Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

linaclotide hard capsules, 290 micrograms (Constella®) SMC No. (869/13)

Almirall SA

10 May 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

linaclotide (Constella®) is accepted for restricted use within NHS Scotland.

Indication under review: symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

SMC restriction: linaclotide is restricted for use in patients with moderate to severe IBS-C who have not responded adequately to or cannot tolerate all other suitable treatment options.

In two pivotal phase III studies linaclotide was superior to placebo for the co-primary endpoints of abdominal pain/discomfort responders and IBS degree-of-relief responders at 12 weeks. There are no comparative efficacy data versus first- or second-line treatments.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

Dosing Information

Linaclotide 290 micrograms once daily. Physicians should periodically assess the need for continued treatment. If patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefit of continued treatment reconsidered.

Product availability date

May 2013.

Summary of evidence on comparative efficacy

Linaclotide is structurally related to the endogenous guanylin peptide family and is thought to act within the lumen of the intestine through the activation of the guanylate cyclase subtype C receptor. The subsequent increase in cyclic guanosine monophosphate results in increased intestinal fluid secretion and accelerated transit. In addition, the threshold for colonic nociception is raised, which is thought to reduce sensation of pain.[1] Linaclotide is a first in class locally acting Guanylate Cyclase-C (GC-C) receptor agonist for the symptomatic treatment of irritable bowel syndrome with constipation (IBS-C). IBS-C is managed symptomatically with laxatives and antispasmodic agents and second-line with off-label antidepressants.[2]

The submitting company has requested that SMC considers linaclotide when positioned for use in adult patients with moderate to severe IBS-C who have not responded adequately to or cannot tolerate antispasmodics and/or laxatives.

Two similarly designed phase III studies have been conducted in adult patients with IBS-C based on modified Rome-II criteria.[1,3-5] For a diagnosis of IBS-C, modified Rome-II criteria required patients to report abdominal discomfort or pain with ≥2 of the following features for ≥12 weeks, which need not be consecutive, in the 12 months preceding the screening visit:
(a) relieved with defaecation
(b) onset associated with a change in frequency of stool, and
(c) onset associated with a change in form [appearance] of stool.

For inclusion, patients must also have reported <3 spontaneous bowel movements per week and reported ≥1 of the following symptoms for 12 weeks in the preceding 12 months:
(a) straining during >25% of bowel movements (BMs),
(b) lumpy or hard stools during >25% of BMs, and
(c) a sensation of incomplete evacuation during >25% of BMs.

The study comprised an initial screening period of up to 21 days where prohibited medicines were discontinued, followed by 14 to 21 day baseline (pre-treatment) period where daily and weekly assessment of symptoms was recorded. Patients with a mean score of ≥3 for daily abdominal pain (on an 11-point numerical rating scale, where 0=no abdominal pain and

10=severe abdominal pain) and an average of <3 complete spontaneous bowel movements per week and ≤5 spontaneous bowel movements per week were then randomised to treatment with linaclotide 290 micrograms daily or placebo for 26 weeks in study MCP-103-302 and 12 weeks in study LIN-MD-31. A 4-week randomised withdrawal period was included in study LIN-MD-31 only.

The co-primary endpoints for the European Medicines Agency (EMA) were abdominal pain/discomfort responders and IBS degree-of-relief responders at 12 weeks assessed in the intent-to-treat population. An abdominal pain/discomfort responder 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 for at least 6 weeks out of the first 12 weeks of treatment. Abdominal pain and abdominal discomfort were individually assessed daily using an 11-point numeric rating scale; patients were asked to rate their worst abdominal pain and their abdominal discomfort over the last 24 hours on a scale from '0' (none) to '10' (very severe). An IBS degree-of-relief responder was a patient who was 'considerably relieved' or 'completely relieved' (i.e. a score of 1 or 2 on a 7 point scale), in response to the degree-of-relief of IBS symptoms question for at least 6 weeks out of the first 12 weeks of treatment.

In both studies linaclotide was significantly superior to placebo for the co-primary endpoints (see table below).

