Lubiprostone: new treatment for chronic idiopathic constipation

Steve Chaplin BPharm, MSc and Alex Ford MD, FRCP

Lubiprostone (Amitiza) increases intestinal motility and is licensed for the treatment of chronic idiopathic constipation. In our New products review, Steve Chaplin presents the data relating to its efficacy and adverse events and Dr Alex Ford discusses its place in therapy.

The management of chronic constipation involves attention to causes, lifestyle change and sequential treatment with laxatives.\(^1\) If treatment with at least two different laxatives at maximum tolerated doses has been tried for at least six months but is unsuccessful, women have the option of treatment with prucalopride (Resolor).\(^2\)

**Lubiprostone**

Lubiprostone (Amitiza – Sucampo) is a locally-acting chloride channel activator that increases intestinal fluid secretion. This softens the bowel contents, increases intestinal motility and reduces symptoms.

It is licensed for the treatment of chronic idiopathic constipation and associated symptoms in adults when non-pharmacological measures are unsatisfactory.

A course of treatment lasts two weeks (there is no instruction on repeating courses). The recommended dose is 24µg twice daily, taken with food.

No dose adjustment is recommended in the elderly or those with renal or mild hepatic impairment. Patients with moderate or severe hepatic impairment are at increased risk of adverse effects and should start treatment at a dose of 24µg once daily; this can be increased if treatment is well tolerated but the response is unsatisfactory.

Lubiprostone is poorly absorbed and no clinically significant drug interactions have been identified. It is contraindicated in patients with a known or suspected mechanical gastrointestinal obstruction.

Lubiprostone is currently being appraised by NICE; publication is expected in October 2014.

**Clinical trials**

Three four-week placebo-controlled double blind trials, two of which have been published, provide evidence for the efficacy and safety of lubiprostone.\(^5\) Most patients were women and their mean age was 47. The primary end-point was the frequency of spontaneous bowel movements.
Lubiprostone

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number of spontaneous bowel movements after one week.

Lubiprostone significantly increased spontaneous bowel movements by approximately two per week compared with placebo (from about 1.3–1.6 at baseline to 5.4–5.9 with lubiprostone and 2.9–4.0 with placebo). This was associated with improvements in secondary end-points including stool consistency, straining, and constipation severity, and in patients' assessments of effectiveness.

Defining a full response as four or more spontaneous bowel movements per week and a moderate response as more than three and less than four per week, the rate of full or moderate responders was significantly higher with lubiprostone at week 1 (77–87 vs 59–61 per cent with placebo) and week 2 (67–69 vs 51–54 per cent).

Lubiprostone was associated with less use of rescue medication than placebo but the difference was not statistically significant. Efficacy diminishes after four weeks and the duration of treatment is therefore limited to two weeks.4

Adverse effects

More patients discontinued treatment with lubiprostone than placebo, primarily due to adverse events (7.5 vs 0.8 and 12.6 vs 0.8 per cent in four-week trials5).

The commonest adverse events in the pivotal trials were nausea (27 per cent), diarrhoea (10 per cent), headache (9 per cent) and abdominal pain (6 per cent). Nausea was considered mild to moderate in severity and occurred in the early days of treatment.5

Dyspnoea (a sensation of chest tightness and/or difficulty taking in a breath) was reported by 1.7 per cent of patients in trials.

Symptoms generally began within 30–60 minutes of the first dose; they usually resolved within a few hours but recurrence has been frequently reported with further doses.6

Place in therapy

Symptoms of chronic idiopathic constipation include persistently difficult, infrequent or incomplete defecation in the absence of any physiological abnormality. The condition is extremely common, affecting up to 20 per cent of individuals in the community.2

Traditionally, sufferers are told to increase dietary fibre intake in order to alleviate symptoms, but there is little evidence from randomised controlled trials that this approach is of any benefit.3

In a multinational survey of patients with chronic idiopathic constipation, between 16 and 40 per cent reported that they used laxatives, with almost two-thirds using them on at least a monthly basis.4 However, levels of dissatisfaction with laxatives are high, primarily due to concerns about efficacy and safety.5

As a result, novel drug therapies for the disorder have been developed. Lubiprostone acts on chloride channels in the intestinal enterocyte, leading to an increase in the chloride concentration of intestinal fluid, thereby stimulating intestinal fluid secretion and accelerating transit.

The efficacy of the drug has been studied in several placebo-controlled trials.6–8 A meta-analysis of these studies, containing 610 patients, demonstrated that lubiprostone was superior to placebo for the treatment of chronic idiopathic constipation, with a number needed to treat to improve one patient’s symptoms of four.9

However, adverse events were significantly more common with lubiprostone. The relative risk of any adverse event with lubiprostone was 1.79, and the relative risks of diarrhoea and nausea were 4.4 and 7.2 respectively, although rates of headache were not significantly higher with lubiprostone.

The adverse event profile may limit the use of lubiprostone in usual clinical practice, but for now a trial of the drug seems reasonable in individuals with chronic idiopathic constipation who have failed treatment with more conventional therapies such as fibre, or osmotic or stimulant laxatives.

References

1. NICE Clinical Knowledge Summaries. Chronic constipation. January 2013. (http://cks.nice.org.uk/constipation#forscenerecommendation:1)

Declaration of interests

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.

References


Declaration of interests

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Dr Ford is associate professor and honorary consultant gastroenterologist, Leeds Institute of Biomedical and Clinical Sciences, Leeds University and Leeds Teaching Hospitals Trust