

Irritable bowel syndrome with constipation in adults: linaclotide

Evidence summary

Published: 9 April 2013

[nice.org.uk/guidance/esnm16](https://www.nice.org.uk/guidance/esnm16)

Overview

The content of this evidence summary was up-to-date in April 2013. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Key points from the evidence

Linaclotide (Constella) is a first-in-class, oral, once-daily guanylate cyclase-C receptor agonist (GCCA), licensed for the symptomatic treatment of moderate-to-severe irritable bowel syndrome with constipation (IBS-C) in adults. It received a European marketing authorisation in November 2012 and is expected to be launched during the first half of 2013.

Linaclotide has been evaluated in 2 double-blind, randomised, placebo-controlled trials of patients with IBS-C ([Rao et al. 2012](#) [Trial 1] and [Chey et al. 2012](#) [Trial 2]). An analysis of both trials, presenting the pre-specified analysis of primary efficacy end points as required by the [European Medicines Agency](#) (EMA), was also published in 2013 ([Quigley et al. 2013](#)). In both trials, a statistically greater proportion of linaclotide-treated patients, compared with placebo-treated patients, met the 2 co-primary efficacy end points required by the EMA, which were '12-week abdominal pain/discomfort responders' (trial 1: 54.8% compared with 41.8%; trial 2: 54.1% compared with 38.5%; $p < 0.001$) and 'IBS degree-of-relief responders' (trial 1: 37.0% compared with 18.5%; trial 2: 39.4% compared with 16.6%; $p < 0.0001$). A significantly greater percentage of patients treated with linaclotide also met the composite primary end point required by the US [Food](#)

and Drug Administration (FDA) of 'improvement of $\geq 30\%$ in average daily worst abdominal pain score and increase by ≥ 1 complete spontaneous bowel movement (CSBM) from baseline for $\geq 50\%$ of the weeks assessed' (trial 1: 33.6% [linaclotide] compared with 21.0% [placebo]; trial 2: 33.7% [linaclotide] compared with 13.9% [placebo]; in both trials $p < 0.001$ and number needed to treat [NNT] was 5 and 8). A statistically greater number of patients treated with linaclotide also met the 3 additional efficacy end points required by the FDA compared with the placebo-treated patients ($p < 0.05$). The most common treatment-related adverse event was diarrhoea.

The NICE clinical guideline Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care (NICE clinical guideline 61) was published in 2008. It identifies self-help as a key component of the management of IBS, and advises that people should receive information on general lifestyle, physical activity and diet. Based on the nature and severity of symptoms, pharmacological management may be considered, with the choice of agent(s) depending on the predominant symptom(s). Treatments include antispasmodic agents for abdominal pain, and laxatives or antimotility agents, depending on the presence of constipation or diarrhoea. Off-label use of a tricyclic antidepressant (TCA) or a selective serotonin reuptake inhibitor (SSRI) may be considered for people whose condition does not respond to first-line treatments.

Local decision makers will need to consider the place of linaclotide alongside existing treatments that may be used to manage symptoms of IBS-C, such as the concomitant use of antispasmodics and laxatives. The publication of head-to-head studies against existing treatments would facilitate a better understanding of its place in the management of IBS-C.

Key evidence

Trial 1: Rao S, Lembo AJ, Shiff SJ et al. (2012) A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *American Journal of Gastroenterology* 107: 1714–24

Trial 2: Chey WD, Lembo AJ, Lavins BJ et al. (2012) Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *American Journal of Gastroenterology* 107: 1702–12

Trial 1 and 2 – analysis of EMA co-primary end points: Quigley EM, Tack J, Chey WD et al. (2013) Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints. *Alimentary Pharmacology and Therapeutics* 37: 49–61

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Relevance to NICE guidance programmes

Linaclotide was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

Introduction

Irritable bowel syndrome (IBS) is a common, chronic, relapsing, gastrointestinal disorder of unknown cause. It is characterised by abdominal pain or discomfort associated with defaecation, abdominal bloating and bowel dysfunction (constipation, diarrhoea or both). IBS can affect sleep, cause stress, anxiety and lethargy, and decrease work productivity and quality of life (see the NICE clinical guideline on [IBS in adults](#)).

IBS most often affects people between the ages of 20 and 30 years, and is twice as common in women as in men. Prevalence in the general population is estimated to be between 10% and 20% (see the NICE clinical guideline on [IBS in adults](#)). IBS may be classified according to the predominant bowel habit: IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS, and untyped IBS. [Quigley et al. \(2013\)](#) reports that approximately 1 in 3 people with IBS experience constipation as the predominant bowel symptom.

