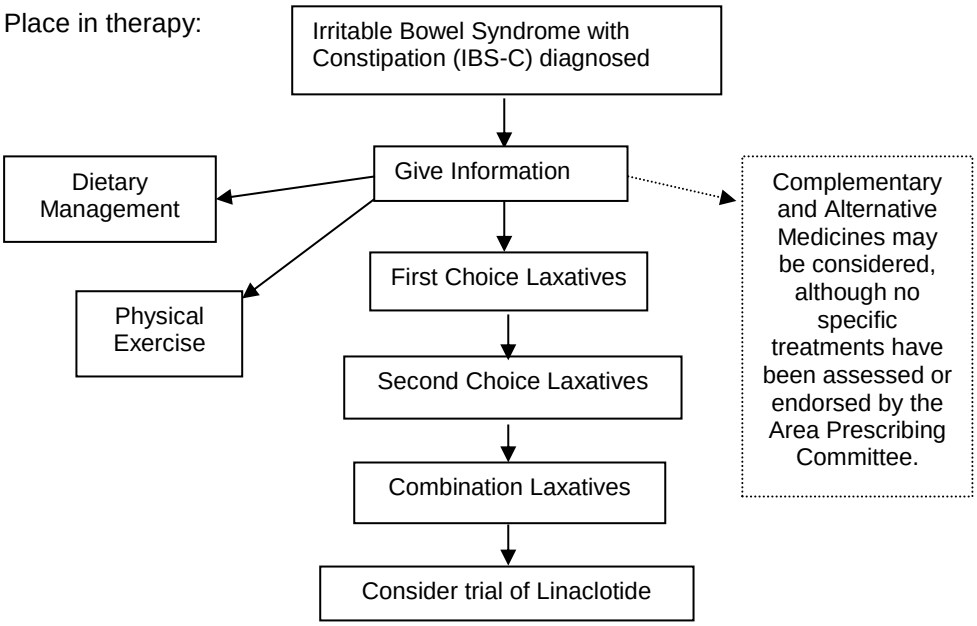
Linaclotide (Constella®)

Background Information	Linaclotide is a Guanylate Cyclase-C receptor agonist (GCCA) with visceral analgesic and secretory activities. Both linaclotide and its active metabolite bind to the GC-C receptor on the luminal surface of the intestinal epithelium, leading to an increase in concentrations of cyclic guanosine monophosphate (cGMP), both extracellularly and intracellularly. Extracellular cGMP decreases pain-fiber activity, resulting in reduced visceral pain in animal models. Intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in increased intestinal fluid and accelerated transit.
BNF therapeutic class	1.4 Irritable Bowel Syndrome, Laxatives, Guanylate Cyclase-C Receptor Agonists
Indication	Linaclotide is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Place in therapy:  The laxatives currently available on Formulary are as follows: • Osmotic Laxatives = Lactulose, Macrogols, Phosphate Enemas • Bulk Forming Laxatives = Ispaghula Husk, Methylcellulose • Stimulant Laxatives = Bisacodyl, Docusate Sodium, Glycerol Suppositories, Senna, Sodium Picosulfate • Faecal Softeners = Arachis Oil, Docusate Sodium Laxatives should be prescribed based on their clinical appropriateness taking into account patient specific factors, however NICE recommends the following general guidance with regards to laxative prescribing: • Start treatment with a bulk-forming laxative. ○ It is important to maintain good hydration when taking bulk-forming laxatives. This may be difficult for some people (for example the frail or elderly).

	• If stools remain hard, add or switch to an osmotic laxative.
	  ○ Use macrogols as first choice of an osmotic laxative.
	  ○ Use lactulose if macrogols are not effective, or not tolerated.
	• If stools are soft but the person still finds them difficult to pass or complains of inadequate emptying, add a stimulant laxative.

Dosage and administration	The recommended dose is one capsule (290 micrograms) once daily, at least 30 minutes before a meal. Physicians should periodically assess the need for continued treatment. The efficacy of linaclotide has been established in double-blind placebo-controlled studies for up to 6 months. If patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefit and risks of continuing treatment reconsidered. Constella® is available as hard capsules (containing 290micrograms of linaclotide per capsule) and should be dispensed in the original container. Any remaining capsules should be discarded 18 weeks after opening.
Cautions and Contraindication	Linaclotide is contraindicated in patients with gastrointestinal obstruction. Use in patients with inflammatory bowel disease is not recommended due to lack of safety and efficacy data in this patient group. It should be used with caution in patients predisposed to fluid and electrolyte disturbances (e.g. elderly, patients with cardiovascular disease, diabetes, hypertension). No dosage adjustments are required for elderly patients, or those with hepatic or renal impairment. Linaclotide should be avoided in pregnancy as a precautionary measure, although animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Breast-feeding is not expected to result in exposure of the infant to linaclotide and Constella can be used during breast-feeding.
Adverse Drug Reactions	The most frequently reported adverse reaction associated with linaclotide therapy was diarrhoea, mainly mild to moderate in intensity, occurring in less than 20% of patients. In rare and more severe cases, this may – as a consequence – lead to the occurrence of dehydration, hypokalaemia, blood bicarbonate decrease, dizziness, and orthostatic hypotension. Patients should be made aware of the possible occurrence of diarrhoea during treatment. Should prolonged (e.g. more than 1 week) or severe diarrhoea occur, medical advice should be sought and temporary discontinuation of linaclotide until diarrhoea episode is resolved may be considered. Regarding duration of diarrhoea, duration of more than 28 days was reported in 50% (n=80) of patients with diarrhoea; approximately one third of diarrhoea cases resolved within 7 days. Other common adverse reactions (>1%) were abdominal pain, abdominal distension and flatulence.
Monitoring	There is no routine monitoring necessary with the administration of linaclotide. It is advised that U&E's are checked periodically in patients predisposed to electrolyte disturbances, should prolonged or severe diarrhoea occur, or as other clinical circumstances dictate.
Interactions	No drug-drug interaction studies have been performed for linaclotide, although the drug is rarely detectable in plasma following administration of the recommended clinical doses. *In vitro* studies have shown that linaclotide is neither a substrate nor an inhibitor/inducer of the cytochrome P450 enzyme system and does not interact with a series of common efflux and uptake transporters.

***Amber with Guidance**= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

	Taking linaclotide with or after food produced more frequent and looser stools, as well as more gastrointestinal adverse events, than when taking it under fasting conditions. **Concomitant treatment with proton pump inhibitors, laxatives or NSAIDs may increase the risk of diarrhoea.** In cases of severe or prolonged diarrhoea, absorption of other oral medicinal products may be affected. **The efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception.** Caution should be exercised when prescribing medicinal products absorbed in the intestinal tract with a narrow therapeutic index such as levothyroxine as their efficacy may be reduced.

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Development Process

This guidance was originally produced by Gillian Turrell, Lead Pharmacist for Medicines Information and Cardiology, BHNFT, in consultation with Dr Kapil Kapur, Consultant Gastroenterologist and Clinical Director for Medicine, BHNFT, following an AMBER classification status of Linaclotide by the Barnsley Area Prescribing Committee.

The guideline has been reviewed and updated. It was subject to consultation and endorsement by the Area Prescribing Committee on 11th August 2021.