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# Lubiprostone

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## Contents



## Abstract

▲ Lubiprostone (Amitiza™) is an oral bicyclic fatty acid that selectively activates type 2 chloride channels in the apical membrane of the gastrointestinal epithelium, resulting in increased fluid secretion.

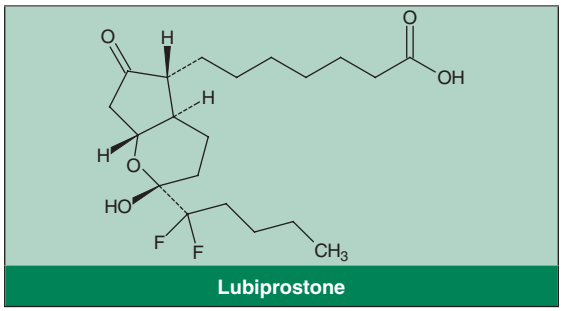
▲ In two pivotal, randomised, double-blind, multicentre phase III studies in patients with chronic idiopathic constipation, the frequency of spontaneous bowel movements (SBMs) was significantly greater in patients receiving lubiprostone 24μg twice daily than in those receiving placebo at each weekly timepoint throughout both 4-week studies ($p < 0.05$).

▲ At week 1 in one pivotal trial, the mean frequency of SBMs in the lubiprostone group was 5.9 per week compared with 4.0 per week in the placebo group ($p < 0.0001$) [baseline SBMs 1.3 and 1.5 per week].

▲ Significantly greater improvements occurred with lubiprostone than placebo in the degree of straining, stool consistency and constipation severity (where reported) in both pivotal studies ($p < 0.05$ for all comparisons at all timepoints).

▲ Lubiprostone was generally well tolerated in clinical trials with no reports of treatment-related serious adverse events in pivotal trials. Nausea was the most common adverse event, occurring in up to 31% of patients receiving lubiprostone.

| Features and properties of lubiprostone (SPI-0211, RU-0211, Amitiza™) | |
|---|---|
| **Indication** | |
| Chronic idiopathic constipation in adults | |
| **Mechanism of action** | |
| Selective type-2 chloride channel activator | |
| **Dosage and administration** | |
| Recommended dosage | 24μg twice daily |
| Route of administration | Oral |
| **Pharmacokinetic profile of M3, the major active metabolite of lubiprostone, after a single oral dose of 24μg** | |
| Peak plasma concentration ($C_{max}$) | 42 pg/mL |
| Time to $C_{max}$ | 1.14h |
| Area under the plasma concentration-time curve | 59 pg • h/mL |
| Elimination half-life | 0.9–1.4h |
| **Adverse events** | |
| Most frequent | Nausea, diarrhoea and headache |



Lubiprostone

Symptoms of constipation are very common and the prevalence of the condition has been reported to be as high as 20%.[1] However, the efficacy of most traditional treatment options for chronic constipation remains unproven in the long term, and pharmacological therapy is not often based on an adequate understanding of the underlying pathophysiology.[2]

Recent progress in constipation therapy has largely focused on two types of agents: those that stimulate serotonin 5-$HT_4$ receptors in the enteric nervous system, thereby enhancing peristaltic action, and a chloride channel activator, lubiprostone (Amitiza™)[1], which increases intestinal fluid secretion, leading to softer stools and improved motility.[2] This article reviews the pharmacological properties of lubiprostone and its clinical efficacy and tolerability in adults with chronic idiopathic constipation.

## 1. Pharmacodynamic Profile

### Mechanism of Action

Lubiprostone is an oral bicyclic fatty acid that selectively activates type 2 chloride channels (ClC-2) in the apical membrane of the gastrointestinal epithelium. An increase in the secretion of chloride-rich intestinal fluid increases intestinal motility and facilitates the passage of softened stool through the intestines and relieves the symptoms of constipation.[3]