The NICE clinical guideline on [IBS in adults](#) (published in February 2008) advises that people with IBS should be given information that explains the importance of self-help in managing their IBS. This includes information on general lifestyle, physical activity and diet (for example, limiting fresh fruit to 3 portions a day and avoiding high-fibre diets). Decisions about pharmacological management should be based on the nature and severity of symptoms. If drugs are considered necessary, the choice of agent will depend on the predominant symptom(s). An antispasmodic agent may be considered for people with abdominal pain. For IBS-C, laxatives should be considered, but the use of lactulose discouraged. A tricyclic antidepressant (TCA) should be considered for people whose condition has not responded to first-line drug treatment (a selective serotonin reuptake inhibitor may be used if TCAs are not effective). Referral for psychological therapies

(cognitive behavioural therapy, hypnotherapy and/or psychological therapy) should also be considered for people with refractory IBS, whose condition has not responded to pharmacological treatments after 12 months.

Product overview

Drug action

Linaclotide is a first-in-class, oral, once-daily, guanylate cyclase-C receptor agonist (GCCA) that 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.

Licensed indication

Linaclotide was [licensed](#) in November 2012 for the symptomatic treatment of moderate-to-severe irritable bowel syndrome with constipation (IBS-C) in adults. It is expected to be launched in the UK during the first half of 2013.

Course and cost

The recommended dosage for linaclotide is 1 capsule (290 micrograms) once daily. Physicians should periodically assess the need for continued treatment. The manufacturer has indicated a list price for linaclotide of £37.56 for 28 hard capsules (Almirall Limited: personal communication January 2013). This translates to an annual treatment cost of £489.62.

Evidence review

This evidence review is based on 2 published, phase III, placebo-controlled, [randomised](#) trials of linaclotide efficacy and safety (see table 1). Data from a third publication ([Quigley et al. 2013](#)), which presented the efficacy end points as required by the European Medicines Agency (EMA) from both trials, are also included in table 1.

The 2 trials were similar in design and were conducted by the same group of investigators. Both trials investigated the efficacy and safety of linaclotide compared with placebo in adults with irritable bowel syndrome with constipation (IBS-C). In trial 1, patients were treated for 12 weeks, followed by re-randomisation to a further 4 weeks of treatment to assess withdrawal of linaclotide. In trial 2, patients were treated for 26 weeks; however, the first 12 weeks were used to assess the

primary, and most of the secondary, end points (safety end points were assessed over the 26 weeks).

In both trials, rescue medication (bisacodyl 5 mg tablet or 10 mg suppository) was allowed for severe constipation. Trial 1 also reported that patients on a stable, continuous regimen of fibre, bulk laxatives, stool softeners or probiotics during the 30 days before the screening visit were allowed to continue, provided they maintained a stable dosage throughout the trial. Use of concomitant medication was not reported in trial 2.

Trial 1 ([Rao et al. 2012](#) and [Quigley et al. 2013](#))

- Design: 12-week, multi-centre, double-blind, randomised, placebo-controlled trial conducted in the USA and Canada. Allocation was concealed.
- Population: 800 patients (90.5% women, 9.5% men) aged 18 to 84 years, with a mean body mass index (BMI) of about 28, and meeting modified Rome II criteria for IBS-C. Patients had a mean value of 0.2 complete spontaneous bowel movements (CSBMs) per week.
- Intervention and comparison: After a pre-treatment baseline period of 14 to 21 days, patients were randomised in a 1:1 ratio to double-blind treatment with an oral capsule once daily containing either 290 micrograms of linaclotide or placebo, for 12 weeks. Patients who completed 12 weeks of treatment entered a 4-week, double-blind 'randomised withdrawal' phase, in which patients who were taking placebo were given linaclotide, and those who were taking linaclotide were randomised to either linaclotide or placebo.
- Primary end points:
 - Two pre-specified primary end points were required by the EMA, as reported by [Quigley et al. \(2013\)](#):
 - ◇ i. '12-week abdominal pain/discomfort responders', defined as patients who, for at least 6 weeks out of the first 12 weeks of treatment, had an improvement of 30% or more from baseline in either mean worst abdominal pain score or mean abdominal discomfort score for that week, with neither of these scores worsening from baseline for that week
 - ◇ ii. '12-week IBS degree-of-relief responders', defined as patients whose response to the 'degree-of-relief of IBS symptoms question' was 'considerably relieved' or 'completely relieved' for at least 6 weeks out of the first 12 weeks of treatment.

