

**LUBIPROSTONE: A NOVEL DRUG TO TREAT CONSTIPATION**\*Kamlesh Garg<sup>1</sup>, Surinder Kumar<sup>2</sup>, Ruchika Nanda<sup>3</sup>, Suraj B<sup>4</sup><sup>1</sup>Assistant Professor, Department of Pharmacology, VMMC and Safdarjung Hospital, New Delhi<sup>2</sup>Medical officer, Department of Anesthesia, VMMC and Safdarjung Hospital, New Delhi<sup>3</sup>Assistant Professor, Department of Pharmacology, Dr HSJ Institute of Dental Sciences, Panjab University, Chandigarh<sup>4</sup>Junior Resident, Department of Pharmacology, VMMC and Safdarjung Hospital, New Delhi**ABSTRACT**

Lubiprostone, a bicyclic fatty acid, is a novel drug of new class of agents called prostones. It is approved by US FDA for the treatment of chronic constipation and constipation associated irritable bowel syndrome (IBS-C). It activates specific chloride channels in the gastrointestinal tract to stimulate intestinal fluid secretion, increase gastrointestinal transit and improve symptoms of constipation. Lubiprostone is well tolerated in majority of the patients with nausea being the most common adverse effect. Lubiprostone represents a new approach of treatment in cases of resistant or intolerable cases of chronic constipation with proven efficacy and safety.

**KEY WORDS:** Lubiprostone, chronic constipation, IBS-C, spontaneous bowel movement.**INTRODUCTION:**

Chronic constipation is a common clinical problem with the estimated prevalence of about 12-19%.<sup>[1,2]</sup> Women and those over 65 years of age are more commonly affected.<sup>[3]</sup> Although not a life-threatening illness, chronic constipation markedly affects the physical and psychological quality of life.<sup>[4]</sup> Constipation can be defined as "Patients with fewer than three bowel movements per week or having consistent difficulty with defecation such as hard or infrequent stools, prolonged time spent in the toilet or a sense of incomplete emptying".<sup>[5]</sup> Pathophysiologically, constipation is generally classified as either primary (irritable bowel syndrome with constipation [IBS-C], colonic inertia, pelvic floor dysfunction) or secondary in nature ( eg. Metabolic, endocrine, surgical, psychiatric, drug induced). Life style modifications and traditional drugs like bulk laxatives (psyllium), osmotic laxatives (magnesium citrate), emollients (docusate sodium) and stimulant purgatives (cascara) improve symptoms in some of the patients, but other patients may need some new drugs.<sup>[4]</sup>

Lubiprostone, a novel compound, is member of a new class of agents called prostones and was approved by FDA for treatment of chronic constipation in 2006 at a dose of 24µg twice daily in both men and women over the age of 18 years and then in 2008 for the treatment of IBS-C in women only at a dose of 8µg twice daily.<sup>[6,7]</sup> Lubiprostone is a oral bicyclic fatty acid metabolite analogue of prostaglandin E1.<sup>[8]</sup> It activates specific chloride channels in gastrointestinal tract resulting in luminal Cl<sup>-</sup> secretion and water movement responsible for its laxative effect.<sup>[9]</sup>

**PHARMACOKINETICS:**

**Absorption:** Lubiprostone is converted to active metabolite M3 which is systemically absorbed. Peak values of M3 occurs at 1.10 hours after a single oral dose i.e. 24µg of Lubiprostone.<sup>[6]</sup>

**Metabolism:** Lubiprostone is metabolized within gastrointestinal tract, particularly in the stomach and the jejunum, by microsomal carbonyl reductase system.<sup>[6]</sup>

**Distribution:** Active metabolite M3 is absorbed and 94% is bound to plasma proteins.<sup>[4]</sup>

**Excretion:** 63% of the active metabolite M3 is excreted in urine and 30% is excreted in stools by the the end of one week with oral single dose i.e. 72µg of Lubiprostone.<sup>[4]</sup> The estimated half life of Lubiprostone is 3 hours and M3 is 0.9-1.4 hours.<sup>[6]</sup>

**PHARMACODYNAMICS:**

Lubiprostone specifically activates ClC-2 Channels on the apical membrane of epithelial cells of small and large intestine.<sup>[4]</sup> The active secretion of chloride from epithelial ClC-2 Channel into the lumen is followed by the passive paracellular and secretion of sodium and water resulting in isotonic fluid secretion in intestinal lumen.<sup>[6]</sup> The secretion of fluids into the gastrointestinal tract adds fluid to stool and promotes in increased intestinal transit, likely through the stimulation of localized mechanoreceptors, thereby initiating a peristaltic wave and promoting spontaneous bowel movement (SBM).<sup>[4,7]</sup>

**EFFICACY:**

The efficacy of lubiprostone has been shown in different clinical trials of patients suffering from chronic constipation as well as constipation predominant irritable bowel syndrome (IBS-C) (Table I). The primary end point in various clinical trials of chronic constipation and IBS-C was number of SBM's and IBS symptoms like abdominal discomfort/pain/bloating/constipation severity/straining/stool consistency respectively.

