

# Bile acid malabsorption: colesevelam

Evidence summary

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[www.nice.org.uk/guidance/esuom22](http://www.nice.org.uk/guidance/esuom22)

## Key points from the evidence

The content of this evidence summary was up-to-date in October 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

The use of colesevelam for bile acid malabsorption is reported in 2 small case series (n=45 and n=5), which found that colesevelam improved diarrhoea and gastrointestinal symptoms in people with this condition. A randomised controlled trial (RCT) found no improvement in outcomes with colesevelam in 24 women with diarrhoea-predominant irritable bowel syndrome, 4 of whom had evidence of bile acid malabsorption. However, the study may have been underpowered to detect any differences between the groups. Colesevelam appears to be well tolerated; the most frequent adverse effects are flatulence and constipation.

**Regulatory status:** off-label

<b>Effectiveness</b>	<b>Safety</b>
<ul style="list-style-type: none"><li>• In an RCT in 24 women with diarrhoea-predominant irritable bowel syndrome, there was no statistically significant difference in gastric, small bowel and overall colonic transit, or ascending colonic emptying with colesevelam compared with placebo.</li><li>• Colesevelam improved diarrhoea and other gastrointestinal symptoms in 45 people with a diagnosis of cancer and symptoms of bile acid malabsorption.</li><li>• Colesevelam resolved diarrhoea in 5 people with bile acid malabsorption who could not tolerate colestyramine.</li></ul>	<ul style="list-style-type: none"><li>• According to the summary of product characteristics, the adverse effects of colesevelam include flatulence and constipation, which affect at least 1 in 10 people who take it. Other adverse effects include headache, vomiting, diarrhoea, dyspepsia, abdominal pain, abnormal stools, nausea and abdominal distension.</li><li>• No patients withdrew from treatment because of adverse effects in the RCT.</li><li>• Out of 45 patients in the larger case series, 5 withdrew from treatment because of adverse effects.</li></ul>

Patient factors	Resource implications
<ul style="list-style-type: none"><li>• Colesevelam is available in tablet form. The other available bile acid sequestrants, colestyramine and colestipol, are powders that require mixing with water or other liquids and may taste unpleasant.</li><li>• Colesevelam may affect the bioavailability of other medicines.</li><li>• Colesevelam may be taken once daily when used to treat hypercholesterolaemia. However, it is unclear whether a once-daily dose is effective for bile acid malabsorption.</li></ul>	<ul style="list-style-type: none"><li>• At the dosage used in the studies, colesevelam currently costs between £0.97 and £2.91 per day.</li><li>• The dosage of colestyramine licensed for the relief of diarrhoea currently costs between £0.65 and £1.29 per day for standard sachets. Sugar-free sachets are more expensive.</li><li>• Colestipol is not currently licensed for bile acid malabsorption. However, the cost is estimated to be between £0.50 and £3.01 per day.</li></ul>

## Key points

Colesevelam is a bile acid sequestrant that is licensed by the [European Medicines Agency](#) to reduce levels of total cholesterol and low-density lipoprotein cholesterol in people with primary hypercholesterolaemia.

This evidence summary describes the efficacy and safety of colesevelam for treating bile acid malabsorption. The use of colesevelam for this indication is off-label.

No RCTs were identified that compared colesevelam with placebo or other treatments in people with bile acid malabsorption. One RCT was identified that compared colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome, 4 of whom had evidence of bile acid malabsorption. Two case series were identified that reported on the efficacy of colesevelam for bile acid malabsorption.

In a small RCT, [Odunsi-Shiyanbade et al. \(2010\)](#) compared the effects of colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome. Four of the women had raised fasting serum  $7\alpha$ -hydroxy-4-cholesten-3-one (7C4), a marker for bile acid malabsorption. After treatment, there was no statistically significant difference in

gastric, small bowel and overall colonic transit, or ascending colonic emptying, with colesevelam compared with placebo. Stool passage was statistically significantly easier in women who received colesevelam compared with women who received placebo. However, it is unclear whether this difference is of clinical importance. There was no difference between the groups in stool frequency or consistency.

Results were not reported separately for the women with evidence of bile acid malabsorption. However, higher baseline fasting serum levels of 7C4 were associated with higher ascending colon half-lives (a marker for reduced colonic transit times;  $p < 0.001$ ) after treatment with colesevelam. The authors suggested that 7C4 levels may predict responsiveness to colesevelam in women with diarrhoea-predominant irritable bowel syndrome.

In one case series, [Wedlake et al. \(2009\)](#) found that colesevelam improved diarrhoea, frequency and urgency of defecation, steatorrhoea, abdominal pain and faecal incontinence in 45 people with a diagnosis of cancer and symptoms of bile acid malabsorption for 3 months or more. The most common reasons for bile acid malabsorption were pelvic radiotherapy and small-bowel resection or right hemicolectomy. In 30 of these people, symptoms had not responded to previous treatment with another bile acid sequestrant, colestyramine.