Table: results of co-primary endpoints for studies MCP-103-302 and LIN-MD-31

	Study MCP-103-302			**Study LIN-MD-31**		
	Linaclotide	Placebo	OR (95% CI) p-value	Linaclotide	Placebo	OR (95% CI) p-value
N (ITT)	401	403		405	395	
abdominal pain/discomfort responders at week 12 n (%)	217 (54%)	155 (38%)	1.90 (1.43 to 2.52) p<0.0001	222 (55%)	165 (42%)	1.70 (1.28 to 2.25) p=0.0002
degree-of-relief responder at week 12 n (%)	158 (39%)	67 (17%)	3.26 (2.34 to 4.53) p<0.0001	150 (37%)	73 (18%)	2.61 (1.89 to 3.62) p<0.0001

ITT=intent-to-treat, OR=odds ratio, CI=confidence interval

In study MCP-103-302, linaclotide was also significantly superior to placebo at 26 weeks: abdominal pain/discomfort responder 54% (215/401) versus 36% (145/403), OR 2.06 (95% CI 1.55 to 2.73), and IBS degree-of-relief responder 37% (149/401) versus 17% (68/403), OR 2.90 (95% CI 2.09 to 4.04). In both studies, linaclotide was superior to placebo for secondary endpoints including complete spontaneous bowel movement frequency rate, stool consistency, severity of straining and bloating.

Quality of life (QoL) was assessed using the IBS-QoL tool that comprised an overall average score plus eight subscale scores (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual relationships). In both studies the improvement in

overall score and all subscales (except interference with activity subscale in study LIN-MD-31) was significantly greater for linaclotide than placebo. QoL was also measured using the EQ-5D which assessed mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses on each of these subscales were converted to a corresponding utility index and patients also rated their health state from '0' (worst imaginable) to '100' (best imaginable) using a visual analogue scale (EQ-5D VAS). There were significant differences in favour of linaclotide for the EQ-5D utility index for both studies and in EQ-5D VAS for study MCP-103-302 only.

In study LIN-MD-31 patients who completed 12 weeks of the double-blind treatment period were eligible to enter the double-blind 4-week randomised withdrawal period in which patients initially randomised to linaclotide were re-randomised (1:1) to linaclotide 290 microgram or placebo, and patients previously randomised to placebo were assigned to receive linaclotide 290 microgram once a day. Patients who were treated with linaclotide during the 12-week period, and then re-randomised to placebo in the randomised withdrawal period had a reduction in the improvements attained over the course of linaclotide treatment. However there was no evidence of a rebound effect after linaclotide withdrawal.

Summary of evidence on comparative safety

In study MCP-103-302, treatment emergent adverse events were reported in a significantly higher proportion of patients on linaclotide than placebo: 65% (263/402) versus 57% (228/403). Overall, adverse events resulted in the premature discontinuation of 10% (41/402) versus 2.5% (10/403) of patients taking linaclotide and placebo, respectively. The incidence of diarrhoea was significantly higher in the linaclotide group (20% [79/402]) than the placebo group 2.5% [10/403]) and was the reason for treatment discontinuation in 4.5% versus 0.2% of linaclotide- and placebo-treated patients, respectively. Adverse events occurring in a numerically higher proportion of patients in the linaclotide than placebo group included flatulence (3.7% [15/402] versus 2.2% [9/403]) and viral gastroenteritis (3.7% [15/402] versus 2.2% [9/403]). Abdominal pain occurred in a similar proportion of patients (around 4%) in each group.[1,4]

In study LIN-MD-31, treatment emergent adverse events were reported in a similar proportion of patients in both groups (53% and 56% in the placebo and linaclotide groups respectively). More patients discontinued treatment due to adverse events in the linaclotide group (7.9% [32/406]) than placebo group (2.8% [11/396]). Diarrhoea, the most common treatment emergent adverse event, was reported in 19% (79/406) versus 3.5% (14/396) of patients and resulted in treatment discontinuation in 5.7% versus 0.3% of linaclotide and placebo-treated patients, respectively.[1,5]

Two ongoing, long-term open-label safety studies have recruited 2,147 patients with IBS-C.[1] Data are available at a cut-off of June 2011, where the mean treatment duration was 200 days. The most common treatment emergent adverse events were diarrhoea (32% [693/2147]), sinusitis (6.4% [137/2,147]), abdominal pain (6.3% [135/2,147]), urinary tract infection (5.9% [127/2,147]), upper respiratory tract infection (5.5% [119/2,147]) and nausea (4.9% [105/2,147]).

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers linaclotide when positioned for use in adult patients with moderate to severe IBS-C who have not responded adequately to or cannot tolerate antispasmodics and/or laxatives. The pivotal studies did not specifically recruit

such patients. However the submitting company stated that the mean duration of diagnosed IBS-C was 13.2 years in the studies and therefore considered that patients would have already tried first-line treatments.

The pivotal studies have demonstrated efficacy of linaclotide over placebo for the symptomatic treatment of IBS-C but the studies have some limitations. The proportion of patients on concomitant antidepressant treatment was 20% to 30%, although in each study the proportions were similar between groups. Overall, the EMA considered that the evidence was robust.

