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AMITIZA 24 MICROGRAM SOFT CAPSULES

PL 21341/0003

UKPAR

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Sucampo Pharma Europe Limited a Marketing Authorisation (licence) for the medicinal product AMITIZA 24 micrograms Soft Capsules (PL 21341/0003) on 10 September 2012. This is a prescription-only medicine (POM).

AMITIZA 24 micrograms Soft Capsules contains the active ingredient, lubiprostone and works by increasing the amount of fluids into the bowels. This helps the passage of stool and reduces the feeling of uncomfortable and difficult bowel movements that occurs with constipation. AMITIZA 24 micrograms Soft Capsules is used to treat chronic idiopathic constipation.

Based on the data submitted by Sucampo Pharma Europe Limited it was judged that the benefits of AMITIZA 24 micrograms Soft Capsules outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product AMITIZA 24 micrograms Soft Capsules (PL 21341/0003) to Sucampo Pharma Europe Limited on 10th September 2012. This product is a prescription-only medicine.

This application was submitted as full application according to Article 8(3) of Directive 2001/83/EC as amended. The product is indicated for the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g., educational measures, physical activity) are inappropriate. The product contains a new bicyclic fatty acid compound, lubiprostone.

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.

An extensive battery of GLP non-clinical studies designed to assess the toxicity of lubiprostone and its metabolites have been conducted.

Clinical studies include seven Phase I studies, two Phase II studies, and seven Phase III studies (three pivotal studies and four long-term safety studies); two of the Phase I studies, one Phase II study, one pivotal study and one of the long-term studies were conducted in Japan. Three separate clinical studies of lubiprostone were conducted in subjects with renal or hepatic impairment, as well as paediatric patients diagnosed with chronic constipation.

The applicant has submitted a satisfactory pharmacovigilance system and fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The applicant submitted a suitable Risk Management Plan.

The applicant has submitted a suitable Environmental Risk Assessment.

The application was referred to Commission on Human Medicines on 10th July 2012; recommendations were made and have been carried out by the applicant. A Marketing Authorisation was granted on 12th September 2012.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Lubiprostone

INN/ BAN: Lubiprostone

Chemical name: \((-\)-\((2R,4aR,5R,7aR)\)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[\(b\)]pyran-5-yl\)heptanoic acid

Structure

\[
\text{C}_20\text{H}_{32}\text{F}_2\text{O}_5
\]

Molecular weight: 390.46

General Properties

Description: White odourless crystals or crystalline powder

Solubility: Soluble in ether, ethanol, 2-propanol, acetonitrile, DMSO and practically insoluble in water and n-hexane

The active substance, lubiprostone, is currently not the subject of a European Pharmacopeia (Ph.Eur) or British Pharmacopeia (BP) monograph.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active substance are not of animal, biological or genetically modified origin.

Appropriate data have been supplied to characterise the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been supplied.

**MEDICINAL PRODUCT**

**Description and Composition**

The finished product is presented as an oval, clear, soft gelatine capsule imprinted with the letters “SPI”. Each soft capsule contains 24 micrograms of the active ingredient, lubiprostone dissolved in medium-chain triglycerides.

Other ingredients consist of pharmaceutical excipients: the capsule contains medium-chain triglycerides (MCT); the gelatine capsule shell consists of gelatine, sorbitol liquid partially dehydrated (E420), purified water and the ink composition is made up of propylene glycol, black iron oxide, polyvinyl acetate phthalate and polyethylene glycol. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used to make up the capsule shell and its content complies with their respective European Pharmacopoeia monographs. The excipients used in the printing ink all comply with in-house specifications which are satisfactory. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin none of the excipients used contain material derived from animal or human origin. The applicant has provided from each supplier, Certificates of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), confirming that the gelatin has been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). None of the excipients are sourced from genetically modified organisms. There are no novel excipients used.

**Pharmaceutical Development**

Pharmaceutical development was conducted to support the clinical studies carried out for the finished product.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on commercial scale batches and results were acceptable.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the
proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
The finished product is licensed for marketing in high density polyethylene (HDPE) bottles containing rayon filler with a screw cap. Each bottle contains 56 capsules and is packed with the Patient Information Leaflet (PIL) into cardboard outer carton.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 4 years before first opening the bottle and a shelf-life of 4 weeks after first opening have been set. The storage conditions are as follows: “Keep the container tightly closed”, “Store in the original container in order to protect from moisture”, “Do not store above 30°C”, “Do not freeze” and “After first opening the container use within four weeks after first opening”.