In the other case series, [Puleston et al. \(2005\)](#) found that diarrhoea resolved with colesevelam in 5 people with bile acid malabsorption who could not tolerate colestyramine.

The [summary of product characteristics](#) for 625 mg colesevelam tablets states that the most frequent adverse effects are flatulence and constipation, which affect at least 1 in 10 people.

In [Odunsi-Shiyanbade et al. \(2010\)](#), the most common adverse effects of colesevelam (reported in between 17 and 40% of people) were headache, flatulence, nausea, lower abdominal cramps and green-coloured stools. The authors state that these adverse effects occurred at similar rates in the placebo group, although the statistical significance of any differences between the groups was not reported. There were no serious adverse events and no women had to stop the study because of an adverse event.

In [Wedlake et al. \(2009\)](#), adverse effects reported with colesevelam included bloating, constipation, heartburn, abdominal pain, flatulence, perianal soreness, weight gain and leg

and facial oedema. Each of these adverse effects occurred in 7% or fewer people. Five people (11%) stopped colesevelam because of adverse effects. No adverse effects were seen in the 5 people taking colesevelam in the case series reported by [Puleston et al. \(2005\)](#).

#### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Overview for healthcare professionals

### Regulatory status of colesevelam

Colesevelam ([Cholestagel](#), Sanofi) is licensed by the [European Medicines Agency](#) to reduce levels of total cholesterol and low-density lipoprotein cholesterol in people with primary hypercholesterolaemia. Colesevelam can be prescribed in combination with statins and/or ezetimibe, or as monotherapy if statins are inappropriate or not tolerated.

Colesevelam is not licensed to treat bile acid malabsorption; therefore, the use of colesevelam for this indication is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using colesevelam outside its authorised indications.

## Evidence statements

No randomised controlled trials (RCTs) were identified that compared colesevelam with placebo or other treatments in people with bile acid malabsorption. One RCT was identified that compared colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome, 4 of whom had evidence of bile acid malabsorption. Two case series were identified that reported on the efficacy of colesevelam for bile acid malabsorption.

- A small RCT compared the effects of colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome. Four of the women had raised fasting serum 7-hydroxy-4-cholesten-3-one (7C4), a marker for bile acid malabsorption. After treatment, there was no statistically significant difference in gastric, small bowel and overall colonic transit, or ascending colonic emptying, with colesevelam compared with placebo. Stool passage was statistically significantly easier in women who received colesevelam compared with those who received placebo. However, it is unclear whether this difference is of clinical importance. There was no difference between the groups in stool frequency or consistency (Odunsi-Shiyanbade et al. 2010).
- According to a retrospective review of electronic patient records and a patient questionnaire, colesevelam improved diarrhoea, frequency and urgency of defecation, steatorrhoea, abdominal pain and faecal incontinence in 45 people with a diagnosis of cancer and symptoms of bile acid malabsorption for 3 months or more (Wedlake et al. 2009). The most common reasons for bile acid malabsorption were pelvic radiotherapy (64%) and small-bowel resection or right hemicolectomy (27%). Symptoms had not responded to prior colestyramine treatment in 30 people (67%).
- Colesevelam resolved diarrhoea in 5 people with bile acid malabsorption who could not tolerate colestyramine (Puleston et al. 2005).
- According to the summary of product characteristics for Cholestagel, the most frequent adverse effects are flatulence and constipation, which affect at least 1 in 10 people. Other common adverse effects include headache, vomiting, diarrhoea, dyspepsia, abdominal pain, abnormal stools, nausea and abdominal distension.

## Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is

given in the [Evidence review](#) section.

## Efficacy

No RCTs were identified that compared colesevelam with placebo or other treatments in people with bile acid malabsorption.

One RCT was identified that compared the effects of colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome, 4 of whom had evidence of bile acid malabsorption.

Two case series were identified that reported on the efficacy of colesevelam for treating bile acid malabsorption. One included people who developed bile acid malabsorption after cancer treatment; the other included people with bile acid malabsorption who could not tolerate colestyramine.

### **Colesevelam compared with placebo in diarrhoea-predominant irritable bowel syndrome**

[Odunsi-Shiyanbade et al. \(2010\)](#) conducted a small [double-blind](#) RCT that assessed the effect of colesevelam on gastrointestinal and colonic transit, bowel function, and colonic permeability in 24 women with diarrhoea-predominant irritable bowel syndrome. The women were randomised to receive 1.875 g colesevelam or placebo twice daily for 12–14 days. Three women in the placebo group and 1 in the colesevelam group had evidence of bile acid malabsorption (fasting serum 7C4 61 nanograms/ml or more [an indirect measure of bile acid synthesis that is used to screen for bile acid malabsorption]). However, the results for these women were not reported separately.

The primary end points were colonic geometric centre at 24 hours (a measure of colonic transit, with a higher geometric centre implying a faster colonic transit) and ascending colon emptying half-life (the time taken for 50% of a radiolabeled meal to empty from the colon). Other outcomes included bowel function (for example, daily bowel frequency and consistency) and colonic mucosal permeability.

