Linaclotide Prescribing Information Sheet		
V1	Dec 2021	Review date: Dec 2024

NHS
Nottinghamshire Area Prescribing Committee

Linaclotide

Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

Licensed Indications

Linaclotide is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

Therapeutic Summary

Linaclotide is a first-in-class, oral, once-daily Guanylate Cyclase-C receptor agonist (GCCA) with visceral analgesic and secretory activities. Linaclotide causes decreased visceral pain, increased intestinal fluid secretion and accelerated intestinal transit. The summary of product characteristics states that linaclotide is metabolised locally in the gastrointestinal tract and is minimally detectable in plasma after therapeutic oral doses.

Medicines Initiation

Linaclotide should only be prescribed by a clinician with experience of treating moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.
Consider linaclotide for people with IBS only if:

- optimal or maximum tolerated doses of previous laxatives from different classes have not helped **and**
- they have had constipation for at least 12 months.

Products available

Constella 290 micrograms hard capsules

Special precautions for storage

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
The bottle contains one or more sealed canisters containing silica gel to keep the capsules dry. Keep the canisters in the bottle.

Dosages and route of administration

Linaclotide is taken orally.

Adults: One capsule (290 micrograms) once daily. The capsule should be taken at least 30 minutes before a meal.

<u>Special populations</u>

Elderly patients (>65 years): Although no dose adjustment is required, the treatment should be carefully monitored and periodically re-assessed.

Patients with renal or hepatic impairment: No dose adjustments are required for patients with hepatic or renal impairment.

Paediatric population: This medicinal product should not be used in children and adolescents. The safety and efficacy of Linaclotide in children aged 0 to 18 years have not yet been established. No data are available.

Duration of treatment

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, the patient should be re-examined and the benefit and risks of continuing treatment reconsidered beyond this duration.

Adverse Effects

Possible adverse effects of linaclotide include:
Abdominal distention, abdominal pain, diarrhoea, dizziness, flatulence. If diarrhoea is severe or prolonged, consider stopping treatment.
Cases of intestinal (IN) perforation have been reported after use of linaclotide in people with conditions that may be linked to localized/diffuse IN wall weakness. Immediate medical care should be sought in case of severe, persistent, or worsening abdominal pain and treatment stopped.
Decreased appetite, dehydration, faecal incontinence, hypokalaemia, orthostatic hypotension.

Monitoring Requirements and Responsibilities

No blood monitoring is required; however, efficacy will be reviewed after 4 weeks by the recommending clinician. Further review should be completed to assess the risks and benefits of longer-term treatment ideally at 12 weeks.
Following this the on-going need for the medication should be routinely reviewed by the prescribing GP and deprescribing considered after 6 months.

Explicit criteria for review and discontinuation of the medicine

Contraindications

- Hypersensitivity to linaclotide or to any of the excipients.
- Patients with known or suspected mechanical gastrointestinal obstruction.
- Patients with suspected Crohns disease or ulcerative colitis

Precautions
Linaclotide should be used after organic diseases have been ruled out and a diagnosis of moderate to severe IBS-C is established.

Patients should be aware of the possible occurrence of diarrhoea and lower gastrointestinal bleeding during treatment. They should be instructed to inform their physician if severe or prolonged diarrhoea or lower gastrointestinal bleeding occurs.
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. Additional caution should be exercised in patients who are prone to a

disturbance of water or electrolyte balance (e.g. elderly, patients with cardiovascular (CV) diseases, diabetes, hypertension), and electrolyte control should be considered.

Adverse reactions associated with Linaclotide therapy include diarrhoea, mainly mild to moderate in intensity, occurring in less than 20% of patients. In rare and more severe cases, this may consequently lead to the occurrence of dehydration, hypokalaemia, blood bicarbonate decrease, dizziness, and orthostatic hypotension.

Linaclotide has not been studied in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis; therefore it is not recommended to use Linaclotide in these patients.

Elderly patients
There are limited data in elderly patients. Because of the higher risk of diarrhoea seen in the clinical trials, special attention should be given to these patients and the treatment benefit-risk ratio should be carefully and periodically assessed.

Paediatric population
Linaclotide should not be used in children and adolescents as it has not been studied in this population. As GC-C receptor is known to be overexpressed at early ages, children younger than 2 years may be particularly sensitive to linaclotide effects.

Pregnancy
There is limited amount of data from the use of linaclotide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Linaclotide during pregnancy.

Lactation
Linaclotide is minimally absorbed following oral administration. In a milk-only lactation study in seven lactating women, who were already taking linaclotide therapeutically, neither linaclotide nor its active metabolite were detected in the milk. Therefore, breastfeeding is not expected to result in exposure of the infant to linaclotide and can be used during breast-feeding.
The effects of linaclotide or its metabolite on milk production in lactating women have not been studied.

Fertility
Animal studies indicate that there is no effect on male or female fertility.

Clinically relevant medicine interactions and their management

No interaction studies have been performed. Linaclotide is rarely detectable in plasma following administration of the recommended clinical doses and *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.

A food interaction clinical study in healthy subjects showed that linaclotide was not detectable in plasma either in fed or in fasted conditions at the therapeutic doses. Taking Linaclotide in the fed condition produced more frequent and looser stools, as well as more gastrointestinal adverse events, than when taking it under fasting conditions. The capsule should be taken 30 minutes before a meal.

Concomitant treatment with proton pump inhibitors, laxatives or NSAIDs may increase the risk of diarrhoea. Caution should be used when co-administering Linaclotide with such medications.

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 (see the prescribing information of the oral contraceptive).

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.

References

1. Constella 290 micrograms hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Last updated on eMC 04.10.21. Last accessed 15.10.21.
2. NICE Guidelines- Irritable bowel syndrome in adults: diagnosis and management. Clinical Guideline 61; Published: 23 February 2008. Last updated 04.04.2017 https://www.nice.org.uk/guidance/cg61
3. NICE Advice Irritable bowel syndrome with constipation in adults: Linaclotide Evidence summary. Nice.org.uk/guidance/esnm16; Published: 9 April 2013 https://www.nice.org.uk/advice/esnm16/chapter/Overview
4. Linaclotide Prescribing Information- Irritable Bowel Syndrome. Clinical Knowledge Summaries. Last revised in June 2021. https://cks.nice.org.uk/topics/irritable-bowel-syndrome/prescribing-information/linaclotide/