- Four pre-specified primary end points were required by the FDA, as reported by [Rao et al. \(2012\)](#):
 - ◇ i. 'FDA responders', defined patients with an improvement of 30% or more in average daily worst abdominal pain score and with an increase of 1 or more CSBM from baseline for 50% or more of the weeks assessed
 - ◇ ii. patients with an improvement of 30% or more in the weekly average of the daily worst abdominal pain score for 9 or more of the 12 weeks of the treatment period
 - ◇ iii. patients with 3 or more CSBMs and an increase of 1 or more CSBM from baseline for 9 or more of 12 weeks
 - ◇ iv. 'combined responders', defined as patients meeting the criteria for both end points ii and iii in the same week.
- Secondary end points included the 12-week change from baseline in abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency, severity of straining, constipation severity, IBS severity, relief of IBS symptoms and degree of relief.

Trial 2 ([Chey et al. 2012](#) and [Quigley et al. 2013](#))

- Design: 26-week, multi-centre, double-blind, randomised, placebo-controlled trial conducted in the USA. Allocation was concealed.
- Population: 804 patients (87% and 92% were women in the placebo and linaclotide groups respectively) aged 18 to 87 years, with a mean BMI of about 28, and meeting modified Rome II criteria for IBS-C. Patients had a mean value of 0.2 CSBMs per week.
- Intervention and comparison: After a pre-treatment baseline period of 14 to 21 days, patients were randomised in a 1:1 ratio to double-blind treatment with an oral capsule once daily containing either 290 micrograms of linaclotide or placebo, for 26 weeks.
- End points were the same as those in trial 1, and were measured after 12 weeks of treatment. The primary and secondary end points were also evaluated over the entire 26-week treatment period as 'additional' end points. A number of additional secondary end points were assessed, including 12-week and 26-week change-from-baseline end points for abdominal fullness and abdominal cramping, abdominal- and bowel-symptom responders, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction.

Table 1 Summary of the trials

	Placebo	Linaclotide 290 micrograms daily for 12 weeks (trial 1) or 26 weeks (trial 2)	Analysis
Trial 1 (Rao et al. 2012 and Quigley et al. 2013)			
Randomised	n=397	n=406	
Efficacy ^a	n=395	n=405	
Primary EMA efficacy end points:			
% patients defined as 12-week abdominal pain/ discomfort responders	41.8% (165/ 395)	54.8% (222/405)	Difference 13% p<0.001
% patients defined as 12-week IBS degree-of- relief responders	18.5% (73/ 395)	37% (150/405)	Difference 18.5% p<0.0001
Primary FDA end points:			
% patients defined as FDA responders	21.0% (83/ 395)	33.6% (136/405)	Difference 12.6% <u>Odds</u> <u>ratio</u> : 1.9 95% CI 1.4 to 2.7 p<0.0001 NNT: 8.0 (5.4 to 15.5)

% patients with improvement of $\geq 30\%$ in abdominal pain for $\geq 9/12$ weeks (end point ii)	27.1% (107/ 395)	34.3% (139/405)	Difference 7.2% Odds ratio: 1.4 95% CI 1.0 to 1.9 p=0.0262 NNT: 13.8 (7.4 to 116.1)
% patients with ≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline for $\geq 9/12$ weeks (end point iii)	6.3% (25/ 395)	19.5% (79/405)	Difference 13.2% Odds ratio: 3.7 95% CI 2.3 to 5.9 p<0.0001 NNT: 7.6 (5.6 to 11.6)
% patients defined as 'combined responders' (meeting criteria for both end points 'ii' and 'iii'[see above] in the same week for $\geq 9/12$ weeks)	5.1% (20/ 395)	12.1% (49/405)	Difference 7.0% Odds ratio: 2.6 95% CI 1.5 to 4.5 p=0.0004 NNT: 14.2 (9.2 to 31.3)
Selected secondary end points:			