In a double blind placebo controlled multicentric study, involving 242 subjects Lubiprostone 24 µg was administered twice daily to 120 patients of constipation as compared to placebo given to 122 patients for 4 weeks. The larger number of patients on lubiprostone had an SBM in 48 hours as compared to placebo (p=0.0013). Symptoms of constipation like straining, frequency and stool consistency was also improved for 1-4 weeks. Nausea and headache were the most common adverse effect that occurred during the study.<sup>[2]</sup>

Similarly Lubiprostone 24µg was administered twice daily in a multicentric trial including 237 subjects of chronic constipation. Patients on Lubiprostone experienced significant improvement in weekly bowel movements as well as in subjective measures of constipation (p=0.0001).<sup>[10]</sup>

Johanson and Ueno evaluated the efficacy and safety of Lubiprostone in 129 subjects of chronic constipation at doses 24µg, 48µg and 72µg per day as

compared to placebo for 3 weeks. Patients in treatment group had a significant increase in average number of weekly SBM's and improvement in associated symptoms of constipation over the entire study period (p=0.046) as compared to placebo without any serious drug related adverse events. Increased incidence of side effects were noted when 72 µg/day dose was used.<sup>[11]</sup>

A large open label multicentric study involving 880 subjects with chronic constipation receiving 24µg twice daily dose of Lubiprostone for 24-48 weeks showed improvement in frequency of bowel movements and other constipation related symptoms.<sup>[12]</sup>

Lubiprostone revealed no rebound effects in a withdrawal study of 128 patients after receiving 24µg twice daily of Lubiprostone for 4 weeks.<sup>[13]</sup> Lubiprostone has also been evaluated in 59 males of chronic constipation and found to be more efficacious than placebo.(P=0.0503).<sup>[14]</sup>

In a phase II multicentre placebo controlled trial in 195 patients of IBS-C, Lubiprostone has significantly improved the gastrointestinal symptoms like abdominal discomfort/pain score and 16µg/day was found to be the most efficacious and safest dose.<sup>[15]</sup> Even, in phase III multicentric, double blind placebo controlled studies involving 1000-1171 patients of IBS-C, it has been shown that Lubiprostone in the dose of 8µg BD achieve a better overall response as compared to placebo (p=0.001).<sup>[16,17]</sup>

**Table I: Lubiprostone in various clinical studies of patients of chronic constipation (CC) and constipation predominant irritable bowel syndrome (IBS-C)**

Type of study (Clinical condition)	Duration of study (weeks)	No. of patients enrolled	Mean Age (years)	Dose/day of Lubiprostone used (µg)	p value	Common adverse effect occurred
*RPCT <sup>[2]</sup> (CC)	4	242	48.6	48	0.0013	Nausea and headache
RPCT <sup>[10]</sup> (CC)	4	237	45.8	48	0.0001	Nausea, headache and diarrhea
RPCT <sup>[11]</sup> (CC)	3	129	48.3	24, 48, 72	0.046	Nausea
Large open label study <sup>[12]</sup> (CC)	24	308	-	48	<0.0001	Nausea
Large open label study <sup>[12]</sup> (CC)	48	572	-	48	<0.0001	Nausea
Randomized withdrawal study <sup>[13]</sup> (CC)	7	128	-	48	0.0464	No rebound effect

RPCT in males <sup>[14]</sup> (CC)	4	59	-	-	0.0503	-
RPCT <sup>[15]</sup> (IBS-C)	12	195	45.8	16,32, 48	0.39	Nausea, diarrhea, abdominal pain and distension
RPCT <sup>[16]</sup> (IBS-C)	12	1000	-	16	0.001	-
RPCT <sup>[17]</sup> (IBS-C)	12	1171	41.5	16	0.001	Nausea and diarrhoea

\* Randomized placebo controlled trial

#### ADVERSE EVENTS, CONTRAINDICATIONS AND DRUG INTERACTIONS:

The most commonly side effect reported with Lubiprostone in clinical trials was nausea (31%). Other adverse events included diarrhea (13%), headache (13%), abdominal distention (7%), abdominal pain (7%), flatulence (6%), sinusitis (5%) vomiting (5%) and dizziness (4%).<sup>[6]</sup> Lubiprostone should have a few drug-drug interactions because it acts locally in the gastrointestinal tract, having quick onset of action, rapidly metabolized on the cell surface and is minimally absorbed. Moreover, Lubiprostone is metabolized by microsomal carbonyl reductase, not by cytochrome P450, confirming its low likelihood of drug-drug interactions.<sup>[4,6]</sup>

#### DOSAGE AND ADMINISTRATION:

Lubiprostone is available for oral use in the form of soft gelatin capsule under the trade name Amitiza marketed by Sucampo/Takeda Pharmaceuticals.<sup>[4,7]</sup> Recommended daily dosage for chronic constipation is 24µg twice daily for both men and women over the age of 18 years and 8 µg twice daily for the women suffering from constipation predominant irritable bowel syndrome (IBS-C).<sup>[6]</sup>

#### DOSE ADJUSTMENT IN SPECIAL POPULATION:

Lubiprostone is not recommended or approved in patients younger than 18 years of age.<sup>[6]</sup> The results of pooled data indicates that Lubiprostone is effective as well as safe in the treatment of constipation in the elderly.<sup>[4]</sup> Due to lack of well-controlled studies in pregnant women and its association with increased fetal loss in guinea pig model, the drug is rated as pregnancy category "C" by the FDA. So Lubiprostone is not recommended during pregnancy and it should be prescribed only if the benefits significantly outweigh potential risks.<sup>[4]</sup> The drug is also not recommended for breast feeding women because of limited data available.<sup>[4]</sup>

Unfortunately, no studies have been conducted to assess the pharmacokinetic profile of lubiprostone in

patients with hepatic or renal impairment.<sup>[4,6]</sup> So data are not available to comment on the use of this drug in such patients.

#### CONCLUSION:

Lubiprostone represents a new approach to the treatment of chronic constipation and is an alternative for patients who are resistant to or intolerant to currently available prescription medications. It should be noted that lubiprostone has been proven safe and efficacious in placebo-controlled trials and presents a viable, wholly new alternative to existing therapy.

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