Summary of Product Characteristics

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Amitiza 24 Microgram Soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 24 micrograms of lubiprostone. Excipient: sorbitol liquid, partially dehydrated, less than 10 mg.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft.

An oval, amber capsule imprinted with SPI.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lubiprostone is indicated for the treatment of chronic idiopathic constipation in adults when response to diet and other non-pharmacological measures (e.g., educational measures, physical activity) are inappropriate.

4.2 Posology and method of administration

In adults (>18 years of age)

The recommended dose is one 24 microgram capsule taken twice daily. A course of treatment for constipation with Lubiprostone is 2 to 4 weeks. Efficacy beyond 4 weeks has not been demonstrated in placebo-controlled studies (see section 5.1). Treatment with lubiprostone should be stopped if there is no response to lubiprostone after at least 2 weeks.

In the elderly (>65 years of age)

No dosage changes are required based on age (see Section 5.1).

Paediatric population (<18 years of age)

The safety and efficacy of Lubiprostone in children and adolescents aged under 18 have not yet been established. Currently available data are described in Section 5.2 but no recommendation on a posology can be made.

Patients with renal impairment

No dosage adjustment is required in patients with renal impairment.

Patients with hepatic impairment

No dosage adjustment is required for patients with mild hepatic impairment. For patients with moderate or severe hepatic impairment (Child-Pugh classification B or C), the initial dosage should be decreased to 24 micrograms (1 capsule once a day after breakfast or supper). If this initial dose is tolerated and an adequate response has not been obtained after an appropriate interval, the dose can be increased to full dosing (one 24-microgram capsule, twice daily) with appropriate monitoring of patient response.

Method of administration

Lubiprostone soft capsules are for oral use, taken with food. The capsules should be swallowed whole with a sufficient amount of water.

4.3 Contraindications

Lubiprostone should not be used in patients with a known or suspected mechanical gastrointestinal obstruction.

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The efficacy of lubiprostone beyond 4 weeks has not been demonstrated in placebo-controlled trials (see section 5.1). Therefore, a course of treatment with lubiprostone should not exceed 4 weeks. Treatment should be stopped if there is no response to lubiprostone after at least 2 weeks.

Patients taking Lubiprostone may experience nausea (see Section 4.8). If this occurs, concomitant consumption of food (preferably a meal) with Lubiprostone may reduce symptoms of nausea.

Lubiprostone should not be prescribed to patients that have severe diarrhoea. Patients should be aware of the possible occurrence of diarrhoea during treatment. Patients should be instructed to inform their physician if severe diarrhoea occurs (see Section 4.8).

Dyspnoea or chest discomfort/pain (usually described as a sensation of chest tightness and/or difficulty taking in a breath) has been reported shortly after taking Lubiprostone, and some patients have discontinued treatment (see Section 4.8). These symptoms generally resolve within a few hours of dosing, but recurrence has been frequently reported with subsequent doses. If these symptoms occur, the patient should seek medical advice, before resuming treatment.

In patients with symptoms suggestive of gastrointestinal obstruction, the treating physician should perform a thorough evaluation to confirm the absence of such conditions prior to initiating or continuing therapy with Lubiprostone.

For patients with moderate or severe hepatic impairment (Child-Pugh classification B or C), the initial dosage should be decreased to 24 micrograms (see Section 4.2). Patients with severe hepatic impairment (Child-Pugh classification C) may experience higher systemic drug exposure (see Section 4.8). If this initial dose is tolerated but an adequate response has not been obtained after an appropriate interval, the dose can be increased to full dosing (one-24 microgram capsule, twice daily) with appropriate monitoring of patient response.

Due to the use of sorbitol as an excipient, patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No in vivo drug–drug interaction studies have been performed. Based upon the results of in vitro human microsome studies, there is low likelihood of drug–drug interactions.

In vitro studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further in vitro studies indicate microsomal carbonyl reductase may be involved in the

extensive biotransformation of lubiprostone to the metabolite M3.

Additionally, in vitro studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and in vitro studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone.

