Drugs 2009; 69 (9): 1229-1237
0012-6667/09/0009-1229/$55.55/0

Lubiprostone

In Constipation-Predominant Irritable Bowel Syndrome

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Contents

Abstract

▲ Lubiprostone is an oral bicyclic fatty acid that selectively activates type 2 chloride channels in the apical membrane of human gastrointestinal epithelial cells, thereby increasing chloride-rich fluid secretion. Although the mechanism is unclear, this may then decrease intestinal transit time, allowing the passage of stool and alleviating symptoms of constipation.

▲ Oral lubiprostone was effective in the treatment of patients with constipation-predominant irritable bowel syndrome (IBS-C) in large (n = 193–583) phase II (dose-finding) and phase III randomized, double-blind, placebo-controlled, multicentre trials.

▲ The number of patients with IBS-C demonstrating an overall response to treatment (primary endpoint) in the two phase III trials was significantly greater in patients receiving lubiprostone 8 μg twice daily for 3 months than in those receiving placebo. In addition, a randomized, 4-week withdrawal period at the end of one of the phase III trials demonstrated that discontinuation of lubiprostone was not associated with rebound of IBS symptoms.

▲ Lubiprostone was generally well tolerated in clinical trials, with the majority of adverse events being of mild to moderate severity. In patients with IBS-C who received lubiprostone 8 μg twice daily, nausea was the most frequently occurring adverse event that was considered possibly or probably treatment related. No serious treatment-related adverse events were reported in a 36-week open-label extension to the phase III trials.

Features and properties of lubiprostone (Amitiza®)	
Featured indication	
Constipation-predominant irritable bowel syndrome in women aged ≥18 years	
Mechanism of action	
Selective activator of type 2 chloride channels	
Dosage and administration	
Dose	8 μg
Frequency of administration	Twice daily
Route of administration	Oral
Pharmacokinetic profile of M3, the only measurable active metabolite of lubiprostone, after a single oral dose of lubiprostone 24 μg	
Peak plasma concentration (C_{max})	41.5 pg/mL
Time to C_{max}	1.1 h
Area under the plasma concentration-time curve	57.1 pg • h/mL
Elimination half-life	0.9–1.4 h
Most frequent adverse events possibly or probably related to lubiprostone treatment	
Nausea, diarrhoea, abdominal pain and abdominal distension	

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that is characterized by abdominal pain or discomfort and altered bowel habits.[1] According to the Rome III criteria for IBS,[2] the disorder can be classified into four subtypes (constipation-predominant [IBS-C], diarrhoea-predominant, mixed or unsubtyped), as determined by the predominant consistency of the stool. The disorder has a worldwide prevalence of 4–22%, depending upon the population investigated and the diagnostic criterion used, and is more prevalent in women than in men.[1]

Treatment of IBS usually centres on the management of individual symptoms and should take into account the type and severity of symptoms and whether psychosocial issues are present.[1,3] Osmotic or stimulant laxatives, fibre and other bulking agents are all used with varying degrees of success in patients with IBS-C,[3-5] although little clinical evidence is available to make formal recommendations regarding their use in this patient population.[5] In addition, these agents have limited efficacy in the overall management of the IBS symptom complex.[6] The partial serotonin 5-HT_4 receptor agonist tegaserod has also shown efficacy in the management of IBS-C in clinical trials.[3,7] However, use of this drug was restricted by the US FDA under a treatment investigational new drug application (T-IND) protocol because of the significantly higher number of serious cardiovascular ischaemic events that occurred with tegaserod compared with placebo (0.1% vs 0.01%) in a pooled analysis of data from 29 clinical trials (n = 11 614).[8,9] The drug manufacturer has now voluntarily made tegaserod available only under an emergency T-IND.[10]

Lubiprostone (Amitiza®) is a type 2 chloride channel (CIC-2) activator that is approved in the US[11] for use in adults with chronic idiopathic constipation and in women aged ≥18 years with IBS-C. The efficacy and tolerability of lubiprostone in patients with chronic idiopathic constipation have been reviewed previously.[12] This article reviews the pharmacological properties of lubiprostone and its clinical efficacy and tolerability in patients with IBS-C. Medical literature on the use of lubiprostone in patients with IBS-C was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacological Profile

