# LINACLOTIDE

## Constella® in the symptomatic management of irritable bowel syndrome with constipation.

## The indication was granted... so what?

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**ABSTRACT**

**Although authorized for irritable bowel syndrome with constipation it offers only symptomatic relief.**

**In the best of cases, one in five patients can benefit from treatment.**

**On the other hand, one in five patients can suffer from diarrhea as a secondary effect which can last for more than 28 days in half the cases.**

**There are no available studies evaluating linaclotide versus other recommended comparators (laxatives and spasmolytics).**

### Indications[1]

Linaclotide is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Reimbursement of this drug has been restricted by the National Health System to patients with severe irritable bowel syndrome with constipation (IBS-C) who have not responded adequately or present intolerance to any of the elective options of treatment.

### Mechanism of action[1]

Linaclotide is a Guanylate Cyclase-C receptor agonist with visceral analgesic and secretory activities. It is metabolized locally in the digestive system leading to destyrosine, its main active metabolite. At the same time, linaclotide is a homologue of the most potent thermostable enterotoxin which explains why diarrhea is the most frequent secondary effect.

### Dosage and administration[1]

The recommended dose is one capsule (290 mcg) daily, administered orally at least 30 minutes before each meal.

Treatment should not be prolonged for more than 4 weeks if no therapeutic response is obtained.

Once opened the capsules should be employed within 18 weeks and should remain tightly sealed to protect them from humidity.

### Clinical efficacy

The efficacy of linaclotide has been evaluated versus placebo in two multicenter phase III, randomized and double-blind clinical trials.[4-5] In the design of both trials the requisites from both the EMA and FDA[6-8] were met by defining four primary endpoints: good response, improvement in pain/discomfort, rate of spontaneous loose stool, and the composite pain-loose stool variables.

A total of 1,604 patients (90.5% women) were included. In no case was "severity" of the disease defined.[11] Patients who did not respond to or could not tolerate other treatments for IBS-C were excluded from the trials. In both studies rescue medication was permitted with bisacodil, as well as the concomitant use of laxatives, fiber in diet, and probiotics. The primary endpoint of these two studies was to evaluate the efficacy and safety profile of linaclotide in the first weeks of treatment, although in the second trial there was an additional assessment after 26 weeks (see table below).

*A similar percentage of patients improving and suffering from diarrhoea*

The maximum therapeutic response on intestinal function was observed during the first week of treatment, but at week 8 no statistically significant effect on improvement in pain was observed. Placebo response rates were rather high and so were no-response rates to linaclotide. It is rather difficult to establish the profile of patients that may benefit from this drug.[9]

**TRIAL BY RAO ET AL.**

| Outcome | Response to placebo (n=395) % | Response to linaclotide (n=405) % | NNT* |
|---|---|---|---|
| Pain after 12 weeks (EMA) | 41.8 | 54.8 | 7.6 |
| Symptomatic relief after 12 weeks (EMA) | 18.5 | 37.0 | 5.4 |

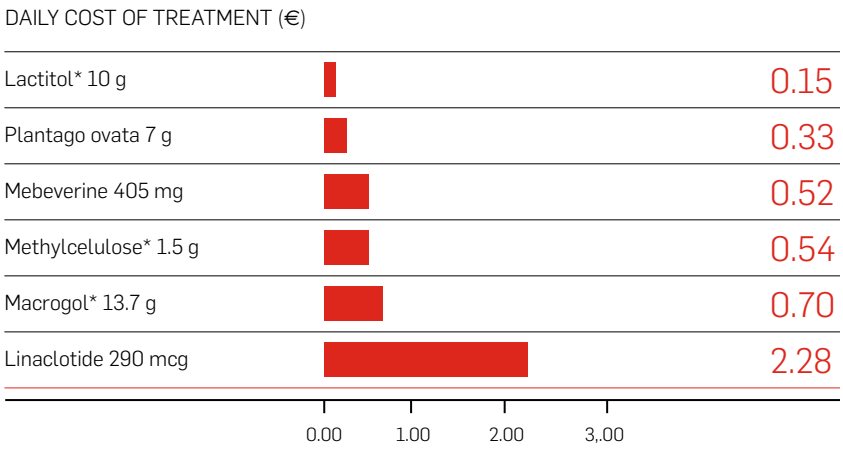
**TRIAL BY CHEY ET AL.**

| Outcome | Response to placebo (n=403) % | Response to linaclotide (n=401) % | NNT |
|---|---|---|---|
| Pain after 12 weeks (EMA) | 38.5 | 54.1 | 6.4 |
| Pain after 12 weeks (EMA) | 16.6 | 39.4 | 4.4 |