After treatment, there was no statistically significant difference in gastric, small bowel and overall colonic transit, or ascending colonic emptying with colesevelam compared with placebo. Higher baseline fasting serum levels of 7C4 were associated with higher ascending colon half-lives (a marker for reduced colonic transit times;  $p < 0.001$ ) after

colesevelam treatment. The authors suggested that 7C4 levels may predict responsiveness to colesevelam in women with diarrhoea-predominant irritable bowel syndrome.

There was no difference between the colesevelam and placebo groups in the number of bowel movements (mean 2 per day in both groups; statistical significance not reported) or in stool consistency (Bristol Stool Form Scale, mean score 4.57 with placebo and 3.78 with colesevelam,  $p=0.12$ ). Stool passage was statistically significantly easier in women who received colesevelam, compared with women who received placebo (4.18 with colesevelam compared with 4.39 with placebo, on a scale of 1 to 7, with 1 representing manual disimpaction and 7 incontinence;  $p=0.047$ ). However, it is unclear whether this difference is of clinical importance. There was no significant difference in colonic mucosal permeability between the colesevelam and placebo groups.

See table 1 for a summary of the results.

### **Colesevelam for treating bile acid malabsorption (case series)**

Wedlake et al. (2009) reported a retrospective review of 45 people (37 women) who had completed cancer treatment or were undergoing treatment for ongoing or relapsed cancer, and who had chronic symptoms of bile acid malabsorption for 3 months or more for which they had been prescribed colesevelam (1.25 g 3 times daily with or after food). The most common reasons for bile acid malabsorption were pelvic radiotherapy (64%) and small-bowel resection or right hemicolectomy (27%). Bile acid malabsorption was confirmed by SeHCAT scan in 27 people (60%). Symptoms had not responded to prior colestyramine treatment in 30 people (67%).

Hospital electronic patient records were reviewed retrospectively for all 45 people to assess the effects of 2–6 weeks of colesevelam treatment on 6 gastrointestinal symptoms, which had been recorded prospectively in the patient record. Outcomes were also assessed by a patient questionnaire, which was sent to 36 of the 45 people included in the case series (excluding those who were terminally ill). Out of 36 people, 30 (83%) responded. The median treatment period in these people was 27 months. When data from the electronic patient records and questionnaires were combined, it was found that 30 people (67%) were still taking colesevelam at their last follow-up (up to 4 years).

In people who experienced each symptom, the following were improved after colesevelam treatment (proportions of people):

- diarrhoea (record review 88%; questionnaire 80%)
- frequency of defecation (record review 77%; questionnaire 83%)
- steatorrhoea (record review 76%; questionnaire 80%)
- urgency of defecation (record review 76%; questionnaire 80%)
- abdominal pain (record review 74%; questionnaire 58%)
- faecal incontinence (record review 69%; questionnaire 74%).

Based on the review of patient records, of the 30 people whose symptoms did not respond to prior colestyramine treatment, colesevelam improved diarrhoea in 83%, urgency of defecation in 74%, frequency of defecation in 72%, steatorrhoea in 71%, abdominal pain in 68% and faecal incontinence in 62%.

Puleston et al. (2005) reported on the use of colesevelam in 5 people with bile acid malabsorption who could not tolerate colestyramine. Colesevelam resolved diarrhoea with no adverse effects at doses between 1.25 g and 3.75 g per day for 2–7 months.

**Table 1 Summary of** Odunsi-Shiyanbade et al. (2010)

	Placebo	Colesevelam	Analysis
Randomised	n=12	n=12	
Efficacy	n=12	n=12	
Geometric centre at 24 hours <sup>a</sup>	3.30±0.3	2.68±0.32	p=0.18
Ascending colon emptying half-life <sup>b</sup>	14.9±3.58	18.85±2.88	NR
Stool frequency per day (mean ± standard error)	2.25±0.34	2.14±0.31	NR
Stool consistency (Bristol Stool Form Scale; mean ± standard error)	4.57±0.35	3.78±0.27	p=0.12
Ease of stool passage (scale, 1–7; mean ± standard error)	4.39±0.11	4.18±0.14	p=0.047
Safety	n=12	n=12	
People reporting serious adverse events	0	0	NR

Headache	33% 4/12	40% 5/12	NR
Lower abdominal cramps	0% 0/12	17% 2/12	NR
Flatulence	8% 1/12	24% 3/12	NR
Green-coloured stools	17% 2/12	17% 2/12	NR
Nausea	24% 3/12	17% 2/12	NR
<p>n, number of people; NR, not reported.</p> <p><sup>a</sup> A measure of colonic transit: a higher geometric centre implies a faster colonic transit.</p> <p><sup>b</sup> The time taken for 50% of a radiolabeled meal to empty from the colon.</p>			

## Safety

The [summary of product characteristics](#) for colesevelam states that the most frequent adverse effects are flatulence and constipation. These affected at least 1 in 10 people in controlled clinical studies and during post-approval use for hypercholesterolaemia. Other common adverse effects (affecting between 1 in 100 and 1 in 10 people) are headache, vomiting, diarrhoea, dyspepsia, abdominal pain, abnormal stools, nausea, abdominal distension and raised serum triglycerides.