Mechanism of Action

- Lubiprostone is a bicyclic fatty acid that is derived from prostaglandin E1.[5,13] It selectively activates CIC-2 channels in the apical membrane of human gastrointestinal epithelial cells thereby increasing the secretion of chloride-rich fluid into the intestinal lumen.[5,11] Although the exact mechanism is unclear, it is thought that this may then decrease intestinal transit time, allowing the passage of stool and alleviating symptoms of constipation.[5]
- Electrogenic chloride transport was increased by lubiprostone in *in vitro* studies.[13] The transepithelial transport of chloride across the apical membranes of T84 gastrointestinal epithelial cells, which contain both CIC-2 and cystic fibrosis transmembrane regulator (CFTR) chloride channels, was increased by lubiprostone, with a 50% effective concentration (EC_{50}) of ≈18 nmol/L, as determined by short-circuit current.
- Lubiprostone activated CIC-2, but not CFTR channels, *in vitro*.[13] In whole cell patch clamp studies using human epithelial kidney (HEK)-293 cells expressing transfected human CIC-2, lubiprostone dose-dependently activated CIC-2 channels, with an EC_{50} of ≈17 nmol/L.[13] By contrast, lubiprostone did not affect chloride currents in HEK-293 cells expressing transfected human CFTR chloride channels or nontransfected HEK-293 cells.[13]
- Dose-dependent increases in intestinal fluid volume and chloride concentration were seen after lubiprostone administration in rats (reviewed by McKeage et al.[12]). Thirty minutes after a single oral dose of lubiprostone 1, 10 or 100 μg/kg or vehicle, intestinal fluid volumes were increased by 1.5, 3.3, 5.3 and 0.9 mL ($p < 0.01$ for lubiprostone 10 and 100 μg/kg doses vs vehicle), respectively, and

intestinal fluid chloride concentrations were increased by 82, 110, 127 and 42 mEq/L ($p < 0.01$ for all doses vs vehicle), respectively.

- Serum electrolyte balance was not altered by lubiprostone in *in vivo* studies in rats[12] or in clinical trials.[14] In patients with chronic idiopathic constipation who received lubiprostone 24 μg or placebo twice daily for 3–48 weeks,[14] there were no significant between-group differences in terms of serum calcium, chloride, magnesium, phosphorus, potassium or sodium levels at the end of treatment. In addition, changes in serum electrolyte levels from baseline to end of treatment were not significantly different in patients who received lubiprostone.[14]

Pharmacodynamic Effects on Gastrointestinal Function

- Lubiprostone treatment accelerated small and large bowel transit time, slowed gastric emptying, increased fasting gastric volume and reduced the maximum tolerated gastric volume after a fully satiating meal to a significantly ($p \leq 0.05$) greater extent than placebo in 30 healthy volunteers who received lubiprostone 24 μg or placebo twice daily in a randomized, double-blind study.[15]
- In a randomized, double-blind trial in 60 healthy volunteers,[16] the relative change in colonic tone from fasting to 30 minutes postprandially (a measure of the contractile response of colonic tone to food ingestion) was decreased to a significantly ($p = 0.014$) greater extent in men and women receiving lubiprostone 24 μg/day than in those receiving placebo. Although the prokinetic motor effects (i.e. reduction in colonic tone) seen with lubiprostone may promote laxation by reducing resistance to flow, they are unlikely to be the mechanism behind the accelerated small and large bowel transit time.[16]
- Results from this double-blind trial[16] are partially supported by an *in vitro* study[17] in which lubiprostone inhibited electrically stimulated neuronal contractions in rat and human isolated colon circular muscle (log concentration required to inhibit 50% of a mechanical response = 8.9 and 8.7 mol/L). However, lubiprostone also induced a contraction in rat and human isolated stomach longitudinal muscle ($-\log_{10}$ concentration causing 50% maximal stimulation = 7.0 and 6.4 mol/L) in this study.[17]
- Lubiprostone induced the *in vitro* recovery of ischaemic-injured porcine intestinal mucosa.[18] For example, lubiprostone 0.01–1 μmol/L dose-dependently increased transepithelial electrical resistance (TER) back to pre-ischaemic control levels. The change in TER from time 0 to 180 minutes was 25 ohms/cm^2 with lubiprostone 1 μmol/L.[18] Short-circuit currents were also increased dose-dependently with lubiprostone 0.01–1 μmol/L.[18]

