Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Title of paper:	Review of bile acid sequestrants in bile acid malabsorption (BAM) including colesevelam (approved in 2013) and colestyramine (which was not previously included on the PAD)		
Meeting date:	1st May 2024		
Agenda item:	To be completed by APC secretary	**Attachment(s):**	
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Paper type	Established Medicines, section review		
For:	Approval		

Executive Summary: *(provide a short description of the subject matter and draw attention to the issues / facts and the proposal)*

Bile acid diarrhoea (BAD) (also known as bile salt malabsorption and bile acid malabsorption) is treated with bile acid sequestrants (BAS). The two BAS currently available in the UK are colesevelam tablets and colestyramine sachets (both with sugar and sugar free). Colestipol is no longer available apart from via special order so will not be considered in this paper.

Colestyramine is licensed for the relief of diarrhoea in a number of conditions associated with BAD including: ileal resection, Crohn's disease, vagotomy, diabetic vagal neuropathy and radiation-induced diarrhoea. This does not reflect the full spectrum of conditions associated with BAD meaning colestyramine is used off-licence for other cohorts of patients with BAD including those with either Type 2 BAD (eg diarrhoea predominant irritable bowel disease) or Type 3 BAD (eg BAD in association with other gastrointestinal pathology such as post-cholecystectomy patients). Colesevelam is only licensed for the treatment of hypercholesterolemia and therefore is used off-licence for treatment of patients with BAD. The BNF does however recommend a dose for colesevelam for bile acid malabsorption.

Currently there is an entry on the Prescribing Advisory Database (PAD) for the treatment of BAD with colesevelam with shared care. The only entry for colestyramine is for lipid modification, although the colesevelam shared care document is clear that colestyramine should be used first line for this indication. The prescribing of both colestyramine and colesevelam for BAD has been occurring in Surrey Heartlands for many years, but the traffic light classifications for drugs treating this indication have not been previously addressed as a whole.

The aim of this paper is to support accurate entry onto the PAD for the use of both colestyramine and colesevelam for the treatement of BAD, and to propose a traffic light classification change from Amber Shared Care to Blue, for initiation on advice of the specialists.

Good quality randomised controlled trials for BAD are lacking. Specific trials for patients with BAD secondary to ileal resection, active Crohn's disease, cancer chemotherapy or after pelvic irradiation show clinical response to bile acid sequestrants.[1,2,3,4] There are currently no head to head clinical trials between the BAS.

Despite lack of good quality trial evidence, there are years of clinical experience in using BAS in BAD and as a result, they are established medicines for this condition. The British Society of Gastroenterology guidelines for the investigation of chronic diarrhoea in adults, GP notebook and NICE evidence summary for colesevelam do not specify superiority of one BAS over another for BAD.[5,6,7]

Historically colestyramine has been used first line for BAD due to greater clinical experience (as the agent available longest on the market) and good predicted response rate in severe disease as shown by SeHCAT testing.[8,9] A systematic review on the management of chronic diarrhoea related to BAD identified 30 relevant publications (1241 patients) and concluded that not only was cholestyramine the most studied treatment but it also showed a benefit in 70% (of 801) patients included in the studies in the review which involved colestytamine alone.[10] Due to absence of randomised controlled trials available, evidence regarding colesevelam in general is lacking. There is an indication that colesevelam is beneficial in patients who have failed on colestyramine but numbers are too small to be statistically significant.[11]

Colestyramine and colesevelam are binding agents and thus have a high affinity for bile acids in the gastrointestinal tract forming complexes with them. The main disadvantage of colestyramine is that.an unpleasant taste, which can lead to poor tolerance of and poor adherence to treatment.[10] Other side effects include constipation, nausea, borborygmi, flatulence, bloating and abdominal pain. For patients who do not tolerate colestyramine, the tablet formulation for colesevelam may improve acceptability and tolerability and is therefore a useful option.