- *In vitro*, lubiprostone dose-dependently increased electrogenic chloride transport across the apical membrane of T84 gastrointestinal epithelial cells with a 50% effective concentration ($EC_{50}$) of ≈18 nmol/L, measured by short circuit current, thereby demonstrating that apical membrane chloride channels were potently activated.[4]
- Furthermore, lubiprostone dose-dependently activated whole cell ClC-2 chloride currents in human epithelial kidney (HEK) cells expressing transfected human ClC-2, with an $EC_{50}$ of ≈17 nmol/L.[4] By contrast, lubiprostone had no effect on endogenous chloride currents in non-transfected HEK cells or on cystic fibrosis transmembrane regulator (CFTR) chloride channel currents measured in CFTR-transfected HEK cells.[4]
- Lubiprostone caused an increase in the secretion of intestinal chloride-rich enteric fluid without affecting serum electrolyte levels in rats.[5] Intestinal fluid volume, measured at 30 minutes, increased dose dependently following oral lubiprostone 1, 10 or 100 μg/kg (1.5, 3.3 and 5.3mL, respectively) compared with vehicle (0.9mL; $p < 0.01$ for the 10 and 100 μg/kg doses).[5] Similarly, intestinal fluid chloride concentrations also increased in a dose-dependent manner (82, 110 and 127 mEq/L vs 42 mEq/L, respectively; $p < 0.01$ for all comparisons). By contrast, serum chloride, sodium and potassium levels were not altered with any dose of lubiprostone.[5]

### Effects on Gastrointestinal Function

- Lubiprostone 24μg twice daily accelerated small bowel and colonic transit significantly more than placebo, as measured scintigraphically, in a randomised, double-blind, parallel-group study in 30 healthy volunteers.[6] Small bowel transit times were 93 minutes in the lubiprostone group compared with 131 minutes in the placebo group ($p = 0.017$; data estimated from a graph).[6] Lubiprostone also accelerated the overall colonic transit, as demonstrated by geometric centre measurements 24 hours after ingestion of the radiolabeled meal ($p = 0.03$ vs placebo).[6]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• Compared with the placebo group, the group receiving lubiprostone had a greater mean fasting gastric volume (234 vs 294mL; p = 0.048) [measured using $^{99m}$Tc tomography], slower gastric emptying (half emptying time 106 vs 132min; p = 0.003) and lower maximum tolerated volume (1242 vs 1091mL; p = 0.05) [measured using the Ensure® 'satiation' test] after a fully satiating meal.[6] Lubiprostone had no significant effect on postprandial symptoms 30 minutes after the meal or on postprandial gastric volume.[6]

## 2. Pharmacokinetic Profile

Limited data have been published on the pharmacokinetics of lubiprostone in patients with chronic idiopathic constipation. Therefore, most of the data in this section are taken from the manufacturer's prescribing information.[3]

• Lubiprostone has low systemic bioavailablity after oral administration, and the plasma concentration of the drug is too low to quantify (i.e. <10 pg/mL).[3] Thus, standard pharmacokinetic parameters, such as area under the plasma concentration-time curve (AUC), peak plasma concentration ($C_{max}$) and elimination half-life ($t_{1/2}$), cannot be calculated reliably.[3]

• M3 is the only measurable active metabolite of lubiprostone.[3] After a single oral dose of lubiprostone 24μg, the peak plasma level of M3 was achieved in about 1.14 hours. The $C_{max}$ of M3 was 42 pg/mL and the mean AUC was 59 pg • h/mL. The AUC of M3 increased dose proportionally after single doses of lubiprostone 24 and 144μg.[3]

• *In vitro*, lubiprostone was approximately 94% protein-bound in human plasma.[3] When radiolabelled lubiprostone was administered orally to rats, most of the drug was found to localise in the gastrointestinal tract.[7] By 48 hours after administration, almost all of the radioactive drug was eliminated.[7]

• Lubiprostone is rapidly and extensively metabolised by carbonyl reductase to form M3, which makes up <10% of a radiolabelled lubiprostone dose.[3] Based on animal studies, it is thought that lubiprostone is metabolised in the stomach and jejunum in humans.[3]

• The $t_{1/2}$ of M3 ranged from 0.9 to 1.4 hours. Following single-dose administration of radiolabelled oral lubiprostone 72μg, 60% of the radioactivity was recovered in the urine within 24 hours and 30% in the faeces by 168 hours. Only trace amounts of lubiprostone and M3 could be detected in human faeces.[3]