% of patients with $\geq 30\%$ decrease in abdominal bloating for at least 6/12 weeks	29.9%	43.5%	Difference 13.6% 95% CI 5.0 to 14.3 $p < 0.0001$ NNT 7.4
Mean CSBMs per week (mean change from baseline)	1.0 0.7	2.6 2.3	Difference 1.6 $p < 0.0001$
% of patients reporting adequate relief from IBS symptoms for $\geq 9/12$ of the weeks	21.3% (84/ 395)	36.8% (149/405)	Difference 15.5% $p < 0.0001$ NNT: 6.4 (4.6 to 10.7)
Safety ^b	n=396	n=406	
Patients reporting serious adverse events (n)	0.5% (2/396)	0.5% (2/406)	ns
Diarrhoea (n)	3.5% (14/ 396)	19.5% (79/406)	$p < 0.0001$
Discontinuation due to diarrhoea	0.3% (1/396)	5.7% (23/406)	p not reported
Trial 2 (Chey et al. 2012 and Quigley et al. 2013)			
Randomised	n=403	n=402	
Efficacy ^{a,c}	n=403	n=401	
Primary EMA efficacy end points:			
% patients defined as 12-week abdominal pain/ discomfort responders	38.5%	54.1%	Difference 15.6% $p < 0.0001$

% patients defined as 12-week IBS degree-of-relief responders	16.6%	39.4%	Difference 22.8% p<0.0001
Primary FDA end points:			
% patients defined as FDA responders for ≥6/12 or 13/26 weeks	13.9% (56/ 403)	33.7% (135/401)	Difference 19.8% p<0.0001 NNT: 5.1 (95% CI 3.9 to 7.1)
% patients with improvement of ≥30% in average daily worst abdominal pain for ≥9/12 or 20/26 weeks (end point ii)	19.6% (79/ 403)	38.9% (156/401)	Difference 19.3% p<0.0001 NNT: 5.2 (95% CI 3.9 to 7.6)
% patients with ≥3 CSBMs and an increase of ≥1 CSBM from baseline for ≥9/12 or 20/26 weeks (end point iii)	5.0% (20/ 403)	18.0% (72/401)	Difference 13.0% p<0.0001 NNT: 7.7 (95% CI 5.8 to 11.5)
% patients defined as 'combined responders' (meeting criteria for both end points 'ii' and 'iii' [see above] in the same week for ≥9/12 or 20/26 weeks)	3.0% (12/ 403)	12.7% (51/401)	Difference 9.7% p<0.0001 NNT: 10.3 (95% CI 7.5 to 16.4)
Selected secondary end points:			

% of patients reporting adequate relief from IBS symptoms for $\geq 9/12$ weeks	17.6%	41.9%	Difference 24.3% NNT: 4.1 (95% CI 3.3 to 5.5) $p < 0.0001$
Safety ^{b,d}	n=403	n=402	
Patients with ≥ 1 treatment-emergent adverse event	56.6% (228/ 403)	65.4% (263/402)	$p < 0.05$
Diarrhoea (n)	2.5% (10/ 403)	19.7% (79/402)	$p < 0.0001$
Discontinuation due to diarrhoea	0.2% (1/403)	4.5% (18/402)	p not reported

Abbreviations: CI, confidence interval; CSBM, complete spontaneous bowel movement; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IBS, irritable bowel syndrome; NNT, number needed to treat; ns, not significant.

^a Included all patients who took ≥ 1 dose of trial medication and had ≥ 1 post-randomisation entry of primary efficacy end point.

^b Included all patients who took ≥ 1 dose of trial medication.

^c 12-week results reported.

^d 26-week results reported.

Clinical effectiveness

In both trials, a statistically greater proportion of patients treated with linaclotide compared with those treated with placebo met the 2 efficacy end points required by the EMA and the 4 efficacy end points required by the FDA, over the first 12 weeks of treatment. All secondary end points, including change in the number of CSBMs, abdominal pain, abdominal discomfort, abdominal bloating and IBS severity, were significantly more improved with linaclotide than with placebo.

In the 4-week 'randomised withdrawal' phase of the trial by [Rao et al. \(2012\)](#), patients who switched from linaclotide to placebo were reported to show an increase in the worst abdominal

pain ($p < 0.05$ compared with those continuing on linaclotide in weeks 14 to 16) and a decrease in CSBMs ($p < 0.001$ compared with those continuing on linaclotide in weeks 13 to 16) to levels similar to those in the original placebo group. Patients who switched from placebo to linaclotide showed improvement in these end points to levels similar to those in the original linaclotide group (p values not reported).

Safety

Adverse events were assessed over 12 weeks in trial 1, and over 26 weeks in trial 2. Diarrhoea was reported significantly more frequently with linaclotide than placebo in both trials, and led to discontinuation from the trial in 5.7% and 4.5% of patients treated with linaclotide in the 2 trials respectively, compared with 0.3% and 0.2% of patients treated with placebo. The incidences of other reported adverse events were similar in the linaclotide- and placebo-treated groups in both trials, except for abdominal pain and flatulence in trial 1, which were significantly more frequently reported with linaclotide than with placebo.

