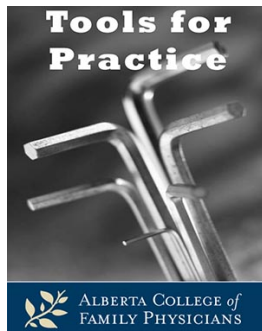


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## Moving along the management of constipation predominant IBS – Is it worth the cost?

**Clinical Question: What is the efficacy and safety of linaclotide in constipation predominant irritable bowel syndrome (IBS-C)?**

**Bottom Line:** Compared to placebo, for every seven patients treated with linaclotide one more will be a “responder” [30% improvement in pain and one additional “complete” spontaneous bowel movement (CSBM) per week for six weeks in 12]. Overall, patients experience ~3 additional “spontaneous” bowel movements (BM) per week, at the price of \$15 per BM. For every 21 patients treated, one will stop due to diarrhea. Post-marketing surveillance should help clarify long-term safety.

### Evidence:

- Two multicentre, Randomized Controlled Trials (RCTs) (803 and 805 patients)<sup>1,2</sup> comparing linaclotide 290 mcg to placebo in IBS-C, and three systematic reviews.<sup>3-5</sup>
  - Both RCTs had strikingly similar baseline demographics and outcomes at 12 weeks:<sup>1,2</sup>
    - Mean age 44, ~ 90% female, ~78% Caucasian.
    - Baseline abdominal pain ~5.6 on 0-10 point scale, CSBM 0.2/week.
  - Primary outcome:
    - “Responder”: ≥30% reduction in abdominal pain and increase of one CSBM per week for six of the 12 weeks.<sup>1,2</sup>
    - 34% linaclotide versus 14-21% placebo.<sup>1,2</sup>
    - Combined number needed to treat=7.<sup>3,4</sup>
  - Secondary outcomes:
    - ~3 additional spontaneous BM per week (above placebo).<sup>1,2</sup>
    - Average pain reduction in both trials was 1.9 linaclotide versus 1.1 placebo (0-10 scale).
      - Minimally clinically important difference=2.2.<sup>6</sup>
  - Adverse outcomes:
    - Diarrhea resulting in discontinuation:<sup>1,2</sup>
      - 4-6% linaclotide versus 0.2-0.3% placebo.
      - Combined Number Needed to Harm=21.

- Limitations: Unclear recruitment, run in excluded >40% of patients.
- Over 40 publications (abstract and peer-reviewed) on two RCTs with common author (employee of linaclotide manufacturer). Some inconsistent data between abstracts and peer-reviewed publications.<sup>3,7</sup>
- One smaller RCT reported similar outcomes.<sup>8</sup>

#### Context:

- Publication bias likely: Two open-label, 52 and 78-week safety studies with 1,557 and 1,743 patients completed in 2012 and 2013 not fully published<sup>9-11</sup> but have been evaluated by the FDA.<sup>12</sup>
- At least two other IBS-C drugs have been withdrawn due to safety concerns:
  - Tegaserod: 5-HT<sub>4</sub> antagonist due cardiovascular risk.<sup>13</sup>
  - Alosetron: 5-HT<sub>3</sub> antagonist due to ischemic colitis.<sup>14</sup>
- Linaclotide costs approximately \$180 per month or ~\$15 per additional BM.

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#### Disclosure:

Authors do not have any conflicts of interest to declare.

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