• Concomitant administration of a single dose of radiolabelled lubiprostone 72μg with a high-fat meal decreased the $C_{max}$ by 55%, without any change in AUC from time zero to infinity ($AUC_{\infty}$), as demonstrated by total radioactivity measurements.[3] The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone has not been clarified and, at present, it is recommended that the drug be taken with food (section 5).[3]

• The pharmacokinetics of M3, following administration of lubiprostone, were not affected by gender.[3] Lubiprostone has not been studied in patients with renal or hepatic impairment.[3]

## 3. Therapeutic Efficacy

The efficacy of lubiprostone in the treatment of constipation has been established in two pivotal, randomised, double-blind, multicentre, phase III trials[8,9] (for one of the trials,[8] data on various efficacy endpoints are available from separate reports).[8,10,11] Efficacy has also been evaluated in an open-label trial,[12] a randomised-withdrawal study[13] and an early randomised, controlled, dose-finding trial.[14] The results of all five studies are available as abstracts.

Generally, across all studies, chronic idiopathic constipation was defined as experiencing less than three spontaneous bowel movements (SBMs) each week,[8-12,14] as well as a history of very hard stools, a sensation of incomplete emptying, or straining during at least 25% of bowel movements for at least 6 months.[8-11,14] An SBM was defined as any bowel movement that did not occur within 24 hours of the administration of rescue medication.

In the two pivotal, phase III trials (n = 237[8] and n = 242[9]), constipated patients were randomised to twice-daily lubiprostone 24μg or placebo for a period of 4 weeks. Patients underwent a 2-week drug-

free washout period before treatment and a 2-week follow-up period after treatment. In both studies, evaluations were performed at baseline and at weekly intervals until the end of follow-up. Evaluations included patient global assessments of treatment effectiveness, patient symptom assessments and physical and laboratory testing.[3,8-11]

Efficacy criteria were generally similar in these studies.[3,8,9] The primary efficacy endpoint was the frequency of SBMs and secondary endpoints included the time to first SBM, the degree of straining, stool consistency, the percentage of patients with an SBM within 24 hours of the first dose and treatment effectiveness as assessed by the patient.[8-11] Treatment and placebo groups were similar in the two studies with respect to gender, age and race; approximately 90% were female and Caucasian, with a mean age of 47 years (11% were aged ≥65 years).[3,8,9]

An open-label, multicentre study of lubiprostone recruited follow-on patients from an earlier study as well as some new patients with constipation.[12] After a 2-week drug-free washout period, symptomatic patients received lubiprostone 24μg twice daily with food and water, as per the perceived need of the patient, for a period of 24 weeks. Evaluations were performed at baseline and at weeks 1, 4, 8, 12, 18 and 24, as well as at follow-up; data from 304 patients were analysed for efficacy.[12] According to the US prescribing information,[3] two additional open-label, long-term clinical studies were conducted in patients with chronic idiopathic constipation. Overall, the three open-label, long-term studies included 871 patients treated with lubiprostone 24μg twice daily for 24–48 weeks.[3]

In a randomised-withdrawal study of lubiprostone, constipated patients (n = 128) underwent a 2-week drug-free period followed by lubiprostone 24μg twice daily for 4 weeks before being randomly assigned, in a double-blind manner, to continue with treatment or to receive placebo for a further 3 weeks.[13]

The first controlled trial of lubiprostone evaluated three different dose levels.[14] Patients with constipation (n = 127) were randomised, in a double-blind manner, to receive either lubiprostone 24, 48 or 72 μg/day or placebo for 3 weeks. A 2-week drug-free period preceded treatment and patients completed weekly assessment throughout the 5-week period.[14]

Efficacy endpoints in the open-label, randomised-withdrawal and initial, randomised, controlled trials were generally similar and included frequency of SBMs, consistency of bowel movements, degree of straining, abdominal bloating and discomfort, constipation severity and patient assessment of treatment effectiveness.[12-14]