**CLASSIFICATION**

| | |
|---|---|
| 4 | IMPORTANT THERAPEUTIC INNOVATION |
| 3 | MODEST THERAPEUTIC INNOVATION |
| 2 | SOME ADDED VALUE IN SPECIFIC SITUATIONS |
| 1 | NO THERAPEUTIC INNOVATION |
| 0 | **INSUFFICIENT EVIDENCE** |

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.




(*) Not reimbursed for the treatment of IRS.

## Safety

### Adverse reactions[1]

**Very frequent (≥1/10):** diarrhea. **Frequent (≥1/100 - <1/10):** Viral gastroenteritis, gastrointestinal related disorders (abdominal pain, flatulence, abdominal distension) and dizziness.

**Diarrhoea.** This is the most frequent adverse effect (20%). In clinical trials, approximately half of the episodes of diarrhea started during the first week of treatment, and was severe in 2% of the patients treated while 5% of the patients abandoned treatment. The evolution period was more than 28 days in 53% of the cases. This effect was more frequent in elderly patients (>65 years), patients with hypertension and diabetes.

### Contraindications[1]

Hypersensitivity to linaclotide or any of its excipients.

Patients with known or suspected mechanical gastrointestinal obstruction.

### Warnings and precautions[1]

This drug should be used when other organic disease has been ruled out and the diagnosis of moderate to severe IBS-C is confirmed.

Temporary treatment discontinuation should be considered when diarrhea is severe or prolonged. 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.

No studies have been carried out in patients with chronic inflammatory bowel disease, and thus the use of this drug in these patients is not recommended.

### Use in special situations[1]

**Pregnancy/Breastfeeding:** avoid its use. **Children:** it should not be employed in patients uner 18 years of age. **Elderly:** given the high risk of suffering from diarrhea, regular monitoring of the risk-benefit relationship in these patients should be carried out. **Renal or liver impairment:** no dose adjustments are required.

### Interactions[1]

Concomitant treatment with proton pump inhibitors, laxatives or NSAIDs can increase the risk of diarrhea.

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.

## EMA Risk Management Plan[1]

Routine pharmacovigilance measures are described and include monitoring of diarrhea, incontinence and fecal urgency, viral gastroenteritis, potential abuse, off-label use, as well as close monitoring of elderly patients.

## Place in therapeutics

Irritable bowel syndrome (IBS) is a chronic disorder that presents abdominal pain and discomfort and intestinal habit dysfunction with no apparent organic cause. Current management options are of limited efficacy.[9] Practical clinical guidelines recommend diet and hygiene related habits, increase in physical exercise and the correct habits regarding bowel movements. When these measures are not sufficient then the use of laxatives and non-anticholinergic antispasmodic agents are recommended.

Although linaclotide is the first drug to obtain authorization specifically for moderate to severe IBS-C, its main objective still remains symptomatic relief of the disease. In none of the two studies that led to authorization was the efficacy compared to other mentioned treatment alternatives tested. On average, 55% of patients under linaclotide showed improvements in pain and discomfort, and 41% reported considerable or complete remission of symptoms for at least 6 to 12 weeks of treatment, compared to 35% and 18% of the patients under placebo, respectively.

With respect to the safety profile, enterotoxin-homologues produce diarrhea as the most frequent secondary effect, which can last for more than 28 days in more than half of the cases. For this reason, special precaution is recommended with regard to patients at risk of dehydration or electrolyte balance disturbances.

Lastly, given the scarce available evidence and the doubts still pending resolution with regard to whether treatment should be continuous or given only at acute episodes of the syndrome, it is conclusive that the information on linaclotide is insufficient to establish its therapeutic niche in the management of IBS-C. Its use should only be considered when the rest of the treatment options fail, without prolonging treatment for more than 4 weeks if the response is inadequate.

## Presentations

Constella® (Almirall) 290 mcg 28 hard capsules (63.82€). Requires especial authorization for health service reimbursement.

## References

A complete report on linaclotide can be found at: www.bit.navarra.es

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