Kent and Medway Policy Recommendation and Guidance Committee
Policy Recommendation

Policy:	**PR 2019-16: Linaclotide for irritable bowel syndrome with constipation (IBS-C) in adults**
Issue date:	**July 2019**
This policy recommendation replaces PR2016-08.	

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) considered NICE and other national guidance, the evidence base, baseline position, other CCGs policies, the views of stakeholders and the potential impact of changing policy. All decisions were made with reference to the Ethical Framework. Taking these into account the PRGC recommends:

- Linaclotide may be considered for use in adults with moderate to severe IBS-C who fulfil both of the following criteria:
    - they have not responded adequately to or cannot tolerate all other suitable treatment options including optimal or maximum tolerated doses of laxatives from different classes, and
    - they have had constipation for at least 12 months
- The rate of non-responders to linaclotide in phase 3 studies was high. Patients must therefore have a scheduled review after 4 weeks of treatment and linaclotide should be discontinued where symptoms have not improved.
- Linaclotide should form part of a multifaceted approach to management of IBS that emphasises the importance of self-help, general lifestyle, physical activity and diet.

This policy recommendation will be reviewed when new information becomes available that is likely to have a material effect on the current recommendation.

Clinical Commissioning Groups (CCGs) in Kent and Medway will always consider appropriate individual funding requests (IFRs) through their IFR process.

Supporting documents

NEL Health Policy Support Unit (HPSU) (2019) *Linaclotide for irritable bowel syndrome with constipation in adults – Scoping report*

Equality Analysis Screening Tool – Linaclotide for irritable bowel syndrome with constipation in adults (2019).

Key points and rationale

What is irritable bowel syndrome (IBS)?

- IBS is a chronic, relapsing and often life-long disorder of the lower gastrointestinal tract, with no discernible structural or biochemical cause. Typical clinical features are abdominal pain:
  - Associated with a change in stool form and/or frequency.
  - Which may be related to defaecation, and there may be associated bloating.
- IBS may be classified according to the predominant bowel habit: IBS with constipation (IBS-C), IBS with diarrhoea and mixed IBS. NICE state that IBS can affect sleep, cause stress, anxiety and lethargy, and decrease work productivity and quality of life.
- Treatment options for IBS-C include dietary and lifestyle advice, pharmacological therapy (such as laxatives, antispasmodic agents and off-label use of antidepressants, depending on the predominant symptom) and psychological interventions.

What is linaclotide?

Linaclotide (Constella; Allergan Ltd) is a first-in-class, oral, once-daily, guanylate cyclase-C receptor agonist that causes decreased visceral pain, increased intestinal fluid secretion and accelerated intestinal transit.

Linaclotide was launched in 2013 for the symptomatic treatment of moderate to severe IBS-C in adults.

According to the summary of product characteristics, 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.

The annual cost of linaclotide is £490 per person per year, which is more than other medications for IBS-C (see below regarding cost-effectiveness).

What does NICE guidance say?

NICE has published clinical guideline (CG) 61 on IBS in adults (2008, last updated 2017). CG61 was updated in 2015 to include recommendations on linaclotide. According to CG61, linaclotide should be considered for people with IBS if they have had constipation for at least 12 months and optimal or maximum tolerated doses of previous laxatives from different classes have not helped. People taking linaclotide should be followed up after 3 months.

What does other national guidance say?

- According to All Wales Medicines Strategy Group (AWMSG) advice (2014), linaclotide is recommended as an option within NHS Wales in adults with moderate to severe IBS-C who have not responded adequately to or cannot tolerate antispasmodics and/or laxatives.
- According to Scottish Medicines Consortium (SMC) advice (2013), linaclotide is accepted for use within NHS Scotland in adults with moderate to severe IBS-C who have not responded adequately to or cannot tolerate all other suitable treatment options.

What is the evidence base for linaclotide?

The safety and efficacy of linaclotide in adults with IBS-C has been demonstrated in three placebo-controlled phase 3 studies; linaclotide treatment led to sustained improvements in abdominal, bowel and overall symptoms over 12 and 26 weeks. Diarrhoea was the most common adverse event. However, despite clinically relevant benefits across the study populations the rate of non-responders to linaclotide was high, suggesting that a large proportion of individuals will not adequately or fully benefit from treatment with linaclotide. Consistent with these results, linaclotide reduced IBS-C symptoms and improved quality of life compared to baseline levels in three non-comparative real-world studies, but was associated with a high rate of discontinuations; participants who discontinued linaclotide typically did so early.

