for generalised use on the basis of currently available evidence.

What is it?

Colesevelam (Cholestagel[®], Genzyme) is a bile acid sequestrant (BAS).¹ Unlike other BAS (e.g. colestyramine and colestipol) it is formulated as a tablet (625 mg strength). As with other BAS, it is not absorbed but remains in the gastrointestinal tract where it binds bile acids, restricting their absorption and recirculation in lipid synthesis.^{1,2} It is licensed for use alone or in combination with a statin for the reduction of low density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolaemia (PH), at a daily maintenance dose of four to six tablets in one or two divided doses (2.5 to 3.75 g/day).¹

How effective is it?

A randomised, double-blind, 24-week, phase III trial investigated colesevelam as monotherapy. Four different doses of colesevelam (2.25 to 4.50 g/day) were compared with placebo in patients with mild to moderate PH (n = 467).³ A significant dose-dependent reduction in mean LDL-C and mean total cholesterol (TC) was demonstrated at each colesevelam dose (p < 0.001 for each dose vs. placebo). The mean change from baseline in LDL-C and TC for patients treated with 3.75 g/day (the licensed maintenance dose) was -15% and -7%, compared with 0% and +1% with placebo, respectively.

Two randomised, double-blind, placebo controlled, phase II trials have compared the efficacy of colesevelam in PH patients in combination with a UK-available statin.^{4,5} The primary end point in both studies was the mean change in LDL-C from baseline.

In a six week comparative study mean changes in LDL-C were as follows:

- Placebo -4% (n = 33)
- Colesevelam 2.25 g/day -8% (n = 36)
- Colesevelam 3.75 g/day -16% (n = 37)
- Simvastatin 10 mg/day -26% (n = 35)
- Simvastatin 20 mg/day -34% (n = 39)
- Colesevelam 3.75 g plus simvastatin 10 mg daily -42% (n = 34)
- Colesevelam 2.25 g plus simvastatin 20 mg daily -42% (n = 37)

In a four week study colesevelam 3.75 g plus atorvastatin 10 mg daily (n = 18) produced a significantly greater reduction in LDL-C (-48%) than either agent alone (colesevelam -12%, n = 16; atorvastatin -38%, n = 18) and placebo (+3%, n = 19), and was similar to that achieved with atorvastatin 80 mg/day (-53%, n = 20).⁵ Median high density lipoprotein cholesterol increased significantly for all groups including placebo. Median triglyceride (TG) levels significantly decreased in patients taking atorvastatin monotherapy (p < 0.05), but were not significantly affected by colesevelam alone or in combination, or with placebo.

How safe is it?

In short-term studies colesevelam was well tolerated with few systemic effects.^{2,6} Adverse effects are generally mild and limited to the gastrointestinal tract. The most commonly reported adverse effects were flatulence (11%), constipation (10%) and dyspepsia (6%).¹

All BAS have the potential to reduce absorption of other drugs through non-specific binding and in common with other BAS, colesevelam may inhibit the absorption of vitamin K, thyroxine, and oral contraceptive hormones.^{1,2,7} Colesevelam does not affect the absorption of sodium valproate, warfarin, digoxin, quinidine, or metoprolol but does reduce absorption of verapamil.^{1,6,8} If a drug interaction cannot be excluded, the drug should be administered at least one hour before or four hours after colesevelam to minimise the risk of affecting drug absorption.¹

There is currently no long-term safety data for colesevelam. All suspected adverse reactions to black triangle drugs, including colesevelam, should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

What other options are there?

Statins are highly effective at lowering LDL-C and are established as first choice options for the treatment of hypercholesterolaemia.⁹⁻¹¹ Simvastatin and pravastatin are available as generic products with low acquisition costs and are proven to reduce cardiovascular events in long-term studies.¹² Other BAS are available but these are formulated as sachets for mixing into drinks (at least 100 to 150 ml per dose) and typically require taking ≥ 4 times daily.^{1,9}

When should it be used?

There are no direct comparisons of colestevlam with other BAS. Cross-study comparisons suggest similar efficacy but colestyramine and colestipol have substantially lower acquisition costs and longer-term evidence of efficacy and safety is available to support their use.^{7,9}

Colesevelam is available in a more convenient dose form than existing BAS, however its efficacy is modest, with mean reductions of

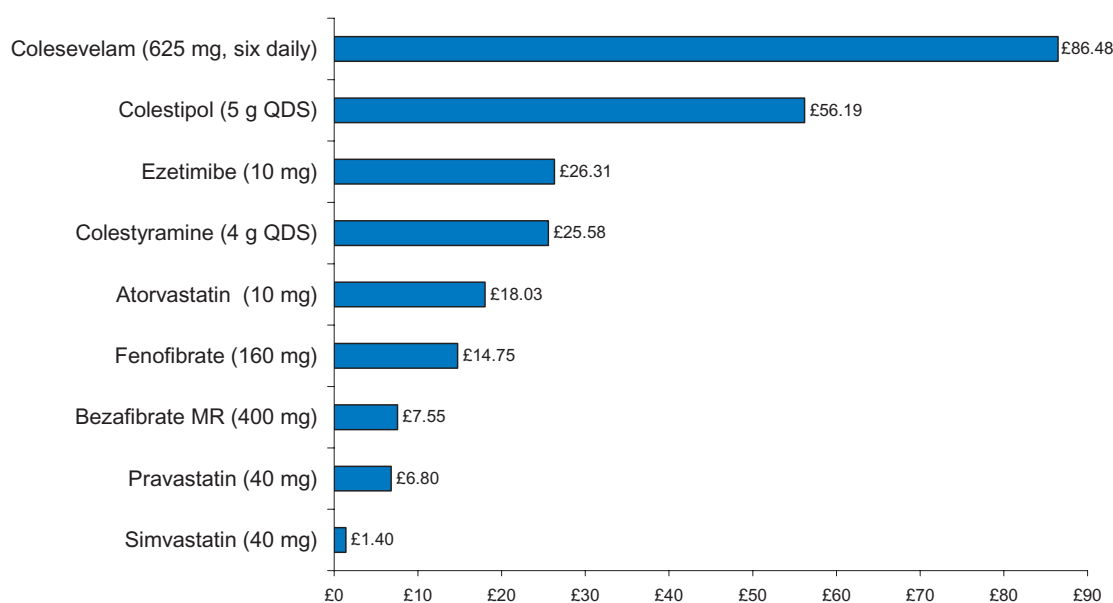
How much does it cost?

LDL-C of about 15% when used as monotherapy and about 10% additional LDL-C lowering when combined with a statin.³⁻⁵ As with other BAS, colestevlam results in small increases in TG levels.^{1,2,7} There are no studies of colestevlam compared with a statin plus ezetimibe, which represents a less costly option than colestevlam alone. The NSF for coronary heart disease recommends a target reduction in LDL-C of 30% from baseline.¹⁰ This would not be achieved in most patients using colestevlam monotherapy.

NICE state that anion exchange resins (i.e. BAS) should not routinely be offered for the primary prevention of cardiovascular disease.¹¹

Colesevelam may be considered as an option in occasional patients needing BAS because of failure to achieve targets with, or intolerance to, statins and other lipid-lowering agents if they are not able to take a less expensive option. However, more widespread use is not currently recommended.

Cost for 28 days treatment (source: Drug Tariff & NHS dm+d, July 2008)



Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY G – guidance, RCT – randomised controlled trial, R – review.

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