Costs

Drug	Pack size Price 1° care	Dose	Price per month 1° care
Colestyramine 4g oral powder sachets	Granules: 50 x 4g sachets, £10.76	Initially 4 g twice daily.Can be increased up to 8g TDS,	£12.91-£38.74
Colestyramine 4g oral powder sachets sugar free	Granules: 50 x 4g sachets, £52.59	Initially 4 g twice daily.Can be increased up to 8g TDS,	£63.11-£189.32
Colesevelam 625mg tablets	Tablets: 180 x 625mg, £70.56	1.25–3.75 g daily in 2–3 divided doses.	£23.52-£70.56

Drug Tarif February 2024

(It should be noted colestyramine is on the Surrey PAD for lipid modification and it is not possible to differentiate what indication these drugs have been prescribed for).

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Current Expenditure in Surrey Heartlands over 6 months (from epact spend Jun-Nov 23)

Drug	Pack size	Number of packs dispensed	**Quantity X Items**	Expenditure	Cost per Unit	Predicted annual spend SH (based on current prices and expenditure
Colestyramine 4g oral powder sachets	50	821	41,047	£8313	£0.20	£16 626
Colestyramine 4g oral powder sachets (Questran)	50	17	850	£172	£0.20	£344
Total Colestyramine 4g oral powder sachets	50	838	41897	£8485	-	£16 970
Colestyramine 4g oral powder sachets sugar free	50	1034	51,694	£51 013	£0.99	£102 026
Colestyramine 4g oral powder sachets sugar free (Questran Light)	50	256	12,816	£3889	£0.30	£7778
Total Colestyramine 4g oral powder sachets sugar free	50	1290	64510	£54 902	-	£109 804
Total Colestyramine (including sugar free and non- sugar free)	50	2128	106407	£63 387	-	£126 774
Colesevelam 625mg tablets	180	2210	397,800	£238 986	£0.60	£477 972
Colesevelam 625mg tablets (Cholestagel)	180	165	29,700	£17 840	£0.60	£35680
Total Colesevelam 625mg tablets	180	2375	427500	£256 826	-	£513 652
Colestipol 5g gran for susp sachets sugar free	30	4	456	£215	£0.47	£430
Total all products	-	4507	534,363	£320 427	-	£640 854

The new price per unit for colesevelam is £0.37 from Jan 24. The price reduction will save us £46k in Jan-Mar and a further £139k next financial year (Apr-Dec 24).

Approximately 40 patients were newly diagnosed with BAM at SaSH in 2022. Extrapolated across the three acute trusts in Surrey Heartlands this equates to 120 patients per year. If all these patients were all prescribed colesevelam tablets instead of colestyramine sugar free sachets this would equate to a cost saving of £27,200 per annum.

Proposed place in therapy

APC to discuss place in therapy for colestyramine with sugar (least expensive), colestyramine sugar free (most expensive) and colesevelam (recently reduced price) in new patients.

Please note that colestyramine is licensed for some of the indications for BAM but colesevelam is not licensed for any.

Proposed change in traffic light status

Current traffic light status is amber shared care for coleveselam; there is currently no traffic light classification for this indication for colestyramine.

This condition is often diagnosed using a selenium homocholic acid taurine or tauroselcholic acid testing (SeHCAT) scan in secondary care. The patient is asked to swallow a synthetic bile salt with a small amount of the radioactive tracer selenium. After 3 to 4 hours a gamma camera is used to detect the radionuclide tracer atom in a whole-body baseline scan in order to provide an initial count or zero-time value. After a week the patient is scanned again to determine a second count. The retained activity is expressed as a percentage of the original value. In usual practice, retention values of less than 15% have been considered abnormal and indicative of bile acid malabsorption. However, there is no definitive cut-off between normal and abnormal.[15]

NICE Guidance DG44 SeHCAT (tauroselcholic [75 selenium] acid) for diagnosing bile acid diarrhoea recommend there is not enough evidence to recommend routine adoption of SeHCAT but that centres already using SeHCAT for diagnosing bile acid diarrhoea may continue to do so, but must collect further data or do further research. Currently SaSH, EPSH and Royal Surrey County Hospital use these scans in certain clinical situations but not all. It is common practice for clinicians to start coleveselam or colestyramine as a trial. The specialists will be advising primary care prescribers to initiate treatment based on the underlying clinical condition and symptoms, and this may include a SeHCAT scan.