However there are no direct or indirect comparative efficacy data versus other treatments for IBS-C. Off-label use of antidepressants is the relevant comparator, in terms of the positioning and a recent Cochrane review concluded that there is good evidence that antidepressants are effective for the treatment of IBS.[6] The submitting company's justification for not undertaking an indirect comparison of linaclotide versus antidepressants because of lack of suitable data appears to be reasonable.

The company presented post hoc sub-group analyses of the pivotal studies that compared patients in the placebo groups who were on concomitant antidepressants (19% to 26% of the ITT population) with patients not on concomitant antidepressants in the linaclotide groups (73% to 81% of the ITT population). In both studies the proportion of abdominal pain/discomfort responders and IBS degree-of-relief responders at 12 weeks was significantly superior for linaclotide than placebo patients on antidepressants. Patient satisfaction (in terms of study medication's ability to relieve IBS), measured on an ordinal 1 to 5 scale, was also significantly superior for linaclotide than placebo patients on antidepressants. There are some limitations with these analyses which the company have provided reassurance on, however, some uncertainties still remain in terms of comparative efficacy of linaclotide versus antidepressants.

Diarrhoea occurred in approximately one-third of patients in the long-term, open-label studies and the incidence was around 20% in the placebo controlled studies.[1] Overall, 2% of patients had severe diarrhoea and 5% discontinued treatment with linaclotide due to diarrhoea in clinical studies.[7] The EMA commented that in the clinical studies the occurrence of diarrhoea did not lead to dehydration, acid-base and electrolyte disturbances, or dizziness, hypotension, or syncope. However, the summary of product characteristics notes the possible occurrence of diarrhoea during treatment and includes management strategies if severe or prolonged diarrhoea occurs.[6]

Approximately 45% of patients did not fully respond to linaclotide treatment in the pivotal phase III studies. The summary of product characteristics advises that the need for continued treatment should be assessed in patients periodically. If patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefit of continued treatment reconsidered.

SMC clinical experts highlighted an unmet need in this patient group and considered a trial of linaclotide to potentially be useful after standard therapies had been considered.

The availability of linaclotide would provide clinicians with an additional symptomatic treatment for IBS-C in an area where there is a lack of documented, reliable and licensed treatment options. The EMA noted that there was a clear unmet need.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing linaclotide with off-label antidepressants in patients with moderate to severe IBS-C who have not responded adequately to or cannot tolerate antispasmodics and/or laxatives. The antidepressant included in the analysis was amitriptyline. A Markov model consisting of four health states defined in terms of treatment satisfaction was used. The time horizon for the analysis was five years. Patients entered the model in the 'not satisfied' health state and following initiation of treatment they could remain in that state or move to 'moderately satisfied', 'satisfied' or 'dead'. A stopping rule was included in the model whereby at each four-week cycle the need to continue treatment was assessed. Patients were assumed to be treated with linaclotide until they transitioned to the 'not satisfied' health state at which point they discontinued treatment. Patients who discontinued linaclotide were assumed to move through the model based on the transition probabilities in the antidepressant arm.

The clinical data used in the economic analysis were taken from the two phase III studies described above. Patient-level data from the secondary outcome measure of treatment satisfaction were used to derive transition probabilities based on the data collected at all visits throughout the study period. In order to provide a comparison with antidepressants, a post-hoc sub-group analysis was conducted to identify patients in the placebo arm receiving concomitant antidepressants. Beyond 26 weeks, the transition probabilities for the extrapolation phase of the model were based on the average of the transitions observed between 4 and 26 weeks.

The model used EQ-5D data collected in the studies. Patients completed the EQ-5D questionnaire at randomisation and at all subsequent trial visits. Average utility values were estimated based on patient-level data across all visits for patients receiving linaclotide and patients receiving placebo with concomitant antidepressants. Resource use estimates were based on clinical expert opinion and included GP and outpatient visits in the base case. Additional costs such as inpatient visits, CT scans and ultrasounds were included in a sensitivity analysis.

In the base case, the company estimated a cost per quality adjusted life year (QALY) of £4,947 based on an incremental cost of £433 and a QALY gain of 0.08753. Threshold analysis indicated the effectiveness of linaclotide could be reduced by 22% before the cost per QALY increased to £30k. The probabilistic sensitivity analysis indicated that the probability linaclotide would be cost-effective was 83% and 85% based on willingness to pay thresholds of £20k and £30k respectively.

A limitation of the company's base case analysis was that it compared patients treated with placebo receiving concomitant antidepressants with patients treated with linaclotide where some patients were also receiving concomitant antidepressants. The submitting company subsequently provided a revised sub-group analysis excluding these patients and this showed the results were similar to the base case (£4,529 per QALY). In addition, a further limitation of the base case result related to the assumptions used to extrapolate data beyond 26 weeks. When the company made more appropriate assumptions regarding the extrapolation, combined with the correction to exclude linaclotide patients receiving concomitant antidepressants, a revised base case cost per QALY of £7,370 resulted (based on an incremental cost of £659 and a QALY gain of 0.089).