- In all randomised studies,[8-11,13,14] including the randomised period of the randomised-withdrawal trial,[13] lubiprostone 24μg twice daily was signifi-

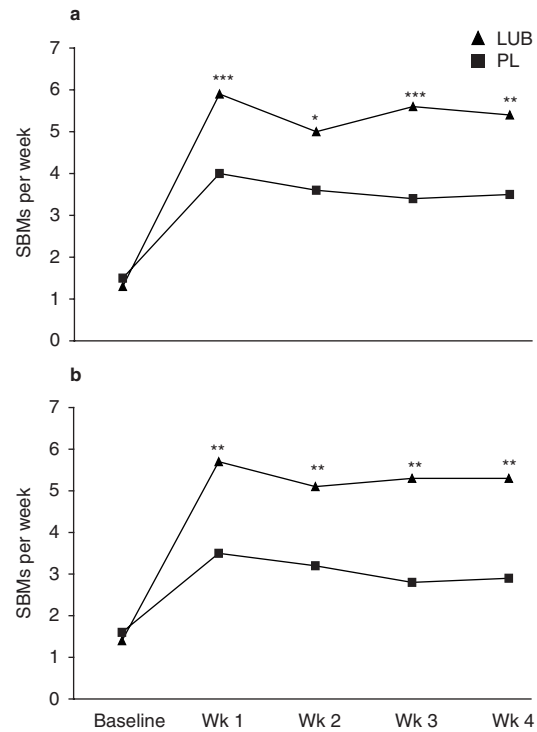



**Fig. 1.** Efficacy of lubiprostone (LUB) in patients with chronic idiopathic constipation. Results (available from the US prescribing information[3]) are from two randomised, double-blind, multicentre, phase III trials (**a**[8] and **b**[9]) in which 237[8] or 242[9] patients received either oral LUB 24μg or placebo (PL) twice daily for 4 weeks, preceded by a 2-week drug-free washout period. The individual number of patients in LUB and PL groups was 119 and 118 in one trial[8] and not reported in the other.[9] **SBM** = spontaneous bowel movement; * $p < 0.05$, ** $p < 0.007$, *** $p \leq 0.0004$ vs PL.

cantly better than placebo for all constipation variables tested.

- The frequency of SBMs each week in the lubiprostone groups was significantly greater than in the placebo groups in the two pivotal, phase III studies[8,9] (figure 1). For example, in the more recent of these studies, the mean frequency of SBMs per week increased from baseline by 4.61 at week 1 in patients receiving lubiprostone compared with an increase of 2.47 in patients receiving placebo ($p < 0.0001$).[8]
- Significant differences in the frequency of SBMs persisted in favour of lubiprostone throughout the 4-week period in both studies ($p < 0.002$[9] and $p < 0.05$[8] vs placebo at all weeks) [figure 1].
- At week 1, in the more recent phase III study, 72% of patients receiving lubiprostone were classified as full responders (i.e. four or more SBMs per week without rescue medication) compared with 49% of patients receiving placebo ($p < 0.0001$).[8]
- In the two pivotal trials, significantly more patients receiving lubiprostone had an SBM within 24 hours of the first dose than patients receiving placebo (57% vs 37%; $p = 0.0024$[9] and 61% vs 31%; $p \leq 0.0001$).[10] According to a *post hoc* analysis, 79% of patients receiving lubiprostone had experienced an SBM within 48 hours, compared with 66% of patients receiving placebo ($p < 0.05$).[10]
- Compared with the placebo group, the lubiprostone group had a significantly greater improvement in the degree of straining ($p < 0.002$),[8,9] stool consistency ($p < 0.001$[9] and $p < 0.0001$[8]) and constipation severity ($p < 0.03$).[8] This lubiprostone-associated improvement persisted throughout both studies.[8,9]
- In patient global assessments of treatment effectiveness, lubiprostone was associated with significantly greater improvements in constipation symptoms than placebo throughout the full study period of both pivotal trials.[9,11] For example, in one study, lubiprostone maintained a significantly higher effectiveness rating (range of 1.86–1.97) than placebo (range of 1.17–1.22) [$p \leq 0.0001$], as measured on a scale of 0 (not at all effective) to 4 (very effective).[11]
- Lubiprostone was associated with significant improvements in constipation severity, bloating and abdominal discomfort over the 24- to 48-month treatment periods in the three open-label studies.[3,12] One of these studies is available as a published abstract and reported all p-values as $< 0.001$.[12] From week 4 to 24 in this study,[12] patient effectiveness ratings increased from 2.12 to 2.35 ($p = 0.01$) [baseline ratings were not collected].
- In the randomised-withdrawal trial, lubiprostone achieved a rapid and sustained increase in SBMs, with frequencies from baseline (1.36 per week) to week 1, 2, 3 and 4 of 6.25, 5.94, 5.52 and 6.20 per week, respectively (all $p < 0.0001$ vs baseline).[13] During the randomised-withdrawal period, the frequency of SBMs progressively declined (albeit not reverting to baseline) in patients receiving placebo, but not in those receiving lubiprostone.[13]
- At week 7 in the randomised-withdrawal study, the weekly frequency of SBMs for patients who had responded to initial treatment with lubiprostone was 5.59 for those who continued to receive lubiprostone compared with 3.04 for those who were randomised to placebo ($p < 0.05$).[13] The relapse rate during the randomised-withdrawal period for patients receiving lubiprostone or placebo was 18% versus 44% ($p = 0.022$).[13]