**Quality Overall Summary**
A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. The labelling texts fulfil the statutory requirements for Braille. The user-testing of the PIL text has been evaluated and is accepted.

The applicant has submitted results of PIL user testing. Colour mock-ups of the labelling The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that is contains.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are satisfactory.

**Conclusion**
There are no objections to approval of AMITIZA 24 microgram Soft Capsules from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

PHARMACOLOGY
Studies using human intestinal T84 and human epithelial kidney (HEK) cell lines have shown that lubiprostone is a potent and selective activator of CIC-2. Activation of this chloride channel, which is located on the intestinal epithelial cell, increases chloride transport into the lumen of the intestine, enhances fluid secretion into the bowels and improves faecal transit. Mechanistic studies indicate that this activation of CIC-2 is via a protein kinase-A-independent mechanism.

Lubiprostone produced a dose-related increase in the weight/volume of gastrointestinal fluid in both mice and rats. This increase in intestinal fluid volume was associated with dose-dependent increases in Cl\(^-\) concentration and total Cl\(^-\) in the gastrointestinal fluid. At single doses >100 times the intended clinical dose lubiprostone increased the secretion of a chloride-rich intestinal fluid but did not affect serum electrolyte levels in a rat model. It is therefore unlikely that treatment with lubiprostone will lead to electrolyte imbalances in the clinic.

Lubiprostone decreased the transit time of intestinal contents in mice with morphine-induced hypomotility. In a similar study, lubiprostone also improved constipation induced by oxycodone. In addition, the activation of CIC-2 by lubiprostone has been reported to accelerate recovery of ischemic-injured porcine ileum \textit{ex vivo}, which was associated with structural changes in the tight junctions of the mucosal epithelium.

The effect of several lubiprostone metabolites on intestinal fluid secretion activity was investigated. These studies indicate that metabolite 15-hydroxy-lubiprostone or M3 (U-E230; U-E231/UE232) has pharmacological (intestinal fluid secretion) activity similar to lubiprostone while the other metabolites are devoid of effects on intestinal fluid secretion at oral doses as high as 10 \(\mu\text{g/kg}\).

Additional studies confirmed that both lubiprostone and M3 metabolite activate Cl\(^-\) channels located on the luminal (apical) side of the intestine, but do not activate channels located on the basolateral membrane.

Lubiprostone exhibited limited effects on smooth muscle contractions, including the isolated uterus, trachea, and ileum. In addition, prostaglandin E and F receptor studies indicate that lubiprostone is a very weak agonist of all four prostaglandin receptors (EP\(_1\), EP\(_2\), EP\(_3\) and FP) compared to natural prostaglandins. As such, it is unlikely that treatment with the proposed product will cause clinically significant pharmacological effects mediated by these receptors.

The effects of lubiprostone on the major organ systems were investigated in a battery of safety pharmacology studies at doses up to >100 times the intended clinical dose. Lubiprostone had no effect on platelet aggregation or the central nervous system. Gastrointestinal effects were only seen at the highest dose tested (1000 \(\mu\text{g/kg}\)), where an acceleration of small intestinal transit was noted in rats. Decreased urinary excretion of Na\(^+\) was seen in the mid-dose group (100 \(\mu\text{g/kg}\)) and decreases in urine volume and the excretion of Na\(^+\), K\(^+\), and Cl\(^-\) was observed in the high dose group (1000 \(\mu\text{g/kg}\)). It is likely these findings are the result of increased intestinal water secretion, which is the primary pharmacological effect of lubiprostone.

Section 5.1 of the SmPC is acceptable.
PHARMACOKINETICS
A comprehensive pharmacokinetic package has been conducted with lubiprostone. The majority of studies were conducted in male animals. In the rat, where studies were carried out in both sexes concentrations of radioactivity and values for $C_{\text{max}}$ and $\text{AUC}_{0-24}$ were higher in both sexes ($C_{\text{max}}$ approximately 3x and higher in both blood and plasma and $\text{AUC}_{0-24}$ approximately 2x and 3x higher in blood and plasma, respectively).