Based on the available information, no plasma protein binding–mediated or cytochrome P450 mediated drug interactions of clinical significance are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of lubiprostone in pregnant women. Studies in animals have shown reproductive toxicity (See Section 5.3).

Lubiprostone should not be used during pregnancy and in women of childbearing potential not using contraception.

Patients who become pregnant or are planning a pregnancy should be advised to consider the risks and benefits of continued Lubiprostone therapy during pregnancy.

Fertility

Lubiprostone, had no effect on the fertility and reproductive function of male and female rats (see section 5.3).

Breastfeeding

It is unknown whether lubiprostone or its metabolites are excreted in human milk. In animal studies, neither lubiprostone nor its active metabolites were detectable in breast milk following oral administration of lubiprostone. However, a risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Lubiprostone therapy, taking into account the benefit of breastfeeding for the child, and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a) Summary of the safety profile

The safety of Lubiprostone has been investigated in 301 patients in 3 pivotal clinical studies. During the pivotal clinical studies conducted on Lubiprostone, a number of adverse drug reactions have been reported. The most common adverse drug reaction reported by patients taking Lubiprostone was nausea, with diarrhoea and headache also being commonly reported. Treatment-emergent adverse events led to premature study discontinuation for 8% of patients in the pivotal clinical studies.

b) Tabulated summary of adverse reactions

Adverse drug reactions from clinical trials and post-marketing experience in adult patients.

The following events have been identified as adverse drug reactions, and are presented in Table 1 below. The frequency category includes all reported events of mild, moderate or severe intensity.

The adverse drug reactions are displayed by system organ class, and are reported by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and not known (cannot be estimated from the available data). Within each frequency grouping adverse drug reactions are presented in order of decreasing severity.

Events noted as having frequency 'Not known' were identified from post-marketing surveillance.

Table 1: Adverse drug reactions for Lubiprostone in clinical studies and post-marketing surveillance in adult patients

	Frequency			
System Organ Class	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1000 to ≤ 1/100)	**Not Known** (from post-marketing)
Cardiac disorders		Palpitations*		Tachycardia (includes increased heart rate)
Gastrointestinal disorders	Nausea*	Diarrhoea* Abdominal distension* Flatulence* Abdominal discomfort* Abdominal pain* Dyspepsia*	Vomiting*	Ischaemic colitis
General disorders and administration site conditions		Oedema (including peripheral)* Chest discomfort*	Chest Pain*	Influenza like illness
Immune System Disorders				Hypersensitivity (‘allergic-type reactions’)
Musculoskeletal, connective tissue disorder and bone disorders			Muscle spasms*	
Nervous system disorders		Headache* Dizziness*	Syncope*	
Respiratory, thoracic, and mediastinal disorders		Dyspnoea*		Throat tightness
Skin and subcutaneous tissue disorders		Hyperhidrosis,		Rash/Urticaria
Vascular disorders		Hot flush*		Hypotension

**Denotes adverse drug reaction observed in both clinical trials and post-marketing surveillance.*

c) Description of selected adverse reactions

Nausea

Nausea is the most commonly reported adverse drug reaction observed in pivotal clinical studies of

Lubiprostone, with 23.6% of patients experiencing at least one treatment-related nausea event; however, of those patients, 93% reported only a single event during treatment with Lubiprostone. Of all reported nausea events, 93.7% were mild to moderate in severity, and 4.0% discontinued treatment as a result of nausea. Administration of Lubiprostone with food has been shown to reduce symptoms of nausea (see Section 4.2 and 4.4).

Diarrhoea

In pivotal clinical studies of Lubiprostone, 8.3% of patients who received Lubiprostone twice daily experienced an adverse drug reaction of diarrhoea; a majority of diarrhoea events (89.7%) were considered to be mild to moderate in severity, and only 1.3% of patients discontinued treatment due to diarrhoea.