The absence of active comparator studies makes it difficult to assess linaclotide's place in therapy or relative effectiveness compared to current options for IBS-C.

According to a cost-effectiveness study, linaclotide can be a cost-effective treatment for adults with moderate-to-severe IBS-C who have previously received antispasmodics and/or laxatives; a position accepted by the AWMSG and SMC, despite acknowledging limitations to the economic case. The study reported an incremental cost-effectiveness ratio (ICER) of £7,370 per quality-adjusted life year

(QALY) for linaclotide versus antidepressants; NICE typically consider interventions with an ICER below £20,000 per QALY to be cost-effective.

What is the baseline position?

- Kent and Medway CCGs currently have a policy in place not to routinely fund linaclotide for IBS-C in adults
- Despite the current local policy, Kent and Medway CCGs spent £30,476 on linaclotide in 2018/19 according to ePACT primary care prescribing data

What is the rationale for PR2019-16?

PR2019-16 is consistent with NICE, AWMSG and SMC recommendations on linaclotide for IBS-C.

When determining the new policy recommendation, PRGC noted that new clinical and cost-effectiveness evidence, including from real-world settings – not previously considered by the committee – strengthens the evidence base supporting the use of linaclotide for IBS-C.

The PRGC policy recommendation is also supported by local specialists.

There was no consensus amongst local specialists or the PRGC on whether initiation of linaclotide should be restricted to secondary care or could be considered in primary care. The PRGC agreed that this issue should be considered during local implementation of PR2019-16.

Change sheet

Reason for review:
Kent and Medway CCGs currently have a policy in place not to routinely fund linaclotide for IBS-C in adults (PR2016-08):

- New clinical and health economic studies have been published since PR2016-08 was determined
- Local specialists and CCG medicines management teams have queried PR2016-08 in light of this new information

Change from baseline:

- Kent and Medway CCGs currently have a policy in place not to routinely fund linaclotide for IBS-C in adults. Despite the current local policy, Kent and Medway CCGs spent £30,476 on linaclotide in 2018/19 according to ePACT primary care prescribing data.
- According to PR2019-16, linaclotide is recommended for IBS-C in certain circumstances

See Table 1 for more information.

Rationale for PR2019-16:
PR2019-16 is consistent with NICE, AWMSG and SMC recommendations on linaclotide for IBS-C.

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The PRGC policy recommendation is also supported by local specialists.

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Estimated impact of implementing PR2019-16:
The cost impact of recommending linaclotide as a second-line option for IBS-C was estimated using two different approaches:

- Using prescribing data from other areas where linaclotide is recommended, the cost impact of funding linaclotide as a second-line option for IBS-C is estimated to be less than £50k per year across Kent and Medway[1].
- Using literature and company estimates of the size of the target population, uptake rates and offset costs, the estimated total cost of funding linaclotide as a second-line option for IBS-C across Kent and Medway CCGs is: £25k in year 1 rising to £195k in year 5 (this estimate does not take into account baseline expenditure – see above).

[1] Note that other factors are likely to impact on activity and expenditure in other areas which cannot be accounted for in this estimate (e.g. presence and configuration of local care pathways and capacity). This estimate takes account of baseline expenditure but does not take account of any potential offset costs due to displaced drug treatments or other reduced health care resource use with linaclotide therapy.

Table 1 – PRGC recommended changes to existing policy on linaclotide for IBS-C

Current local policy (PR 2016-08)	PR 2019-16

• Linaclotide is not routinely funded on the local NHS for the treatment of irritable bowel syndrome with constipation (IBS-C)
• Pharmacological management of IBS should otherwise be in line with NICE guidelines CG61: *Irritable bowel syndrome in adults: diagnosis and management**
	• Linaclotide may be considered for use in adults with moderate to severe IBS-C who fulfil both of the following criteria:
	  ○ they have not responded adequately to or cannot tolerate all other suitable treatment options including optimal or maximum tolerated doses of laxatives from different classes, and
	  ○ they have had constipation for at least 12 months
	• The rate of non-responders to linaclotide in phase 3 studies was high. Patients must therefore have a scheduled review after 4 weeks of treatment and linaclotide should be discontinued where symptoms have not improved.
	• Linaclotide should form part of a multifaceted approach to management of IBS that emphasises the importance of self-help, general lifestyle, physical activity and diet.

*Red = deletions; green = additions. *This statement has been withdrawn; pharmacological treatment of IBS is well established with the exception of linaclotide for IBS-C. When NICE updated CG61 in 2015 (CG61 was first published in 2008), the only new recommendation on pharmacological treatment of IBS concerned linaclotide.*