Colesevelam

Background Information	Bile acid sequestrants act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma.
BNF therapeutic class	Bile acid sequestrant.
Indication	Although unlicensed, colesevelam can be used in the treatment of bile acid malabsorption.
Dosage and administration	*Bile acid malabsorption* The BNF dose suggests 1.25g-3.75g daily in 2 to 3 divided doses. *Elderly population* There is no need for dose adjustment when colesevelam is administered to elderly patients. *Paediatric population* The safety and efficacy of colesevelam in children aged 0 to 17 years have not yet been established. *Method of administration* Colesevelam tablets should be taken orally with a meal and liquid. The tablets should be swallowed whole and not broken, crushed or chewed.
Cautions and Contraindication	***Contraindications*** • Hypersensitivity to the active substance or to any of the excipients listed • Bowel or biliary obstruction ***Special warnings and precautions for use*** *Interaction with ciclosporin* For patients on ciclosporin starting or stopping colesevelam or patients on colesevelam with a need to start ciclosporin: colesevelam reduces the bioavailability of ciclosporin. Patients starting on ciclosporin already taking colesevelam should have their ciclosporin blood concentrations monitored as normal and their dose adjusted as normal. Patients starting on colesevelam already taking ciclosporin should have their blood concentrations monitored prior to combination therapy and frequently monitored immediately starting co-therapy with the ciclosporin dose adjusted accordingly. It should be noted that stopping colesevelam therapy will result in increased ciclosporin blood concentrations. Therefore, patients taking both ciclosporin and colesevelam should have their blood concentrations monitored prior to and frequently after when colesevelam therapy is stopped with their ciclosporin dose adjusted accordingly. *Effects on triglyceride levels* Caution should be exercised when treating patients with triglyceride levels greater than 3.4 mmol/L due to the triglyceride increasing effect with

	colesevelam. Safety and efficacy are not established for patients with triglyceride levels greater than 3.4 mmol/L, since such patients were excluded from the clinical studies. The safety and efficacy of colesevelam in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, liver failure or major gastrointestinal tract surgery have not been established. Consequently, caution should be exercised when colesevelam is used in patients with these disorders. *Constipation* Colesevelam can induce or worsen present constipation. The risk of constipation should especially be considered in patients with coronary heart disease and angina pectoris. *Anticoagulants* Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants, like colesevelam, have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect. *Oral contraceptives* Colesevelam can affect the bioavailability of the oral contraceptive pill when administered simultaneously. It is important to ensure that colesevelam is administered at least 4 hours after the oral contraceptive pill to minimise the risk of any interaction. **Fertility, pregnancy and lactation** *Pregnancy* No clinical data are available on the use of colesevelam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women. *Breast-feeding* The safety of colesevelam has not been established in breast-feeding women. Caution should be exercised when prescribing to breast-feeding women. *Fertility* There are no data on the effect of colesevelam on fertility in humans. A study conducted in rats did not result in any differences in reproductive parameters between the groups that might imply reproductive effects attributable to colesevelam.
Adverse Drug Reactions	*Summary of the safety profile* The most frequently occurring adverse reactions are flatulence and constipation, found within the gastrointestinal disorders system organ class. *Tabulated list of adverse reactions* In controlled clinical studies involving approximately 1400 patients and during post-approval use, the following adverse reactions were reported in patients given colesevelam.

	The reporting rate is classified as 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). **Nervous system disorders** *Common:* Headache **Gastrointestinal disorders** *Very common*: Flatulance, 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
Monitoring	Patients receiving ciclosporin should have their blood-ciclosporin concentration monitored before, during, and after treatment with colesevelam. Patient counselling on administration is advised for colesevelam hydrochloride tablets (avoid other drugs at same time).
Interactions	*In general* Colesevelam may affect the bioavailability of other medicinal products. Therefore when a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, colesevelam should be administered at least four hours before or at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication. For concomitant medications which require administration via divided doses, it should be noted that the required dose of colesevelam can be taken once a day. When administering medicinal products for which alterations in blood levels could have a clinically significant effect on safety or efficacy, physicians should consider monitoring serum levels or effects. Interaction studies have only been performed in adults. In interaction studies in healthy volunteers, colesevelam had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid, and warfarin. Colesevelam decreased the C_{max} and AUC of sustained-release verapamil by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the clinical significance of this finding is unclear. Co-administration of colesevelam and olmesartan decreases the exposure of olmesartan. Olmesartan should be administered at least 4 hours prior to

colesevelam.