The [summary of product characteristics](#) notes that colesevelam may affect the bioavailability of other medicines. Therefore, when a clinically important drug interaction cannot be excluded, colesevelam should be taken at least 4 hours before or 4 hours after the other medicine to minimise the risk of reduced absorption. Colesevelam tablets can be taken once a day if needed. However, it is not known whether a once-daily dose is effective for treating bile acid malabsorption. In [Odunsi-Shiyanbade et al. \(2010\)](#), 1.875 g colesevelam was taken twice daily and, in [Wedlake et al. \(2009\)](#), 1.25 g was taken 3 times daily. The exact dosage regimens were not reported in [Puleston et al. \(2005\)](#).

In [Odunsi-Shiyanbade et al. \(2010\)](#), the most common adverse effects seen with

colesevelam were headache (40%), flatulence (24%), nausea (17%), lower abdominal cramps (17%) and green-coloured stools (17%). The authors state that these adverse effects occurred at similar rates in the placebo group, although the statistical significance of any differences between the groups was not reported. There were no serious adverse events and no women had to stop the study because of an adverse event. See table 1 for more details.

Wedlake et al. (2009) reported bloating, constipation, heartburn, abdominal pain, flatulence, perianal soreness, weight gain, and leg and facial oedema in people treated with colesevelam. Each of these adverse effects occurred in 7% or fewer people treated with colesevelam. After at least 1 year of treatment, 9 people (20%) developed vitamin D deficiency.

Adverse effects led to 5 people stopping colesevelam (11%). Other reasons for stopping treatment were lack of efficacy (n=5); having to take too many tablets or finding them difficult to swallow (n=3); resolution of symptoms (n=2); and switching to another medicine (n=1). One person was lost to follow-up.

In Puleston et al. (2005), no adverse effects were reported by the 5 people with bile acid malabsorption who had not previously tolerated colestyramine.

## Cost effectiveness and cost

According to the Drug Tariff (September 2013), 180 colesevelam tablets (625 mg) cost £87.36.

In the studies reported in this evidence summary, between 2 and 6 colesevelam tablets (625 mg) were taken daily. Current costs for 1.25 g colesevelam per day are £0.97, and for 3.75 g per day £2.91.

## Relevance to NICE guidance programmes

The use of colesevelam for bile acid malabsorption is not appropriate for referral for a NICE technology appraisal and it is not currently planned into any other work programme.

NICE has issued diagnostic guidance on SeHCAT (tauroselcholic [<sup>75</sup>selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-

predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection (NICE diagnostics guidance 7). This recommends SeHCAT for use in research for diagnosing bile malabsorption in these groups.

## Intervention and alternatives

Colesevelam is a bile acid sequestrant that forms a polymeric gel in the gastrointestinal tract. It binds bile acids in the small bowel and prevents the secretory action of bile acids on the colon.

Colesevelam (Cholestagel, Sanofi) is licensed by the European Medicines Agency to reduce levels of total cholesterol and low-density lipoprotein cholesterol in people with primary hypercholesterolaemia. Colesevelam can be prescribed in combination with statins and/or ezetimibe, or as monotherapy if statins are inappropriate or not tolerated.

Colesevelam is not licensed to treat bile acid malabsorption; therefore, the use of colesevelam for this indication is off-label.

## Condition

Bile acid malabsorption is one of several causes of chronic diarrhoea. Estimates of the prevalence of chronic diarrhoea in western populations are between 4% and 5%. Chronic diarrhoea is one of the most common reasons for referral to a gastrointestinal clinic and can account for as many as 1 in 20 referrals.

Bile acids are synthesised in the liver from cholesterol before being transferred in conjugated form to the bile ducts and stored in the gall bladder. After a meal, the gall bladder contracts and bile acids flow into the intestinal lumen to emulsify dietary fats. Most of the bile acids (97%) are then reabsorbed and returned to the liver.

In people with bile acid malabsorption, excess bile in the colon stimulates electrolyte and water secretion, which results in chronic watery diarrhoea. Bile acid malabsorption causes diarrhoea by 1 or more of the following mechanisms:

- inducing secretion of sodium and water
- increasing colonic motility

- stimulating defecation
- inducing mucus secretion
- damaging the mucosa, thereby increasing mucosal permeability.

Bile acid malabsorption has been divided into 3 types depending on aetiology:

- type 1: following ileal resection, disease or bypass of the terminal ileum
- type 2: primary idiopathic malabsorption
- type 3: associated with cholecystectomy, peptic ulcer surgery, chronic pancreatitis, coeliac disease or diabetes mellitus.

Although not life threatening, bile acid malabsorption can have a considerable impact on lifestyle and quality of life because the associated increased frequency of bowel motions may limit the person's ability to travel or leave the house.