Pharmacokinetic Profile

- Oral lubiprostone has low systemic bioavailability and plasma concentrations of the drug are too low to quantify (i.e. <10 pg/mL).[11] Therefore, calculations of lubiprostone pharmacokinetic parameters are not reliable.[11]
- M3 is the only active metabolite of lubiprostone that can be measured.[11] After a single dose of lubiprostone 24 μg, M3 peak plasma concentration (C_{max}) was 41.5 pg/mL, time to reach C_{max} was 1.1 hours and mean area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_t) was 57.1 pg • h/mL.[11] Systemic exposure to M3 (in terms of AUC_t) was dose proportional after single oral doses of lubiprostone 24 or 144 μg.[11]
- As demonstrated by total radioactivity measurements, administration of ^{3}H-labelled lubiprostone 72 μg in conjunction with a high-fat meal reduced C_{max} by 55%, but did not alter AUC from time 0 to infinity.[11] Although the clinical relevance of the effect of a high-fat meal is not clear, administration of lubiprostone with food may reduce symptoms of nausea (section 3) and routine administration with food is recommended in the manufacturer's prescribing information (section 4).[11]
- Lubiprostone is highly bound (≈94%) to plasma proteins, based on *in vitro* studies.[11] In rats that were administered radiolabelled lubiprostone, the drug was mainly confined to the gastrointestinal tissues, and was detected only in minimal concentrations 48 hours after administration.[11]

- Lubiprostone is rapidly and extensively metabolized by carbonyl reductase to form the M3 metabolite, which makes up <10% of a radiolabelled dose of lubiprostone.[11] Lubiprostone metabolism is presumed to occur in the stomach and jejunum of humans, as it does in animals, most likely without any of the dose being absorbed systemically.[11]
- The elimination half-life of M3 was 0.9–1.4 hours.[11] Within 24 hours of a single oral dose of ^{3}H-labelled lubiprostone 72 μg, 60% of the total administered radioactivity was recovered in the urine;[11] 30% of the total administered radioactivity was recovered in the faeces 168 hours after administration. Only trace amounts of lubiprostone and M3 were detected in human faeces.[11]
- Gender had no affect on the pharmacokinetics of M3 following oral lubiprostone.[11] Lubiprostone has not been studied in patients with hepatic or renal impairment.[11]
- Lubiprostone is not a substrate for cytochrome P450 isozymes and does not inhibit or induce these isozymes *in vitro*; therefore, drug-drug interactions with lubiprostone are unlikely.[11]

2. Therapeutic Efficacy

The efficacy of oral lubiprostone in patients with IBS-C has been investigated in a phase II[19] (dose-finding) and two phase III[20,21] randomized, double-blind, placebo-controlled, multicentre trials. Study design, treatment regimens, and the pooled and individual results of the phase III trials are fully published.[22] Additional data from a 4-week randomized withdrawal period[23] conducted after the completion of one[20] of the phase III trials, and a 36-week open-label extension[24] to both of the phase III trials,[20,21] are available as abstracts. For completeness, data from the FDA summary review for lubiprostone[25] are also included.

Patients aged ≥18 years (and <80 years[19]) were eligible for these studies[19,22] if they met the Rome II criteria[26] for IBS-C and had undergone flexible sigmoidoscopy (if aged <50 years) or colonoscopy (if aged ≥50 years) in the previous 5 years to rule out the possibility of other causes of their IBS symptoms. Exclusion criteria included previous abdominal or gastrointestinal surgery (unless it was common and not related to IBS), a history of an organic disorder of the large or small bowel, mechanical obstruction, significant weight loss or rectal bleeding that was not otherwise explained, any other condition that could be associated with constipation, administration of IBS-related medication within 4 weeks of randomization, study medication received within 4 weeks of screening and any other medical and/or psychological disorder that could interfere with the study.[19,22]

Potentially eligible patients entered a 4-week baseline/screening period during which they kept a daily electronic diary detailing the occurrence and time of all spontaneous bowel movements (defined as a bowel movement that occurred without the aid of rescue medication), and rating the severity of IBS symptoms on a scale of 0–4.[19,22] All laxatives and other disallowed medications were discontinued during this period, and patients who had not previously received a flexible sigmoidoscopy or colonoscopy underwent the relevant procedure.[19,22]