There have been very rare reports of reduced phenytoin levels in patients who have received colesevelam administered with phenytoin.

Anticoagulant therapy

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants, like colesevelam, have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect. Specific clinical interaction studies with colesevelam and vitamin K have not been performed.

Levothyroxine

In an interaction study in healthy volunteers, colesevelam reduced the AUC and C_{max} of levothyroxine when administered either concomitantly or after 1 hour. No interaction was observed when colesevelam was administered at least four hours after levothyroxine.

Oral contraceptive pill

In an interaction study in healthy volunteers, colesevelam reduced the C_{max} of norethindrone as well as the AUC and C_{max} of ethinylestradiol when administered simultaneously with the oral contraceptive pill. This interaction was also observed when colesevelam was administered one hour after the oral contraceptive pill. However no interaction was observed when colesevelam was administered four hours after the oral contraceptive pill.

Ciclosporin

In an interaction study in healthy volunteers, co-administration of colesevelam and ciclosporin significantly reduced the $AUC_{0\text{-}inf}$ and C_{max} of ciclosporin by 34% by 44%, respectively. Therefore advice is given to closely monitor ciclosporin blood concentrations. In addition, based on theoretical grounds colesevelam should be administered at least 4 hours after ciclosporin in order to further minimise the risks related to the concomitant administration of ciclosporin and colesevelam. Furthermore, colesevelam should always be administered at the same times consistently since the timing of intake of colesevelam and ciclosporin could theoretically influence the degree of reduced bioavailability of ciclosporin.

Statins

When colesevelam was co-administered with statins in clinical studies, an expected add-on LDL-C lowering effect was observed, and no unexpected effects were observed. Colesevelam had no effect on the bioavailability of lovastatin in an interaction study.

Antidiabetic agents

Co-administration of colesevelam and metformin extended-release (ER) tablets increases the exposure of metformin. Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs.

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastrointestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore glimepiride should be administered at least 4 hours prior to colesevelam.

Co-administration of colesevelam and glipizide decreases the exposure of glipizide. Glipizide should be administered at least 4 hours prior to

	colesevelam. Co-administration of colesevelam and glyburide (also known as glibenclamide) caused a decrease in the $AUC_{0\text{-}inf}$ and C_{max} of glyburide by 32% and 47%, respectively. No interaction was observed when colesevelam was administered four hours after glyburide. Co-administration of colesevelam and repaglinide had no effect on the AUC and caused a 19% reduction in the C_{max} of repaglinide, the clinical significance of which is unknown. No interaction was observed when colesevelam was administered one hour after repaglinide. No interaction was observed when colesevelam and pioglitazone were administered simultaneously in healthy volunteers *Ursodeoxycholic acid* Colesevelam predominantly binds hydrophobic bile acids. In a clinical study colesevelam did not affect the faecal excretion of endogenous (hydrophilic) ursodeoxycholic acid. However, formal interaction studies with ursodeoxycholic acid have not been performed. As noted in general, when a drug interaction cannot be excluded with a concomitant medicinal product, colesevelam should be administered at least four hours before or at least four hours after the concomitant medication to minimise the risk of reduced absorption of the concomitant medication. Monitoring of the clinical effects of treatment with ursodeoxycholic acid should be considered. *Other forms of interaction* Colesevelam did not induce any clinically significant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption. In these patients, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

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References

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Development Process

This guideline was developed following an Amber-G classification of colesevelam for bile acid malabsorption. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 12th August 2020.