## 4. Tolerability

The tolerability of lubiprostone 24μg twice daily has been assessed in clinical studies in patients with chronic idiopathic constipation (see section 3 for study design details).[8,9,12-14] Data from published reports of these studies are supplemented with consolidated tolerability data available from the US prescribing information, which were collected over long (up to 12-month) observational periods in 1429 patients who received lubiprostone 24μg twice daily or placebo in clinical trials.[3]

- Lubiprostone 24μg twice daily was generally well tolerated, with no treatment-related serious adverse event noted in any of the pivotal trials.[8,9,12-14] Across all studies, nausea was the most common drug-related adverse event,[8,9,12,14] occurring in up to 31% of patients receiving lubiprostone.[3] In a

pivotal, phase III study in 237 patients, 21% of patients receiving lubiprostone experienced nausea, compared with 4.2% of those receiving placebo.[8]

- Nausea was mild to moderate in severity in the majority of patients experiencing this event in clinical trials and resulted in treatment discontinuation in 8.7% of these patients.[3] Nevertheless, there was no increase in the risk for experiencing nausea with prolonged exposure to lubiprostone. Administration with food decreased the symptoms of nausea.[3]
- The next most common adverse events were diarrhoea and headache, each occurring in ≈13% of lubiprostone recipients.[3] Diarrhoea was considered severe in 3.4% of patients reporting this event and 2.2% of patients discontinued treatment because of diarrhoea. Importantly, there was no clinically significant effect on serum electrolyte balance in patients receiving lubiprostone. Abdominal distension/pain and flatulence were the other adverse events that occurred in >5% of lubiprostone recipients.[3]
- During the 24-week treatment period of an open-label study, 52% of patients (n = 306) experienced adverse events considered to be at least possibly related to treatment; all of these were non-serious in nature.[12] Discontinuation of lubiprostone as a result of an adverse event occurred in 20% of patients.[12] Nausea and headache were the most common adverse events.[12] As in other open-label studies, patients were allowed to decrease their lubiprostone dosage to 24μg once daily if they experienced nausea.[3]

## 5. Dosage and Administration

Lubiprostone is indicated for the treatment of chronic idiopathic constipation in adults.[3] The drug is available as a 24μg capsule, and the recommended dosage is one capsule orally twice daily with food. The need for continued therapy should be assessed periodically by patients and their physicians. Local prescribing information should be consulted for recommendations regarding specific patient populations, contraindications and precautions.[3]

## 6. Lubiprostone: Current Status in the Treatment of Constipation

Lubiprostone is approved for use in the US for the treatment of adults with chronic idiopathic constipation.[3] The drug has demonstrated clinical efficacy in two well designed, phase III trials in adults with this condition, and was generally well tolerated.

## Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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