## Alternative treatment options

After a definitive diagnosis of bile acid malabsorption, people can be treated with bile acid sequestrants that bind with bile acids in the small bowel and prevent the secretory action of bile acids on the colon. There are currently 3 bile acid sequestrants available: colestyramine, colestipol and colesevelam.

Colestyramine and colestipol are anion exchange resins that have a high affinity for bile acids in the gastrointestinal tract, and form complexes with them. An important disadvantage of colestyramine and colestipol is that they are powders that require mixing with water or another liquid and may have an unpleasant taste, which can lead to poor tolerance of and adherence to treatment. Adverse effects include constipation, nausea, borborygmi, flatulence, bloating and abdominal pain. Colesevelam binds to bile acids with higher affinity than colestyramine or colestipol. It is available in tablet form.

The [summary of product characteristic for Questran](#) states that colestyramine is licensed for the relief of diarrhoea associated with ileal resection, Crohn's disease, vagotomy and diabetic vagal neuropathy, and to control radiation-induced diarrhoea. It is also licensed for hypercholesterolemia and the primary prevention of coronary heart disease, and for the relief of pruritus associated with partial biliary obstruction and primary biliary cirrhosis.

Colestipol is not licensed for treating bile acid malabsorption. The [summary of product characteristics for Colestid](#) states that it is licensed for treating hypercholesterolaemia, alone or in combination with additional lipid-lowering agents.

## Evidence review: efficacy

No [randomised controlled trials](#) (RCTs) were identified that compared colesevelam with placebo or other treatments in people with bile acid malabsorption.

One published RCT was identified that compared colesevelam with placebo in 24 women with diarrhoea-predominant irritable bowel syndrome, 4 of whom had evidence of bile acid malabsorption.

Two case series were identified that reported on the efficacy of colesevelam for treating bile acid malabsorption. One included people who developed bile acid malabsorption after cancer therapy; the other included people with bile acid malabsorption who could not tolerate colestyramine.

## Colesevelam compared with placebo for diarrhoea-predominant irritable bowel syndrome

[Odunsi-Shiyanbade et al. \(2010\)](#) conducted a small [double-blind](#) RCT that assessed the effect of colesevelam on gastrointestinal and colonic transit, bowel function and colonic permeability in 24 women with diarrhoea-predominant irritable bowel syndrome. The women were randomised to receive 1.875 g colesevelam or matching placebo twice daily for 12–14 days.

Three women in the placebo group and 1 in the colesevelam group had evidence of bile acid malabsorption (fasting serum 7-hydroxy-4-cholesten-3-one [7C4] 61 nanograms/ml or more [an indirect measure of bile acid synthesis that is used to screen for bile acid malabsorption]). However, the results for these women were not reported separately.

The mean age of the women was 43 years in the placebo group and 42 years in the colesevelam group. Mean body mass index was 29 kg/m<sup>2</sup> in the placebo group and 32 kg/m<sup>2</sup> in the colesevelam group. Baseline colonic geometric centre at 24 hours (a measure of colonic transit, with a higher geometric centre implying a faster colonic transit) was 3.4 in both groups. Mean fasting serum 7C4 was 38.2 nanograms/ml in the placebo group and

31.8 nanograms/ml in the colesevelam group. It is unclear whether differences between the baseline characteristics of the groups were statistically significant. Allocation was concealed, all women completed the study and adherence was 100%.

The primary end points were colonic geometric centre at 24 hours and ascending colon emptying half-life (the time taken for 50% of a radiolabeled meal to empty from the colon). Other outcomes included bowel function (for example, daily bowel frequency and consistency) and colonic mucosal permeability.

After treatment, there was no statistically significant difference in gastric, small bowel and overall colonic transit, or ascending colonic emptying with colesevelam compared with placebo.

Compared with placebo, colonic geometric centre was lower at 4 hours (0.39 lower on average; statistical significance of difference not reported) and 24 hours (0.62 lower on average,  $p=0.18$ ) in women receiving colesevelam, suggesting slower colonic transit. However, the difference between the groups at 24 hours, the primary outcome, was not statistically significant and at 48 hours the results were similar in both groups (placebo 4.47 compared with colesevelam 4.6; statistical significance not reported). Gastric emptying half-life was, on average, 36.5 minutes longer in women receiving colesevelam, compared with placebo. However, this result did not reach statistical significance ( $p=0.14$ ). Similarly, ascending colon half-life was, on average, 3.95 hours longer in women receiving colesevelam compared with women receiving placebo. The statistical significance of this difference was not reported.

There was no difference between the colesevelam and placebo groups in the number of bowel movements (mean 2 per day in both groups; statistical significance not reported) or in stool consistency (Bristol Stool Form Scale, mean score 4.57 with placebo and 3.78 with colesevelam;  $p=0.12$ ). Stool passage was statistically significantly easier in women who received colesevelam, compared with women who received placebo (4.18 with colesevelam compared with 4.39 with placebo, on a scale of 1 to 7, with 1 representing manual disimpaction and 7 incontinence;  $p=0.047$ ). However, it is unclear whether this difference is of clinical importance. There was no significant difference in colonic mucosal permeability between the colesevelam and placebo groups.