Patients who continued to meet eligibility criteria and had completed >70% of their daily diary during the screening period were then eligible for randomization into the treatment phase of the study if the average monthly assessment of abdominal discomfort/pain was of at least mild severity and if they had two or more of the following symptoms for ≥25% of the time: fewer than three spontaneous bowel movements per week, straining of at least moderate severity with spontaneous bowel movements and/or stool consistency of hard or very hard with spontaneous bowel movements.[19,22]

If a spontaneous bowel movement had not occurred for at least 3 days during the screening or treatment periods, the investigator could authorize a rescue treatment regimen.[19,22] Provided intake was kept stable, daily fibre supplements were allowed throughout the course of the studies.[19,22]

Dose-Finding Study

Patients in the dose-finding trial[19] received lubiprostone 8–24 μg or placebo twice daily for 3 months, with dosage adjustments based on

tolerability. The primary endpoint was the change in mean abdominal discomfort/pain score from baseline to the end of the first month of treatment.[19] Analyses were based on the modified intent-to-treat (mITT) population, which included all patients who received study medication and had data available for at least one of the efficacy endpoints.[19] There were no statistically significant differences in demographic or baseline characteristics between lubiprostone and placebo groups, although ≈90% of patients randomized into the study were female.[19]

- After 1 month of treatment in the phase II dose-finding trial (n = 193 evaluable patients), patients receiving lubiprostone 24 μg twice daily experienced significantly ($p = 0.023$) greater improvements from baseline in abdominal discomfort/pain scores than placebo recipients (primary endpoint); there were no statistically significant differences between the lubiprostone 8 or 12 μg twice daily groups and the placebo group. However, by month 2, all lubiprostone dosages were more effective than placebo with regard to change in abdominal discomfort/pain scores from baseline ($p < 0.05$ vs placebo for each dosage of lubiprostone and for the analysis of covariance for between-dosage differences).
- Based on these efficacy results and tolerability outcomes (section 3), the optimal dosage of lubiprostone and the dosage given in phase III trials was 8 μg twice daily.[19]

Phase III Studies

Patients in the phase III trials (n = 583[20,22] and n = 571[21,22] evaluable patients in the individual trials) received lubiprostone 8 μg or placebo twice daily for 3 months, with dosages adjustments based on tolerability.

In order to assess the effect of randomized withdrawal on IBS-C symptoms, lubiprostone recipients in one[20] of the phase III trials were pre-randomized at study start to continue receiving lubiprostone or switch to placebo for an additional 4-week period once the 3-month study period had been completed;[22,23,25] only lubiprostone recipients who were considered overall responders at the end of the 3-month study period were entered into the 4-week, randomized withdrawal period.[25] To assess the long-term efficacy of lubiprostone, patients in the phase III trials who had >70% compliance with the study drug during the 3-month study period were then enrolled in a 36-week, open-label extension trial;[24] all patients received lubiprostone 8 μg twice daily for the duration of the open-label period.

The primary endpoint of the phase III trials[22] was overall responder status, defined as the achievement of monthly responder status for at least 2 of the 3 months of double-blind treatment. Patients were monthly responders if their self-assessed scores showed at least a moderate improvement in IBS symptoms for all 4 weeks of the month, or a significant improvement for at least 2 weeks of the month, and if there were no scores depicting a moderate or severe worsening of IBS symptoms during that month. The primary endpoint of the open-label extension trial[24] was the monthly response rate. Although the primary endpoint of the 4-week randomized withdrawal period was not specified, the monthly response at month 4 was reported.[23] Analyses were based on the mITT population, which included all patients who received study medication and had data available for at least one of the efficacy endpoints.[22]

There were no statistically significant differences in demographic or baseline characteristics between lubiprostone and placebo groups within individual studies, except for a group difference in age that was not thought to be of clinical relevance.[22] The majority (≈92%) of patients randomized into the studies were female.[22]

- Lubiprostone 8 μg twice daily for 3 months was more effective than placebo in patients with IBS-C in terms of overall response rates in a pooled analysis of phase III trials (primary endpoint).[22] Approximately twice as many lubiprostone (n = 769) as placebo (n = 385) recipients were overall responders in terms of the pooled analysis (18% vs 10%; $p = 0.001$) and each of the individual trials (both 18% vs 10%; $p < 0.05$).
- Lubiprostone was also more effective than placebo with regard to monthly and weekly responder rates in these trials.[22] For example, at months 2