Dyspnoea

In pivotal clinical studies, there were adverse drug reactions of dyspnoea; these were reported in 1.7% of the treated population. Although none were classified as serious adverse drug reactions, some patients discontinued treatment on study because of these reactions. There have been post-marketing reports of dyspnoea when using Lubiprostone. Most have not been characterized as serious adverse events, but some patients have discontinued therapy because of dyspnoea. These events have usually been described as a sensation of chest tightness and/or difficulty taking in a breath, and generally have an acute onset within 30–60 minutes after taking the first dose. They generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses (see Section 4.4).

d) Special Populations

Patients with hepatic impairment

A clinical trial was conducted to compare the pharmacokinetic and safety profile of Lubiprostone in subjects with moderate and severe hepatic impairment (Child-Pugh classification B or C) to matched healthy control subjects. Adverse events after administration of lubiprostone were reported in approximately half of subjects with hepatic impairment, and in none of the healthy control subjects. Observed treatment- related adverse events included diarrhoea, dry mouth and headache and were of mostly mild intensity. There was a trend toward increasing numbers of adverse events reported by severely hepatically impaired subjects as well as by subjects administered a higher dose. The safety results of this trial suggest that adjustment of dosing regimen will improve the drug's tolerability in patients with severe hepatic impairment (see Section 4.2 and 4.4).

Elderly Population

In clinical studies, the frequencies of most individual adverse drug reaction were not appreciably different across age groups, or across treatment groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In a clinical study, subjects who were administered supratherapeutic dosages of Lubiprostone (144 micrograms; 6 times the recommended individual dose) reported several adverse events at an incidence greater than that observed for the recommended dose. In particular, subjects experienced increased occurrences of nausea, diarrhoea, vomiting, dizziness, flushing/hot flash, retching and dyspnoea. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A06AX Other laxatives, ATC code: A06AX03

Mechanism of action

Lubiprostone is a prostone, a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion, without altering electrolyte concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A– independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Additionally, activation of ClC-2 by lubiprostone has been shown to stimulate recovery of mucosal barrier function via the restoration of tight junction protein complexes in ex vivo studies of ischaemic porcine intestine.

Clinical efficacy and safety

Three double-blinded, placebo-controlled studies of similar design were conducted in patients with chronic idiopathic constipation. Constipation was defined as less than three spontaneous bowel movements per week in the absence of rescue medication (enema or suppository) use. A total of 603 patients were randomised; 301 patients received Lubiprostone twice daily (48 micrograms/day) and 302 received placebo twice daily for 4 weeks. The primary endpoint of two studies was spontaneous bowel movement frequency at Week 1; in the third study, the primary endpoint was the change from baseline in spontaneous bowel movement frequency at Week 1. All studies demonstrated that patients treated with Lubiprostone had a higher frequency of spontaneous bowel movements and significantly increased post-treatment changes from baseline in spontaneous bowel movement frequencies during Week 1 as compared to placebo-treated patients. In all studies, results similar to those in Week 1 were also observed at Weeks 2–4 of therapy.

In all studies, Lubiprostone demonstrated an increased proportion of patients achieving spontaneous bowel movements within the first 24 hours after administration, when compared to placebo 57% vs. 37%, (Study 1); 63% vs. 32%, (Study 2); 58% vs. 31% (Study 3). Lubiprostone also demonstrated an overall reduction in time to first spontaneous bowel movement compared to placebo.

Signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, and straining, as well as constipation severity and treatment effectiveness ratings, were also improved with Lubiprostone versus placebo.

The results were consistent in subpopulation analyses for gender, race, and elderly patients.

No serious adverse reactions of electrolyte imbalance were reported in clinical studies, and no clinically significant changes were seen in serum electrolyte levels in patients receiving Lubiprostone.

Following 4 weeks of treatment with Lubiprostone twice daily, withdrawal of Lubiprostone did not result in a rebound effect.

Four open-labelled, long-term studies were conducted in patients with chronic idiopathic constipation. Except for one study, Lubiprostone was used on as need basis. The chosen Lubiprostone dose was 24 micrograms twice daily. These studies comprised 1087 patients who were treated for 24 (one study) or 48 weeks. These studies demonstrated that Lubiprostone decreases abdominal bloating, abdominal discomfort, and constipation severity over the chosen

treatment period.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Lubiprostone in one or more subsets of the paediatric population in the treatment of chronic constipation.