Evidence strengths and limitations

Because patients with IBS-C have heterogeneous and variable symptoms, the choice of valid end points in trials can be challenging. A strength of these 2 very similar trials of linaclotide was the use of a variety of end points, including responses to individual as well as combined symptoms and some global measures.

One of the primary end points recommended by the EMA was a measure of global improvement defined as 'IBS degree of relief'. This more rigorous end point captured an overall view of whether the symptoms of a patient's IBS-C have improved 'considerably' or 'completely', according to the patient. The FDA end points included improvement in abdominal pain and CSBM for at least half the study period. This end point can be considered to be quite rigorous, but may not be valid for patients who appeared to have improvement in pain but not in bowel movement frequency. Other responder end points involving individual symptoms were also used as primary end points, and further symptoms of importance to patients (although not proven as independent variables in IBS-C clinical trials) as well as validated global measures of these symptoms, were included as secondary end points.

In both trials, rescue medication with bisacodyl was permitted. Trial 1 also reported the continued use of fibre, bulk laxatives, stool softeners, or probiotics at a stable dosage during the treatment period. Neither the published trials nor the EMA review provided any additional analysis on the extent of the use of these treatments between linaclotide and placebo groups. Additional analyses

are therefore needed to better understand the benefit of linaclotide in patients continuing the use of laxatives or other treatments in these studies.

Although prevalence of IBS is greater in women than men, the high predominance of women in the studies (approximately 90% were women) is noted, which may limit applying the findings to the wider population.

Several listed authors were employees or paid consultants of Ironwood Pharmaceuticals or Forest Research Institute, which also supported the trials financially and editorially.

The [EMA's review of linaclotide](#) indicates that the final results of a long-term safety study are awaited. A post-authorisation safety study has also been requested to investigate complications of diarrhoea in patients with associated risk factors, and to consider safety in older patients.

The two key trials reviewed in this evidence summary suggest that linaclotide may be an effective treatment, when compared with placebo, for the symptoms of IBS-C. However, assessing linaclotide's place in therapy in the NHS is problematic because of the absence of active comparator studies.

Context

Treatment alternatives

Existing NICE guidance on [irritable bowel syndrome \(IBS\) in adults](#) includes recommendations on dietary and lifestyle interventions. If pharmacological management is necessary, the selection of treatment(s) is determined by the individual person's predominant symptom(s). Treatments may include antispasmodic agents, and laxatives or ant motility agents for the symptoms of constipation or diarrhoea respectively. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may also be used in people whose condition does not respond to first-line treatments, although the evidence for their use in IBS and IBS with constipation (IBS-C) is weak, and TCAs may be inappropriate for people with IBS-C because of TCA-induced constipation. It should also be noted that TCAs are primarily used for treating depression and are only recommended in IBS for their analgesic effect. SSRIs should only be considered if TCAs have been ineffective. Referral for psychological interventions (cognitive behavioural therapy, hypnotherapy and/or psychological therapy) should be considered for people with refractory IBS.

Costs of treatment alternatives

The table below shows selected treatments that are used for IBS in UK practice. Not all available formulations, brands, preparations or available dose strengths are listed due to space constraints.

Treatment and (adult) dosage ^a	Cost ^b for 52 weeks' treatment, except where stated
Linaclotide 290 microgram capsules (1 capsule, once daily)	£489.62
Amitriptyline 10 mg tablets (off-label use; 10 mg at night ^c)	£9.52
Citalopram 20 mg tablets (off-label use; 20 mg once daily)	£11.47
Antispasmodics:	
Alverine citrate 60 mg capsules (60 to 120 mg, once to 3 times daily)	£42.34 to £254.04
Dicycloverine hydrochloride 10 mg tablets (10 to 20 mg, 3 times daily)	£177.94 to £260.06
Hyoscine butylbromide 10 mg tablets (10 mg, 3 times daily; increased up to 20 mg, 4 times daily if necessary)	£44.00 to £117.32
Mebeverine hydrochloride:	£52.67
Standard-release 135 mg tablets: 135 mg, 3 times daily.	£84.19
Modified-release 200 mg tablets: 200 mg, twice daily	
Peppermint oil 0.2 ml gastro-resistant capsules (1 to 2 capsules, 3 times a day)	£91.77 to £183.54
Propantheline bromide 15 mg tablets (15 mg before each meal, 30 mg at bedtime; up to 120 mg may be needed in some patients)	£281.57 (based on 75 mg/day)
Selected laxatives:	
Ispaghula husk (3.5 g twice daily)	£53.53
Methylcellulose 500 mg tablets (3 to 6 500 mg tablets twice daily)	£62.96 to £125.92
Sterculia 62% w/w (1 or 2 x 7 g sachets once or twice daily)	£35.10 to £140.40
Bisacodyl 5 mg tablets (5 to 20 mg daily)	£12.52 to £50.08