The medications themselves are not complex other than patients need to be advised of potential vitamin malabsorption and supplements recommended. Both colesevelam and colestyramine can affect bioavailability of other medicines. It is therefore advised that where minor variations in the therapeutic level of a concomitant medication would be clinically important that colesevelam should be administered at least 4 hours before or 4 hours after the concomitant medication and colestyramine should be taken 1hour after or 4-6hours before concomitant medications. Information about these interactions and malabsorption are in the SPC and Patient Information Leaflet regardless of indication.

It is proposed patients would be given the tools to adjust their dosage to maximum efficacy and to feedback the dose they require to the prescriber within the parameters to be described in the Blue Information Sheet. Doses will be described in the Blue information sheet, and success of the treatment will be assessed on the basis of improvement of the diarrhoea within 3 days of achieving maximum dose.

If the treatment is successful, the treatment needs to be continued indefinitely as it is unlikely that the underlying cause of malabsorption will improve.

It is recommended that colestyramine is given a Blue traffic light status. It is proposed there is a corresponding change in traffic light status for colesevelam from amber shared care to Blue.

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Summary: *(What is the APC being asked to do and why)*

The APC is asked to agree to the following:

a. Colesevelam traffic light classification to change from Amber shared care to Blue (for initiation on advice from specialists).
b. Discuss place in therapy for colestyramine with sugar (least expensive), colestyramine sugar free (most expensive) and colesevelam (recently reduced price) in new patients.
c. New entry for colestyramine with an indication for use in bile acid malabsorption
d. Add traffic light classification for colestyramine as Blue (for initiation on advice from specialists)
e. Colestipol should be made non-Formulary

Blue information sheet for this indication will be prepared as agreed by the APC

Accompanying papers (please list):

1) Hofmann A , Poley J. Cholestyramine treatment of diarrhea associated with ileal resection. N Engl J Med 1969;281:397–402.
2) Fernández-Bañares F , Rosinach M , Piqueras M , et al . Randomised clinical trial: colestyramine vs. hydroxypropyl cellulose in patients with functional chronic watery diarrhoea. Aliment Pharmacol Ther 2015;41:1132–40
3) Bajor A , Törnblom H , Rudling M , *et al.* Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in IBS. Gut 2015;**64**:84–92
4) Beigel F , Teich N , Howaldt S , *et al* .Colesevelam for the treatment of bile acid malabsorption-associated diarrhea in patients with Crohn's disease: a randomized, double-blind, placebo-controlled study. J Crohns Colitis 2014;**8**:1471–9
5) Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of chronic diarrhoea in adults: British society of gastroenterology, 3rd Edition. Gut 2018;67:1380-1399.
6) GPnotebook.Bile salt malabsorption 11/2020
7) NICE. Bile acid malabsorption: colesevelam. 2013. [Online] Available at: https://www.nice.org.uk/advice/esuom22/chapter/Key-points-from-the-evidence (Accessed: 5 October 2022).
8) Mottacki, N et al. Review article: bile acid diarrhoea – pathogenesis, diagnosis and management.Alimentary Pharmacology and Therapeutics *2016;* 43: 884-898
9) Walters JRF, Arasaradnam R, Andreyev HJN, et al. Diagnosis and management of bile acid diarrhoea: a survey of UK expert opinion and practice. Frontline Gastroenterology 2020;11:358-363.
10) Wilcox C, et al. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. Alimentary Pharmacology and Therapeutics *2014*; 39: 923-939.
11) Orekoya O, et al. Quantifying bile acid malabsorption helps predict response and tailor sequestrant therapy. Clinical Medicine *2015;* 15,3:252-7
12) eSPC Questran light, accessed February 2024, https://www.medicines.org.uk/emc/product/10588
13) eSPC Questran, accessed February 2024, https://www.medicines.org.uk/emc/product/10589
14) eSPC Cholestagel, Accessed February 2024, https://www.medicines.org.uk/emc/product/12384/smpc
15) GPnotebook SeHCAT (tauroselcholic (75 selenium) acid) as a test for diagnosing bile acid malabsorption 11/20