

## Factsheet

### LINACLOTIDE (Constella®)

### Irritable Bowel Syndrome – constipation predominant (IBS-C)

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#### FACTSHEET TO FACILITATE PRESCRIBING

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*Indication information*

Linaclotide is approved for use in NCL for the symptomatic treatment of adult patients for moderate to severe constipation predominant IBS (IBS-C) where the following criteria apply:

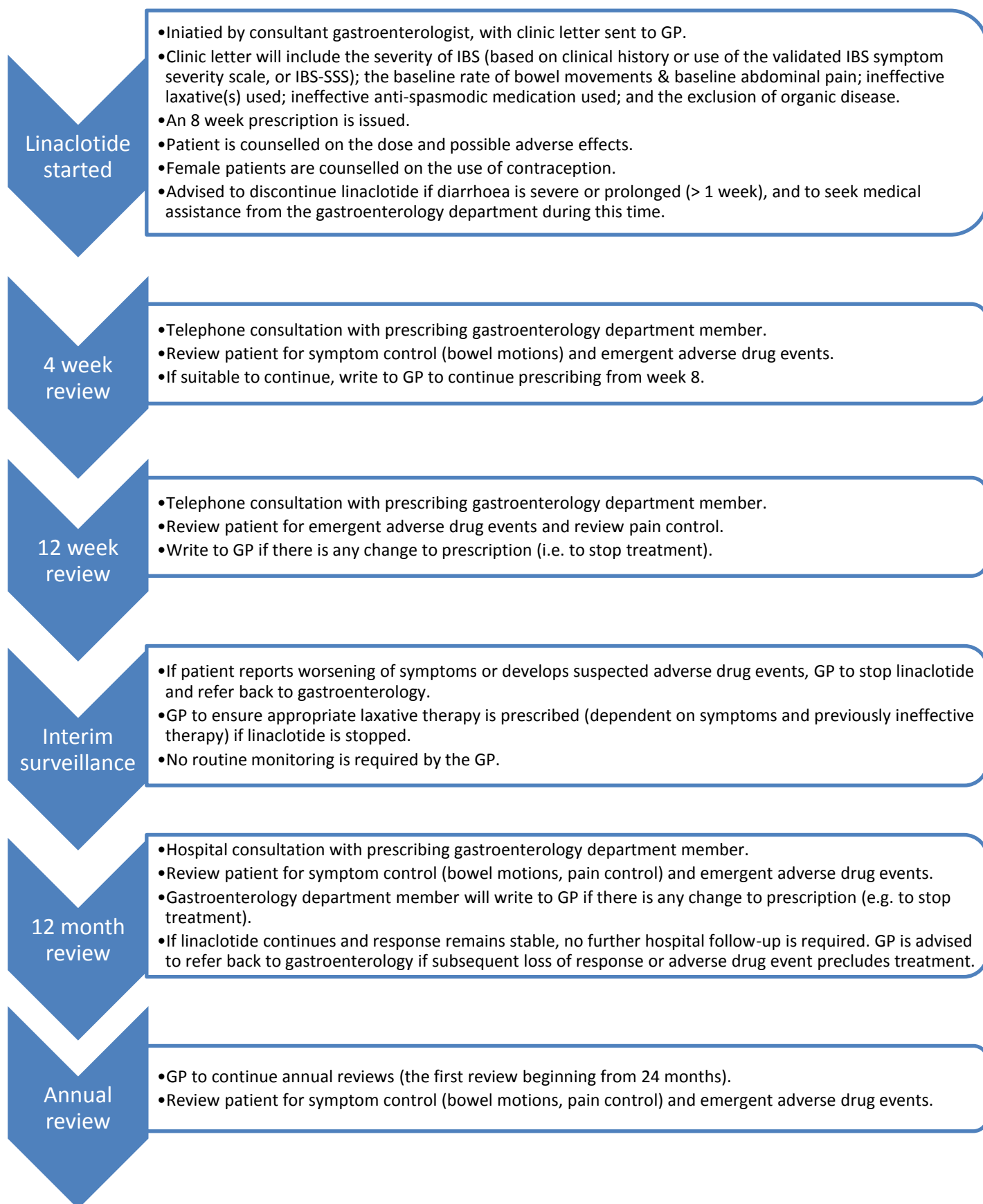
1. Initiation is by a Consultant Gastroenterologist
2. The patient has experienced constipation for at least 12 months
3. The patient has been prescribed **two optimally dosed laxatives** (from different classes), which have been ineffective
4. The patient has been prescribed **an optimally dosed anti-spasmodic**, which has been ineffective