Across species 34% to >70% of an oral dose of $[^{3}\text{H}]$-lubiprostone is absorbed in vivo, with little or no radioactivity associated with the parent drug. Plasma protein binding of lubiprostone is >90% in the mouse, rat, dog, and human and does not appear to be dependent on concentration or gender. Binding of total radioactivity in vivo was between approximately 46 and 61% up to 6 hours after dosing.

Administration of $[^{3}\text{H}]$-lubiprostone to pregnant or lactating rats resulted in detectable levels of radioactivity in fetal tissues and milk, respectively, for the 24 hours post-dose during which it was measured. However, the levels were low, with only 0.01% of the administered dose present in fetuses and 0.1-0.2% present in milk.

Excretion studies indicate that in animals, 73 to 95% of absorbed radioactivity was excreted by 48 hours. In the rat, more radioactivity is excreted in the faeces than in the urine while in the rabbit, dog, and monkey, the majority of radioactivity is excreted in the urine.

Metabolites have been well characterised. The main metabolite is 15-hydroxy-lubiprostone (M3, which is equipotent to lubiprostone with respect to apical membrane intestinal fluid secretion activity) and has been identified in the plasma and urine of all species examined. Subsequent oxidation leads to a number of other metabolites, some of which were only detected in humans (in urine and/or faeces) but at a low level (<3%). The major human metabolites were present in rats and dogs and therefore these are appropriate species in which to conduct the toxicity studies. Lubiprostone is rapidly and extensively metabolised within the gastrointestinal tract. There is significant metabolism of lubiprostone to 15-hydroxy-lubiprostone in human liver microsomes. This does not appear to be CYP450 mediated but instead mediated via carbonyl reductase.

Lubiprostone does not inhibit or induce cytochrome P450 and thus is not likely to cause metabolism-based drug interactions. The applicant has provided information and satisfactory discussion on the potential interactions that may arise from off-target binding of lubiprostone to receptors, ion-channels, enzymes or transporters apart from the intended chloride target. As the action of lubiprostone is mainly local and it is rapidly metabolised, the likelihood of off-target effects appears to be low. In addition, a Novascreen assay was conducted in which no significant binding to any of the receptors or enzymes tested was noted and therefore further supports the argument that off-target activity is unlikely.

TOXICITY
The Applicant has conducted an acceptable toxicity programme for lubiprostone.

Single and repeat dose studies
The most notable test article-related changes were diarrhoea (rats, mice and dogs) and vomiting (dogs). Loose stools or diarrhoea were observed at or above 1 mg/kg/day in
the rat (4 weeks) and 0.1 mg/kg/day in the mouse (13 weeks), and 0.002 mg/kg/day in the dog (39 weeks). At high doses (5 mg/kg/day in mice and 1 mg/kg/day in rats), decreased activity and abdominal distension were associated with these signs.

Loose stools, diarrhoea and vomiting were considered to be related to the pharmacological effect lubiprostone or a local irritation and were not considered to be systemic toxicity. In rats, changes in haematology and some clinical pathology endpoints were noted, but with the exception of decreased serum protein, they were not consistent across studies.

Changes in electrolytes were also noted in the majority of studies. In the 4 week rat study increases in urinary volume and a decrease in urinary K⁺ were noted in females at 1 mg/kg/day. At the end of the 4 week recovery period a significant increase in urine volume and significant decrease in urinary K⁺ were still present along with decreased Na⁺, and Cl⁻ concentrations in females at this dose. Decreases in K⁺ in males at ≥0.04 mg/kg/day, were also noted. In the 26 week rat study urinary concentration of K⁺ was decreased in males at 0.016 mg/kg/day and in both sexes at 0.4 mg/kg/day.