(18% vs 11%; p = 0.003) and 3 (22% vs 15%; p = 0.003) in the pooled analysis, more patients receiving lubiprostone than placebo were deemed monthly responders, and at weeks 2, 4–6, 10 and 12, more lubiprostone than placebo recipients were deemed weekly responders (all $p < 0.05$).[22]

- In addition, in the lubiprostone group, the mean change in IBS symptom scores from baseline to month 3 for all symptom domains was –0.69 to –1.18 in responders compared with –0.28 to –0.46 in nonresponders (all values estimated from a graph).[22]
- Lubiprostone was not associated with significant improvements in health-related quality-of-life (QOL) from baseline to study endpoint compared with placebo with regard to total IBS-QOL questionnaire scores.[22] However, significant ($p \leq 0.025$) improvements from baseline compared with placebo in the IBS-QOL-assessed domains of body image and health worry were demonstrated after 3 months of lubiprostone treatment.[22] Although between-group differences were not significant for the domains of social reaction, food avoidance and dysphoria, scores for these domains were improved by >14 points with lubiprostone, and this was considered clinically relevant.[22]
- In overall responders in the lubiprostone group, discontinuation of lubiprostone was not associated with rebound of IBS symptoms.[23] At the conclusion of the 4-week randomized withdrawal period conducted in overall responders of one of the 3-month phase III trials[20,22] (n = 436), 38% of patients who were randomized to continue lubiprostone and 40% of those who were randomized to placebo were considered monthly responders at the end of month 4.[23,25] In addition, there were no differences between the lubiprostone and placebo groups with regard to the change in IBS symptom scores from baseline to the end of month 4.[23]
- The beneficial effects of lubiprostone on IBS-C symptoms were sustained with longer-term treatment.[24] In patients from both phase III trials who entered the 36-week open-label extension trial (n = 476),[24] 37% of those receiving lubiprostone for the entire 48 weeks (3-month double-blind period followed by 36-week open-label period), and 31% of those receiving placebo for the first 3 months and then lubiprostone for the next 36 weeks, were considered monthly responders at month 12. In addition, for each month during the extension trial, all IBS symptoms were improved from baseline to a significantly greater (p-value not reported) extent in both groups.[24] Despite the lubiprostone treatment effect being small, the FDA states that a lack of other treatments for IBS-C makes lubiprostone a valuable option.[25]

3. Tolerability

This section focuses on tolerability data from the dose-finding[19] and phase III[22] studies described in section 2, including the randomized withdrawal[23] and extension[24] trials conducted in eligible patients who completed the phase III studies. Additional tolerability data from the manufacturer's prescribing information[11] and the FDA summary review for lubiprostone[25] are also discussed.

- Lubiprostone 8 μg twice daily had a more favourable tolerability profile than lubiprostone 16 or 24 μg twice daily in patients with IBS-C, according to results of the dose-finding trial.[19] Adverse events, particularly gastrointestinal adverse events, were numerically more frequent in the higher lubiprostone dosage groups (16 or 24 μg twice daily) than in the lower dosage group (8 μg twice daily). Moreover, 16% and 13% of patients who received lubiprostone 16 or 24 μg twice daily discontinued the study because of adverse events compared with 6% of those receiving lubiprostone 8 μg twice daily.[19] All serious adverse events occurred in the higher dosage groups, although these were not thought to be related to study medication.[19]
- Lubiprostone 8 μg twice daily for up to 12 months was generally well tolerated in patients with IBS-C, with the majority of adverse events being mild to moderate in severity[19,22] and resolving spontaneously.[22]
- Nausea was the most frequently occurring adverse event that was possibly or probably related to lubiprostone treatment, according to a pooled analysis reported in the manufacturer's prescribing

information (figure 1).[11] However, symptoms of nausea may be decreased by administration of lubiprostone with food.[11] Other frequently occurring adverse events that were possibly or probably related to lubiprostone treatment included diarrhoea, abdominal pain and abdominal distension (figure 1).[11]

- Other adverse events thought possibly related to lubiprostone 8 μg twice daily that occurred in ≤1% of patients (but in at least two patients) and were more frequently reported in lubiprostone than placebo recipients in clinical trials included anorexia, anxiety, constipation, depression, dry mouth, dyspepsia, dyspnoea, eructation, erythema, faecal incontinence, fatigue, fibromyalgia, gastritis, gastro-oesophageal reflux disease, hard faeces, increased ALT and/or AST levels, increased weight, lethargy, loose stools, oedema, palpitations, pollakiuria, rectal haemorrhage, urinary tract infection and vomiting.[11]
- Study discontinuations due to adverse events occurred in 5% of lubiprostone recipients and 7% of placebo recipients in phase III trials.[22]