Macrogol – Movicol sugar-free sachets, 30-sachet pack (maintenance dose: 1 to 2 sachets daily)	£81.27 to £162.55
<p>^a Doses taken from the relevant summary of product characteristics; therapeutic equivalence is not implied.</p> <p>^b Costs taken from Drug Tariff, March 2013, except for linaclotide (list price quoted by manufacturer) and sterculia (MIMS, February 2013).</p> <p>^c Starting dose quoted is based on the Clinical Knowledge Summary on irritable bowel syndrome.</p>	

Estimated impact for the NHS

Likely place in therapy

Pharmacological treatments for irritable bowel syndrome (IBS) are based on an evaluation of the person's symptoms, which, in some cases, may necessitate the use of multiple, concomitant treatments. Linaclotide may provide an additional (once daily) single treatment option for people with moderate-to-severe IBS and predominant symptoms of abdominal pain and constipation. The publication of head-to-head studies against existing treatments for IBS with constipation (IBS-C; for example, a bulk-forming laxative plus an antispasmodic agent) would facilitate a better understanding of its place in the management of IBS-C for local decision makers.

The direct acquisition cost of linaclotide is higher than any of the individual treatments listed in the tabulated cost of treatment alternatives, and is also higher than the cost of concomitant use of a bulk-forming laxative (such as ispaghula husk) and an antispasmodic (such as hyoscine butylbromide). However, cost implications will vary from person to person. Other economic impacts, for example on referrals to gastroenterology clinics, are unclear at this stage.

Estimated usage

A survey of people registered in GP practices based in the West Midlands has reported a community-based prevalence of IBS of 10.5%, with constipation as the predominant bowel symptom in 24% of people reporting symptoms of IBS ([Wilson et al. 2004](#)). In this study, almost half of people (46.7%) with IBS were receiving prescribed medication for IBS. Linaclotide may be a treatment option for a subgroup of people with moderate-to-severe symptoms of IBS-C needing pharmacological treatment.

The manufacturer estimates that in an average population of 100,000, 2520 people (2.5%) will be diagnosed with IBS-C. Of these, 1177 (46.7%) will be treated with pharmacological agents and of this group, 453 people (39%) will be dissatisfied with current treatment. Within this dissatisfied subgroup of 453 people, it is estimated that after launch 2% will be prescribed linaclotide in year 1, 5% in year 2, 9% in year 3, 14% in year 4 and 20% in year 5 (Almirall Limited: personal communication February 2013).

References

Almirall Limited (2012) [Constella summary of product characteristics](#) [online; accessed 22nd Feb 2013]

Chey WD, Lembo AJ, Lavins BJ et al. (2012) [Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety](#). *American Journal of Gastroenterology* 107: 1702–12

European Medicines Agency (2012) [Committee for Medicinal Products for Human Use assessment report on Constella](#) [online; accessed 22nd Feb 2013]

National Institute for Health and Clinical Excellence (2008) [Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care](#). NICE clinical guideline 61

National Institute for Health and Clinical Excellence [Irritable bowel syndrome](#). Clinical Knowledge Summaries; accessed 22nd Feb 2013

Quigley EM, Tack J, Chey WD et al. (2013) [Randomised clinical trials: linaclotide phase 3 studies in IBS-C – a prespecified further analysis based on European Medicines Agency-specified endpoints](#). *Alimentary Pharmacology and Therapeutics* 37: 49–61

Rao S, Lembo AJ, Shiff SJ et al. (2012) [A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation](#). *American Journal of Gastroenterology* 107: 1714–24

Wilson S, Roberts L, Roalfe A et al. (2004) [Prevalence of irritable bowel syndrome: a community survey](#). *British Journal of General Practice* 54: 495–502

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – interim process statement](#).

Copyright

© National Institute for Health and Care Excellence, 2013. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.

Contact NICE

National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk; nice@nice.org.uk; 0845 033 7780