In the two week dog study changes in urinary concentration of electrolytes (sodium, potassium and chloride in one male and sodium in one female) were seen at 1 mg/kg/day. In the 4 week dog study a decrease in urinary Na⁺ concentration in males and a decrease in Cl⁻ concentration were noted at 0.07 mg/kg/day. At 0.5 mg/kg/day, urinary concentrations of Na⁺, Cl⁻ and K⁺ were decreased in both sexes. In the dog 39 week study, at Weeks 12 and 25, urinary concentration of Na⁺ was decreased in females at 0.05 mg/kg/day. Other changes in electrolytes were noted at ≥0.01 mg/kg/day; however this was attributed to the daily occurrences of vomiting and changes in faecal appearances.

In relation to the electrolyte findings, there were generally no corresponding changes in relevant blood biochemistry parameters or associated histological findings seen. These changes tended to be non-dose related, inconsistent across studies and might have been due to increased water consumption and the general in-life signs noted in all of these studies at most doses.

Higher adrenal weights and swelling of the adrenal cortex were noted in mice (5 mg/kg/day); higher adrenal weights were also observed in rats (0.4 mg/kg/day in females only), without histological correlates.

QTc was shortened in females at 0.5 mg/kg/day at the end of the treatment period (after 4 weeks) in dogs, however, there were no other treatment-related effects observed in ECG’s in dogs. There were no treatment-related effects observed in ophthalmoscopic evaluations in rats or dogs.

A thickening of the limiting ridge of the fore stomach and the glandular stomach was noted in the 13-week mouse study (0.1 to 5 mg/kg/day); microscopically oedema and acanthosis were noted. In rat studies raised areas of the glandular stomach and thickening of the limiting ridge (males 0.016 mg/kg/day and higher and females 0.08 mg/kg/day and higher) were observed and were associated with oedema and acanthosis and proliferation of the basal cells. This finding was considered particular to the rodent as other species do not have nonglandular stomachs and is not believed to progress. As no gross or microscopic changes were seen in the stomach of dogs treated with
lubiprostone for 39 weeks, at doses up to 0.05 mg/kg/day, it is likely that these findings are species specific and the applicant reasoning can be accepted.

**Toxicokinetic studies**
Mean plasma concentrations increased in a dose-related manner in all studies and exposures (AUC) were in the picogram range. In general, concentrations were comparable in male and females and did not appear to accumulate with repeated dosing.

**Carcinogenicity studies**
In the rodent carcinogenicity studies, non neoplastic and neoplastic lesions were evident in non-glandular stomach, liver and testis. Hyperplasia and proliferative lesions of the nonglandular stomach were noted but there were no tumourigenic effects in mice up to 0.5 mg/kg/day or rats up to 0.4 mg/kg/day. The applicant provided a plausible explanation of these hyperplastic lesions and they are considered unlikely to be of relevance to man. In addition, the stomach of the dogs treated with lubiprostone for 39 weeks at doses up to 0.05 mg/kg/day did not indicate any gross or microscopic changes. For the liver findings, haematopoietic neoplasia and hepatocellular carcinoma occur commonly in older mice. In the rat, the incidence and severity of basophilic cellular alterations were increased in females at high doses (0.4 mg/kg/day) and hepatocellular adenomas were marginally increased in this group. Incidences of hepatocellular adenomas in all females showed a positive trend but the increase at 0.4 mg/kg/day was not statistically significant. None of the control or treated females exhibited hepatocellular carcinomas. The incidence of hepatocellular adenoma and carcinoma was similar between treated and control males. As these findings were generally seen at high doses and in one sex, it can be accepted the positive trends observed are not likely to be relevant to the clinical situation.

There was an increased incidence of interstitial cell tumours in testis of male rats at 0.4 mg/kg/day. Hyperplastic and neoplastic lesions in the testis were combined for the purposes of statistical analysis as chronic hyperplasia can frequently lead to formation of benign tumours in the rat and the borderline between hyperplasia and neoplasia was arbitrary in some cases. Although a direct effect of lubiprostone on the testis cannot be excluded, there is a sufficiently high exposure margin to human exposure to suggest that the findings could have limited relevance to humans.

**Genetic Toxicology studies**
Lubiprostone and metabolites U-E231 and U-E232 did not show mutagenic potential in bacterial reverse mutation assays or produce chromosomal aberrations in CHL cells. Lubiprostone was negative in the forward mutation assay at the TK locus in mouse lymphoma cells and in an in vivo micronucleus test.