The patient will be reviewed by a member of the gastroenterology team **at week 4** after starting treatment. If the patient is responding to and tolerating treatment, the GP will be asked to continue prescribing responsibilities from **week 8**.

**Check list and actions for the GP:**

1. You will have written confirmation within 4 weeks of initiation (with details from the clinic appointment at week 0) of the initiation of the medication, along with: the severity of IBS (based on clinical history or use of the validated IBS symptom severity scale, or IBS-SSS); the baseline rate of bowel movements & baseline abdominal pain; ineffective laxative(s) used; ineffective anti-spasmodic medication used; and the exclusion of organic disease. You will also receive a letter after the week 4 consultation to confirm that it is appropriate to continue prescribing from week 8.
2. The patient will be reviewed by the consultant gastroenterologist (or member of the gastroenterology department) at weeks 0, 4, 12 and then at 12 months post initiation. Interim surveillance is performed ad-hoc by the GP if the patient reports to them with worsening of symptoms or suspected adverse drug events (ADEs). Before the patient is discharged from the hospital service, they also have the option of self-referring to the initiating gastroenterology service by contacting the gastroenterology secretaries.
3. The consultant gastroenterologist will write to the GP should linaclotide treatment be discontinued following one of their routine reviews.
4. In the event that the patient has severe or prolonged (more than 1 week) diarrhoea or lower gastrointestinal bleeding, linaclotide should be discontinued and the patient referred back to the gastroenterology department.  
In the event that the patient suffers worsening symptoms of constipation or abdominal pain, it is appropriate to discontinue linaclotide and prescribe laxatives (the choice of laxative and dose dependent on patients' symptoms and history of ineffective choices).
5. After 12 months, if the patient remains symptom free and tolerating treatment, the patient is discharged from the hospital service. GPs should start and continue annual medication reviews (with the first review starting at month 12). Post hospital service discharge, GPs can refer back to the gastroenterology service if linaclotide fails. Referral can be expedited in severe cases by contacting the gastroenterology secretaries directly (contact details at the end of this document).
6. There is no routine monitoring required to be completed by the GP.

## LINACLOTIDE TREATMENT PATHWAY



## **Dose and Administration**

290 micrograms daily (1 capsule)

The medication is taken as a single capsule on an empty stomach, 30 minutes before eating. Typically it is taken in the morning, but the timing may be adjusted according to the patient's circumstances and speed of onset of laxative effect.

**Renal impairment:** no dose adjustment required

**Hepatic impairment:** no dose adjustment required

**Discontinuing treatment:** Linaclotide can be used life-long, or until treatment failure. A gastroenterology department member will contact the patient for a telephone consultation after 4 weeks. If there is no improvement to bowel habit ( $\geq 1$  complete spontaneous bowel movement per week) or to abdominal pain and bloating (report of symptoms compared to baseline) after the initial one month of therapy, then the medication will be discontinued.

If complete spontaneous bowel movements reduce to the baseline rate (communicated in the clinic letter) or abdominal pain returns to baseline (communicated in clinic letter) then linaclotide can be stopped by the GP and the patient referred back to the gastroenterologist for on-going management. The GP should prescribe laxative medication based on the patient's symptoms and previous ineffective therapies whilst they await gastroenterology review.

If the drug is discontinued due to lack of efficacy or side effects, then the patient may need to be reviewed in hospital care with a view to considering more specialist therapies (psychological therapy, hypnotherapy, etc).