The following limitations were noted:

- The clinical data used in the model were based on a post-hoc sub-group analysis which has some limitations. The submitting company provided some threshold analysis to show the impact of varying the effectiveness of linaclotide on the revised base case cost-effectiveness scenario (£7,370 per QALY). This indicated that the effectiveness of linaclotide would have to be 10.5%, 12.4% and 13.7% less for the cost per QALY to exceed £20,000, £25,000 and £30,000 respectively This analysis was helpful in providing an estimate of the potential variability in the cost-effectiveness results given some of the limitations in the clinical data used in the model.
- An indirect comparison comparing linaclotide with antidepressants was not conducted. The company stated that it was not possible to conduct an indirect comparison due to issues with available data. Statistical advice confirmed that it would have been difficult to conduct a robust indirect comparison in this situation.

Despite these weaknesses, the economic case has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Action on Pain UK.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence published clinical guideline 61; Irritable bowel syndrome in adults (diagnosis and management of irritable bowel syndrome in primary care), in February 2008.[2] Decisions about pharmacological management should be based on the nature and severity of symptoms. The recommendations made below assume that the choice of single or combination medication is determined by the predominant symptom(s) and the following treatments are for IBS-C.

- Antispasmodic agents taken as required, alongside dietary and lifestyle advice.
- Laxatives should be considered for the treatment of constipation in people with IBS, but people should be discouraged from taking lactulose.
- People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well formed stool (corresponding to Bristol Stool Form Scale type 4).
- Tricyclic antidepressants (TCAs) should be considered as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. Treatment should be started at a low dose (5 to 10mg equivalent of amitriptyline), which should be taken once at night and reviewed regularly. The dose may be increased, but does not usually need to exceed 30mg.
- Selective serotonin reuptake inhibitors (SSRIs) should be considered for people with IBS only if TCAs have been shown to be ineffective.
- After prescribing TCAs or SSRIs for the first time at low doses for the treatment of pain or discomfort in IBS, the person should be followed up after 4 weeks and then at 6 to 12 monthly intervals thereafter.

NB: At the time of publication (February 2008) SSRIs and TCAs did not have UK marketing authorisation for the indication described. Informed consent should be obtained and documented.

Additional information: comparators

First line; laxatives plus antispasmodics. Second line; antidepressants.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
linaclotide	**290 micrograms once daily**	**488**
Laxatives		
Bisacodyl	5 to 20mg orally once daily	23 to 91
Ispaghula husk	3.4mg sachet up to three times daily	89
Antispasmodics		
Peppermint oil	one to two capsules three times daily	92 to 183
Hyoscine butylbromide	10mg three times daily to 20mg four times daily	44 to 117
Mebeverine	135mg three times daily	66
Antidepressants		
Amitriptyline*	10 to 30mg once daily	11 to 32
Fluoxetine*	20mg once daily	9

Doses are for general comparison and do not imply therapeutic equivalence. The list of drugs is not exhaustive. Management may require the use of a combination of treatments. Costs are from eVadis on 20 February 2013, except for cost of linaclotide which is from company's submission. *off-label use

Additional information: budget impact

The submitting company estimated that 306 patients would be treated in year 1 rising to 3,133 patients in year 5.

The gross impact on the medicines budget was estimated to be £94k in year 1 and £959k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £91k in year 1 and £937k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

1. European Medicines Agency (EMA). European Public Assessment Report. Linaclotide capsules (Costella®). 20 September 2012. EMEA/H/C/002490 www.ema.europa.eu
2. National Institute for Health and Clinical Excellence. Clinical guideline 61; Irritable bowel syndrome in adults (diagnosis and management of irritable bowel syndrome in primary care) February 2008. www.nice.org
3. Quigley EM, Tack J, Chey WD et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther 2013; 37(1):49-61.
4. Chey WD, Lembo AJ, Lavins BJ et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012; 107(11):1702-1712.
5. Rao S, Lembo AJ, Shiff SJ, et al. A 12- week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndome with constipation. Am J Gastroenterol 2012; 107: 1714 -1724
6. Ruepert L, Quartero AO, de Wit NJ et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2011;(8):CD003460
7. Linaclotide capsules (Costella®) Summary of product characteristics. Almirall SA. European Medicines Agency www.ema.europa.eu. Last accessed 20 February 2013

This assessment is based on data submitted by the applicant company up to and including 16 April 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.