**Reproductive toxicology**
In the fertility and early embryonic development study in rats there was a slight decrease in the weight of the epididymis, without microscopic correlates, and a slight decrease in the number of viable implantations when males were mated with treated females. There were no significant differences in the number of corpora lutea, the implantation index or number/percent of preimplantation losses.

In the rat embryo-fetal development study, there were effects on deliveries, neonatal survival, and in utero growth and development at maternally toxic doses. These effects included death, substantially reduced weight gain even during pregnancy or weight loss, and reduced food consumption. This maternal toxicity was considered to be
responsible for the increased incidence of females with early resorptions, decreased mean fetal weights, and fetal soft tissue malformations at the high dose of 2 mg/kg/day.

In gravid rabbits lubiprostone to did not result in teratogenicity or embryo-lethality at doses up to 0.1 mg/kg/day, the highest dose level used. However decreased weight gain and food consumption was seen at this dose.

In a pre- and post-natal study in rats, there were adverse effects in the F0 females at 1 mg/kg/day (high dose) and 0.2 mg/kg/day (middose). Mean body weights at birth of the pups from dams at 1 mg/kg/day were lower relative to the controls. This was also considered to be caused by maternal toxicity, negatively impacting on in utero growth of these offspring. Three females died during parturition and one female that was pregnant did not deliver and had early resorption of the entire litter. In addition, total litter death occurred in one dam at 0.2 mg/kg/day, and in twelve dams at 1 mg/kg/day. These deaths occurred soon after birth, however, those pups that survived the neonatal period survived the entire lactation period as the weaning index (survival Lactation Day 4-weaning) was similar in all groups.

A distribution study in pregnant and lactating showed very low levels of radioactivity crossing the placenta and entering milk (0.01% and 0.1-0.2% of the dose, respectively) following oral dosing of dams with [3H]-lubiprostone. Lubiprostone and M3 could not be detected in the fetal or milk samples taken during these studies. In an abortifacient study in guinea pigs, lubiprostone produced maternal toxicity, deaths and abortions at the highest dose tested (0.025 mg/kg/day). There was no evidence of abortifacient potential in monkeys. These latter findings are reflected adequately in section 5.3 of the SmPC, but some revision is required to sections 4.6 and 5.3 to fully reflect the available reproductive toxicity data.

Antigenicity, phototoxicity and other toxicity
Lubiprostone was not antigenic in guinea pig models of active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA). Lubiprostone does not absorb visible light and only weakly absorbs UV light at 294nm; the risk of phototoxicity is very low. In an in vitro study of osteoclastogenesis and osteoblastogenesis, lubiprostone appeared to have a direct effect on osteoblast activity at a concentration of 10nM as noted by decreased mineralisation. This could suggest the possibility of reduced bone density in vivo, although other factors in the more complex in vivo environment could counteract this effect.

Impurities
Related substances have been qualified adequately.

Environmental Risk Assessment
An acceptable environmental risk assessment has been conducted by the applicant. Based on logKOW measurements and PECsurfacewater calculations it is unlikely that the indicated use of lubiprostone will pose a threat to the environment.

The SmPC is satisfactory from a non-clinical viewpoint.

There are no objections to the approval of AMITIZA 24 micrograms Soft Capsules from a non-clinical point of view.
CLINICAL ASSESSMENT

BACKGROUND
Lubiprostone is a new active compound for oral administration, 7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl] heptanoic acid.

Lubiprostone is a prostone, which locally and selectively activates chloride channels to promote a chloride-rich intestinal fluid secretion without altering electrolyte concentrations in the serum. It acts by specifically activating type-2 chloride channels (CIC-2), which are a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone enhances motility in the intestine, thereby facilitating the passage of stool. Patch-clamp studies in human cell lines indicate that the biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium. Therefore, systemic absorption of lubiprostone and its only measurable active metabolite, M3, is not required for pharmacological activity. Additionally, CIC-2 plays a role in the restoration of the tight junction complexes and recovery of barrier function within the body. Lubiprostone has been shown to stimulate the recovery of mucosal barrier function in ex vivo studies of the intestine and colon through the restoration of these tight junctions.