5.2 Pharmacokinetic properties

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), Cmax, and t½ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterised. Gender has no effect on the pharmacokinetics of M3 following the oral administration of lubiprostone. Also there are no apparent differences in pharmacokinetics between Western and Japanese clinical trial subjects.

Absorption

Peak plasma levels of M3, after a single oral dose of 24 micrograms of lubiprostone, occur at approximately 1.10 hours. The Cmax was 41.5 pg/mL and the mean AUC0-t was 57.1 pg/hr/mL in Western subjects. AUC0-t of M3 increases dose proportionally after single 24 micrograms and 144 micrograms doses of lubiprostone in Western subjects.

Distribution

In vitro protein binding studies indicate that lubiprostone is approximately 94% bound to human plasma proteins.

Biotransformation

Studies indicate that lubiprostone is rapidly and extensively metabolised by 15- position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, an active metabolite of lubiprostone in both humans and animals is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the same in humans, and studies of lubiprostone metabolism have shown that M3 is observed in plasma at less than 10% of the concentration of administered oral dose of lubiprostone.

Elimination

Lubiprostone could not be detected in plasma; however, M3 has a t½ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 micrograms of 3H-labelled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the faeces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in faeces.

Food effect

A study was conducted with a single 72-microgram dose 3H-labelled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism and excretion. Pharmacokinetic parameters of total radioactivity demonstrated that Cmax decreased by 55% while AUC0-∞ was unchanged when lubiprostone was administered with a high-fat meal.

Paediatric population

In paediatric patients aged 7 to 16 years of age with chronic constipation, mean Cmax and AUC0–t of M3 was 41.8 pg/mL and 58.5 pg•hr/mL, respectively, following a single, oral dose of 24 micrograms of lubiprostone. Absorption of

lubiprostone in paediatric patients is comparable to that of their adult counterparts treated with 24 micrograms of lubiprostone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lubiprostone, at oral doses of up to 1000 micrograms/kg/day, had no effect on the fertility and reproductive function of male and female rats.

In rats receiving oral lubiprostone during organogenesis at doses of up to 2000 micrograms/kg/day (approximately 338 times the maximum recommended human dose based on body surface area {mg/m^2}), there were increased incidences of early resorptions and soft tissue malformations (*situs inversus*, cleft palate) at the 2000 micrograms/kg/day dose; however, these effects were possibly secondary to maternal toxicity at this dose (decreased body weight and food consumption).

No treatment-related developmental effects were seen in rabbits receiving oral lubiprostone during organogenesis at doses up to 100 micrograms/kg/day (approximately 34 times the maximum recommended human dose based on body surface area (mg/m^2)).

In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 micrograms/kg/day (approximately 2 and 6 times the recommended human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation; such losses were observed under conditions of maternal toxicity. In monkeys, no lubiprostone-related fetal loss was seen at doses of 10 and 30 micrograms/kg/day (approximately 3 and 10 times the recommended human dose, respectively, based on body surface area) administered on days 110 to 130 of gestation.

Following oral administration to lactating rats, neither lubiprostone nor its active metabolite was detectable in breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine capsule
Gelatine
Sorbitol, liquid, partially dehydrated (E420)
Purified water
Black ink

Black ink composition:
Propylene glycol
Black iron oxide
Polyvinyl acetate phthalate
Polyethylene glycol

Capsule contents
Medium-chain triglycerides (MCT)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before first opening of container: 4 years.

After first opening of container: 4 weeks.

6.4 Special precautions for storage

Keep the container tightly closed.

Store in the original container in order to protect from light and moisture.
Do not store above 30^{o}C. Do not freeze.
After first opening the container: Use within four weeks.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles containing rayon filler with a screw cap.

28 and 56 capsules are contained in each bottle.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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BUCKS, HP10 0DF
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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

April 2016