Higher baseline fasting serum levels of 7C4 were significantly associated with higher ascending colon half-lives (a marker for reduced colonic transit times;  $p<0.001$ ) in women who received colesevelam. The authors suggested that 7C4 levels may predict

responsiveness to colesevelam in women with diarrhoea-predominant irritable bowel syndrome.

## Colesevelam for treating bile acid malabsorption (case series)

Wedlake et al. (2009) reported a retrospective chart review of 45 people who had completed cancer treatment or were undergoing treatment for ongoing or relapsed cancer, and who had chronic symptoms of bile acid malabsorption for 3 months or more for which they had been prescribed colesevelam (1.25 g 3 times a day with or after food) between 2004 and 2007.

Hospital electronic patient records were reviewed retrospectively for all 45 people to assess the effects of 2–6 weeks of colesevelam treatment on 6 gastrointestinal symptoms, which had been recorded prospectively in the patient record. Outcomes were also assessed by a patient questionnaire, which was sent to 36 of the 45 people included in the case series (excluding those who were terminally ill). Out of 36 people, 30 (83%) responded. The median treatment period in these people was 27 months. When data from the electronic patient records and questionnaires were combined, it was found that 30 people (67%) were still taking colesevelam at their last follow-up (up to 4 years).

Of the 45 people, 37 were women and 8 were men. Their median age was 58 years. Probable causes of bile acid malabsorption were pelvic radiotherapy (n=29), right hemicolectomy or small-bowel resection (n=12), upper gastrointestinal surgery (n=2), high-dose chemotherapy (n=1) and new-onset Crohn's disease (n=1).

Bile acid malabsorption was confirmed by SeHCAT scan in 27 people (7-day absorption 10% or less). SeHCAT scan was not undertaken in the remaining 18 people because they were very ill, could not attend appointments for a scan, or developed loose stools immediately after ileal resection.

Symptoms had not responded to prior colestyramine treatment in 30 (67%) of the 45 people. The other 15 people were prescribed colesevelam as a first treatment either because colestyramine was considered unsuitable or because they requested a tablet rather than a powder.

In people who experienced each symptom, the following were improved after colesevelam

treatment (proportions of people):

- diarrhoea (record review 88%; questionnaire 80%)
- frequency of defecation (record review 77%; questionnaire 83%)
- steatorrhoea (record review 76%; questionnaire 80%)
- urgency of defecation (record review 76%; questionnaire 80%)
- abdominal pain (record review 74%; questionnaire 58%)
- faecal incontinence (record review 69%; questionnaire 74%).

Based on the review of patient records, of the 30 people who did not respond to prior colestyramine treatment, colesevelam improved diarrhoea in 83%, urgency of defecation in 74%, frequency of defecation in 72%, steatorrhoea in 71%, abdominal pain in 68% and faecal incontinence in 62%.

Puleston et al. (2005) reported on the use of colesevelam in 5 people with bile acid malabsorption who could not tolerate colestyramine.

Bile acid malabsorption was caused by right hemicolectomy in 2 people, radiation enteritis in 1 person, and both radiation enteritis and right hemicolectomy in 1 person. In the fifth person, bile acid malabsorption was idiopathic. Two people were male and 3 were female. Their average age was 47 years.

Colesevelam resolved diarrhoea with no adverse effects at doses between 1.25 g per day and 3.75 g per day for 2–7 months. It also resolved steatorrhoea and lethargy in 1 person (these outcomes were not reported on for the other 4 people).

## Evidence review: safety

### Colesevelam compared with placebo for diarrhoea-predominant irritable bowel syndrome

In Odunsi-Shiyanbade et al. (2010), the most common adverse effects seen with colesevelam were headache (colesevelam 40% compared with placebo 33%), flatulence

(colesevelam 24% compared with placebo 8%), nausea (colesevelam 17% compared with placebo 24%), lower abdominal cramps (colesevelam 17% compared with placebo 0%) and green-coloured stools (17% in both groups). The statistical significance of any differences between the groups was not reported. There were no serious adverse events and no participants had to stop the study because of an adverse event.

## Colesevelam for treating bile acid malabsorption (case series)

Wedlake et al. (2009) reported bloating (n=3, 7%), constipation (n=2, 4%), heartburn (n=2, 4%), abdominal pain (n=1, 2%), flatulence (n=1, 2%), perianal soreness (n=1, 2%), weight gain (n=1, 2%), and leg and facial oedema (n=1, 2%) in people taking colesevelam. After at least 1 year of treatment, 9 people (20%) developed vitamin D deficiency.

Adverse effects led to 5 people stopping colesevelam (11%). Other reasons for stopping treatment were lack of efficacy (n=5); having to take too many tablets or finding them difficult to swallow (n=3); resolution of symptoms (n=2); and switching to another medicine (n=1). One person was lost to follow-up.