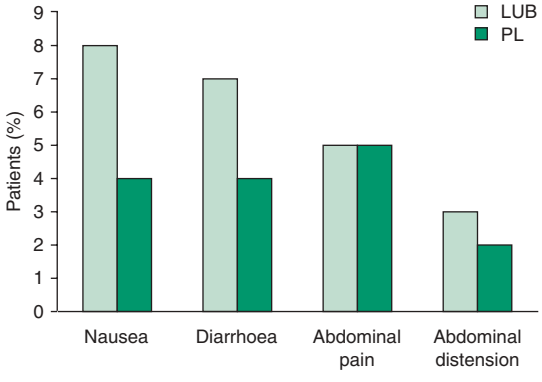

Fig. 1. Tolerability of oral lubiprostone (LUB) 8 μg twice daily in patients with constipation-predominant irritable bowel syndrome. Adverse events thought possibly or probably related to LUB treatment that occurred in ≥1% of patients receiving LUB and more frequently in LUB (n = 1011) recipients than placebo (PL) [n = 435] recipients. Data are from a pooled analysis[11] of adverse events reported in a phase II[19] (dose-finding) and two phase III[20,21] randomized, double-blind, multicentre trials, a randomized withdrawal period[23] following one[20] of the phase III trials and an open-label extension[24] to the phase III trials. Duration of treatment was 3–12 months for LUB recipients and up to 4 months for PL recipients.

- Serious adverse events associated with lubiprostone treatment were rare.[22] In pooled results of phase III trials,[22] serious adverse events were reported in 7 of 779 (0.9%) lubiprostone recipients and 4 of 387 (1.0%) placebo recipients; a case of noncardiac chest pain that resolved the next day was the only serious adverse event that was thought possibly related to lubiprostone. No serious treatment-related adverse events were reported during the 36-week open-label extension period of the phase III trials.[24]
- In clinical trials, dyspnoea occurred in 0.4% of patients with IBS-C.[11] Although only a small proportion of these cases were considered severe, the majority of patients reporting dyspnoea withdrew from the study.[25] Postmarketing experience with lubiprostone 24 μg twice daily demonstrated that dyspnoea usually occurred within 1 hour after administration and was characterized by a sensation of chest or throat tightness;[11,25] most episodes had resolved within 3 hours. In the majority of circumstances, dyspnoea recurred with repeated lubiprostone treatment.[25] One episode of dyspnoea was diagnosed as an anaphylactic reaction by hospital staff;[25] the patient population in which this occurred was not stated.

4. Dosage and Administration

The majority of patients with IBS-C in clinical trials were adult women (section 2); because of this, lubiprostone is approved in the US[11] for use in women with IBS-C who are aged ≥18 years. The recommended dosage of lubiprostone in this population is 8 μg twice daily;[11] medication should be administered with food and water. Lubiprostone is contraindicated in patients who may have, or are known to have, mechanical obstruction of the gastrointestinal tract.[11] In addition, because lubiprostone was shown to be associated with fetal loss in animal studies, it is important that women use effective contraceptive measures during lubiprostone treatment.[11] In women who are already pregnant, an analysis of risk versus benefit should be undertaken prior to lubiprostone prescription.[11]

The manufacturer's prescribing information should be consulted for additional information, including warnings and precautions, adverse reactions, drug interactions and use in special populations.

5. Lubiprostone: Current Status in the Treatment of Constipation-Predominant Irritable Bowel Syndrome

Lubiprostone is approved in the US[11] for use in women aged ≥18 years with IBS-C. In large, 3-month, randomized, double-blind, placebo-controlled, multicentre clinical trials that predominantly enrolled women aged ≥18 years, lubiprostone was effective and well tolerated, with the beneficial improvements in symptoms sustained in a 36-week open-label extension study. Furthermore, during a 4-week randomized withdrawal study, IBS symptoms did not recur once lubiprostone was discontinued.

Acknowledgements and Disclosures

The manuscript was reviewed by: **M. Camilleri**, Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Gastroenterology Research Unit, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; **R. Spiller**, Biomedical Research Unit, Nottingham Digestive Diseases Centre, University Hospital, Nottingham, UK.

The preparation of this review was not supported by external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

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