## **Adverse Effects**

Diarrhoea is a very common side effect of linaclotide, and approximately half of cases of diarrhoea occur in the first week of treatment. The majority of diarrhoea episodes were classified as mild (43%) or moderate (47%). Diarrhoea resolves within one week in about a third of patients.

Should prolonged ( $>1$  week) or severe diarrhoea occur, linaclotide should be discontinued until the episode has resolved. In rare and more severe cases, diarrhoea may – as a consequence – lead to the occurrence of dehydration, hypokalaemia, blood bicarbonate decrease, dizziness, and orthostatic hypotension.

Other common adverse effects to note include dizziness, abdominal pain, flatulence and abdominal distension.

## **Contraindications**

Hypersensitivity to the active substance or to any of the excipients

Suspected GI obstruction

Patients under the age of 18 years

Breast-feeding

Pregnancy

## **Special Warnings and Precautions for Use**

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

Patients are made aware of the possible occurrence of diarrhoea prior to commencing treatment. They should be instructed to inform their GP if severe or prolonged (more than 1 week) diarrhoea or lower gastrointestinal bleeding occurs..

Should prolonged (e.g. more than 1 week) or severe diarrhoea occur, the patient should be informed to temporarily discontinue linaclotide until diarrhoea episode is resolved. Additional caution should be

exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered.

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. Hence the contraindication of patients aged 0 – 17 years is in effect.

#### Pregnancy

The recommendation for the purposes of this factsheet is for women of child bearing age to use active contraception whilst taking linaclotide. Barrier contraception may be required in cases of prolonged or severe diarrhoea<sup>1</sup> (see “interactions”).

Although the SPC states that it is preferable to avoid linaclotide during pregnancy, the specialist recommendation for this medication to be contra-indicated in pregnancy and breast-feeding. The advice of the gastrointestinal consultant is to advise patients who are taking the medication to use active contraception. Should a patient become pregnant whilst taking linaclotide, the patient will need to discontinue linaclotide.

#### Breast-Feeding

The recommendation for the purposes of this factsheet is for women to avoid breast-feeding whilst taking linaclotide. Several sources<sup>1,2</sup> suggests that it may be compatible on a risk-benefit decision, although this is based on animal studies and no human data is available. Therefore, the advice is to remain on the side of caution and advise against the use of linaclotide during breast-feeding.

#### ***Interactions***<sup>1,3</sup>

- Caution is advised when using linaclotide alongside **proton pump inhibitors** or non-steroidal anti-inflammatory drugs (**NSAIDs**), as the risk of developing diarrhoea increases.
- Caution is also advised when using linaclotide with **laxatives** due to the risk of developing diarrhoea (although in some cases it may be clinically necessary to use the two classes of medication alongside each other).
- Taking linaclotide **with food** can produce 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.
- 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.

#### **Clinical Monitoring**

At the time of writing this fact sheet, no specific monitoring is required for linaclotide. Patients are advised at initiation to temporarily withhold linaclotide if suffering from mild diarrhoea, and to permanently discontinue if diarrhoea becomes severe or prolonged. If this is within the 1<sup>st</sup> year and their hospital service has not discharged the patient, the patient may self-refer to the gastroenterology service by contacting their initiating gastroenterology secretaries. They may wish to see their GP for temporary treatment until their clinic appointment.

Patients presenting to their GPs with prolonged or severe diarrhoea should result in discontinuation of the medication. Patients may be referred back to the initiating gastroenterology department by their GP in treatment failure or adverse drug reactions to linaclotide (including prolonged or severe diarrhoea). Referral can be expedited in severe cases by contacting the gastroenterology secretaries directly.

In the absence of diarrhoea symptoms, no regular monitoring is required. Any suspected adverse reactions should be reported using the Yellow Card Scheme.

## Contact Details

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Dr Paul Maxwell/ Dr Janine Wright (consultant gastroenterologists)	020 8887 2683
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## References

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