No adverse effects were reported by Puleston et al. (2005) in the 5 people with bile acid malabsorption, who had not previously tolerated colestyramine.

## Other sources of safety information

The summary of product characteristics for colesevelam states that the most frequent adverse effects are flatulence and constipation. These affected at least 1 in 10 people in controlled clinical studies and during post-approval use for hypercholesterolaemia. Headache, vomiting, diarrhoea, dyspepsia, abdominal pain, abnormal stools, nausea, abdominal distension and increased levels of serum triglycerides were seen in between 1 in 100 and 1 in 10 people. Dysphagia, myalgia and increased levels of serum transaminases affected between 1 in 1000 and 1 in 100 people. Pancreatitis was a very rare adverse effect, affecting less than 1 in 10,000 people.

The summary of product characteristics notes that colesevelam may affect the bioavailability of other medicines. Therefore, when a clinically important drug interaction cannot be excluded, colesevelam should be taken at least 4 hours before or 4 hours after the other medicine to minimise the risk of reduced absorption. The tablets can be taken

once a day if needed. However, it is not known whether a once-daily dose is effective in bile acid malabsorption. In [Odunsi-Shiyanbade et al. \(2010\)](#), 1.875 g colesevelam was taken twice daily and, in [Wedlake et al. \(2009\)](#), 1.25 g was taken 3 times daily. Colesevelam was taken at doses between 1.25 g and 3.75 g per day in [Puleston et al. \(2005\)](#). However, the exact dosage regimens were not reported.

## Evidence review: economic issues

### Cost

No cost effectiveness studies were identified.

According to the [Drug Tariff](#) (September 2013), 180 colesevelam tablets (625 mg) cost £87.36. A dosage of 6 tablets (3.75 g) daily in divided doses was used in [Odunsi-Shiyanbade et al. \(2010\)](#) and [Wedlake et al. \(2009\)](#). In [Puleston et al. \(2005\)](#) dosages ranged between 2 and 6 tablets (1.25–3.75 g) per day. Current costs for 1.25 g colesevelam per day are £0.97, and for 3.75 g per day £2.91.

According to the [Drug Tariff](#) (September 2013), 50 colestyramine 4 g oral powder sachets cost £10.76. The cost of 50 sugar-free sachets is £28.10. The [summary of product characteristic for Questran](#) states that the usual dosage of colestyramine for the relief of diarrhoea is 3 to 6 sachets (12–24 g) daily. This dosage currently costs between £0.65 and £1.29 per day for standard sachets, and £1.69 and £3.37 for sugar-free sachets.

According to [MIMS](#) (September 2013), 30 colestipol 5 g sachets cost £15.05. It is unclear what dose should be used for bile acid malabsorption because this is an unlicensed indication. The [summary of product characteristics for Colestid](#) states that the daily dose of colestipol for hypercholesterolaemia is 1 to 6 sachets (5–30 g). This dose currently costs between £0.50 and £3.01 per day.

### Current drug usage

[NHS prescription cost analysis for England, 2012](#) reported that 21,200 prescriptions for colesevelam were dispensed in primary care in England in 2012 at a net cost of £1,534,800. It is not known for which indications colesevelam was prescribed, but most of the prescriptions are likely to have been for hypercholesterolaemia.

No estimate of the use of colesevelam for bile acid malabsorption in UK clinical practice was available at the time this evidence summary was prepared.

## Evidence strengths and limitations

No randomised controlled trials were identified that compared colesevelam with placebo or other treatments (such as colestyramine or colestipol) in people with bile acid malabsorption.

Odunsi-Shiyanbade et al. (2010) was a small RCT in 24 women with diarrhoea-predominant irritable bowel syndrome. Only 4 women had evidence of bile acid malabsorption and results for these women were not reported separately. Therefore, the results of the study cannot be applied directly to the population considered in this evidence summary. In addition, the study included women only and the results may not be generalisable to men.

Although it was randomised, controlled and blinded, and allocation was concealed and follow-up complete, the study has other limitations. Firstly, it was small and therefore may not have had the statistical power to show a true difference between colesevelam and placebo, should one exist. In addition, follow-up was short term (only 12–14 days).

It is unclear whether differences in baseline characteristics between the groups were statistically significant and may have biased the results. For example, mean fasting serum 7-hydroxy-4-cholesten-3-one (7C4, an indirect measure of bile acid synthesis that is used to screen for bile acid malabsorption) was higher in the placebo group (38.2 nanograms/ml compared with 31.8 nanograms/ml in the colesevelam group). Similarly, of the 4 women with bile acid malabsorption (7C4 61 nanograms/ml or more), 3 were in the placebo group and 1 was in the colesevelam group. However, the study authors report that there were no clinically important differences in 7C4 levels in the 2 groups.

Wedlake et al. (2009) was a review of the electronic patient records of 45 people with a diagnosis of cancer and symptoms of bile acid malabsorption for 3 months or more. Most were women (n=37). Although data on gastrointestinal symptoms had been recorded prospectively, the study had a retrospective design, which poses a risk of inaccurate recording of findings. In addition, it was uncontrolled and unblinded and reported results from a single centre. All people had completed treatment for cancer or were undergoing treatment for ongoing or relapsed cancer and the results might not be generalisable to other populations. In addition, some people had more than one condition that may have

caused their symptoms; some were prescribed other medicines in addition to colesevelam; and some may have benefited from changes in diet.

Puleston et al. (2005) was a small case series of 5 people, reported in a letter. This study also had a retrospective design and was uncontrolled and unblinded.

The authors of all studies note that their findings warrant further investigation in properly powered prospective double-blind controlled trials.

## Summary for patients

A summary written for patients is available on the NICE website.

## References

Bristol-Myers Squibb Holdings Limited (2012) Questran powder for oral suspension 4 g: summary of product characteristics [online; accessed 18 September 2013]

European Medicines Agency (2012) Cholestagel: summary of product characteristics [online; accessed 18 September 2013]

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Health and Social Care Information Centre (2013) Prescription cost analysis England 2012. [online; accessed 18 September 2013]

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National Institute for Health and Clinical Excellence (2012) SeHCAT (Tauroselcholic [<sup>75</sup>Selenium] acid) for the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss. NICE diagnostics guidance 7

NHS Business Services Authority (2013) Drug Tariff [online; accessed 18 September 2013]

Odunsi-Shiyanbade ST, Camilleri M, McKinzie S et al. (2010) Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. *Clinical*

Gastroenterology and Hepatology 8: 159–65

Pharmacia Limited (2008) [Colestid granules for oral suspension: summary of product characteristics](#) [online; accessed 18 September 2013]

Puleston J, Morgan H, Andreyev J (2005) [New treatment for bile salt malabsorption](#). Gut 54: 441–2

Sanofi (2012) [Cholestagel: summary of product characteristics](#) [online; accessed 18 September 2013]

Wedlake L, Thomas K, Lalji A et al. (2009) [Effectiveness and tolerability of colesevelam hydrochloride for bile-acid malabsorption in patients with cancer: a retrospective chart review and patient questionnaire](#). Clinical Therapeutics 31: 2549–58

## Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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## Declarations of interest

No relevant interests declared.

# Appendix: Search strategy and evidence selection

## Search strategy

### General background, guidelines and technology assessments:

Broad internet search: Google: allintitle: Colesevelam; allintitle: Cholestagel; allintitle: welchol; Colesevelam.pdf; Cholestagel.pdf

Trip Database: Colesevelam; Cholestagel; welchol; lodalis

### MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. Colesevelam.tw. (195)
2. Cholestagel.tw. (5)
3. welchol.tw. (16)

4. Iodalis.tw. (0)
5. "bile acid sequestrant".tw. (236)
6. or/1-5 (360)
7. exp Inflammatory Bowel Diseases/ (59129)
8. Gastrointestinal Transit/ (4178)
9. Diarrhea/ (39024)
10. (bile adj3 (malabsorption or absorption)).tw. (994)
11. (Gastroenteritis or bowel or intestinal or gastrointestinal or diarrh?ea? or crohn\$ or colitis or c?eliac).tw. (524995)
12. "Bile Acids and Salts"/ (19161)
13. or/7-12 (559666)
14. 6 and 13 (145)
15. limit 14 to english language (142)

## Embase (via Ovid)

Database: Embase <1988 to 2013 July 17>

Search Strategy:

1. Colesevelam.tw. (268)
2. Cholestagel.tw. (37)
3. welchol.tw. (152)
4. Iodalis.tw. (1)
5. "bile acid sequestrant".tw. (220)
6. or/1-5 (511)
7. exp Inflammatory Bowel Diseases/ (146481)

8. Gastrointestinal Transit/ (2871)
9. Diarrhea/ (127289)
10. (bile adj3 (malabsorption or absorption)).tw. (751)
11. (Gastroenteritis or bowel or intestinal or gastrointestinal or diarrh?ea? or crohn\$ or colitis or c?eliac).tw. (507668)
12. "Bile Acids and Salts"/ (11506)
13. or/7-12 (627137)
14. 6 and 13 (195)
15. limit 14 to (english language and exclude medline journals) (23)

## **Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 Cholestagel

#2 Colesevelam

#1 or #3

## **CRD HTA, DARE and EED database**

((Colesevelam or cholestagel or welchol or lodalis))

## **Grey literature and ongoing trials**

- [NICE Evidence](#)
- [Health Canada – Clinical Trials Search](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

## Manufacturers' websites

[Daiichi Sankyo, Inc \(USA\)](#)

[Valeant \(Canada\)](#)

## Evidence selection

This evidence summary included all identified published studies that have investigated the efficacy and safety of colesevelam in people with bile acid malabsorption. Results presented only as conference abstracts were excluded.

## About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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