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

DOSE AND DOSE REGIMEN
In adults (>18 years of age)
The recommended dose is one 24 microgram capsule taken twice daily. A course of treatment for constipation with AMITIZA is 2 weeks.

Full details concerning the posology are provided in the SmPC.

CLINICAL PHARMACOLOGY
Lubiprostone is a functional fatty acid derivative prostone that locally and selectively activates type-2 chloride channels (CIC-2). Activation of these channels in the gastrointestinal tract increases Cl- transport in the lumen, enhances fluid secretion into the bowel, and improves faecal transit. It appears that the CIC-2 channel plays an important role in the restoration of the tight junction complexes and recovery of barrier function. Lubiprostone may stimulate the recovery of mucosal barrier function in the intestine and colon through the restoration of these tight junctions.

2.1 PHARMACOKINETICS
Human Studies
Studies with Radioactive Lubiprostone
Studies in healthy male and female volunteers demonstrated that 3H-lubiprostone-derived radioactivity does not appear to be taken up by or bind to red blood cells. The mean percentages of radioactivity associated with tritiated water were typically less than 10% in both blood and plasma. Renal excretion is the main route of elimination. Approximately 60% of the radiolabeled dose was recovered in the urine by 24 hours post-dose, and excretion was essentially complete by that time. By 168 hours post-dose, radioactivity excreted in urine remained at approximately 60% of the total dose, which indicated that a minimum of 60% of
the administered radioactivity was absorbed. Faecal recovery through 168 hours accounted for > 20% of the total dose of radioactivity. The mean recovery of 3H-lubiprostone derived radioactivity in the urine and faeces by 168 hours after dosing was ≥ 80% of the dose; the majority of this was excreted within 72 hours.

Administration of 3H-lubiprostone under fed conditions resulted in a decreased rate of absorption (lower Cmax, later Tmax), but there was no change in the extent of absorption (AUC0-t) or urinary or faecal excretion of radioactivity.

These studies also demonstrated that the parent compound, 3H-lubiprostone, was not detected in any of the plasma, urine, and faeces samples examined for metabolic profiling. Additional profiling of metabolite M3 (15-hydroxy-lubiprostone; U-E230) was conducted using selected human plasma samples from male and female subjects under fed and fasted conditions. Peaks corresponding to both epimers of M3 (U-E231 and U-E232) were observed in these samples at mean ratios to the total of 4.3% and 95.7%, respectively. These results suggest that both epimers of M3 are present in human plasma after oral administration of lubiprostone, regardless of sex or treatment condition (fed or fasted), and that the more polar epimer (U-E232) is predominant.

Plasma concentrations of M3 (U-E232; 15-hydroxy-lubiprostone) were measured in a study in healthy male and female volunteers after single doses of 24 mcg or 144 mcg. Plasma concentrations of the metabolite increased in a dose-related manner and the mean AUC0-t at 144 mcg was 5.5-fold higher than at 24 mcg, consistent with the 6-fold increase in dose.

There did not appear to be an effect of gender on either Cmax or AUC0-t at either dose.

**Studies with Non-radioactive Lubiprostone**

In study, RTU/RU0211-99101 healthy volunteers were administered single lubiprostone doses ranging from 6 mcg to 96 mcg, and blood samples were collected over the subsequent 24-hour period. In the second study, study 99102, subjects were administered lubiprostone doses of 72 mcg (24 mcg 3 times daily [TID]), 90 mcg (30 mcg TID), or 108 mcg (36 mcg TID) for 6 days with a single dose on the morning of the seventh day. Blood samples were collected at various times during the 7-day treatment period. Based on the lack of quantifiable plasma levels in these studies, no pharmacokinetic parameters could be estimated. Samples from these studies were stored at -20 °C for approximately 2 years until an appropriate assay was developed; however, it was later shown that plasma samples were not stable under such storage conditions, thereby raising questions as to the validity of these results. To that end, a more recent study was conducted in which subjects received single lubiprostone doses of 24 mcg or 144 mcg. Analysis of the plasma samples from the 144 mcg cohort showed a lubiprostone concentration ≥ LOQ (10 pg/mL) for only a single sample, confirming the lack of measurable plasma concentrations of the parent compound.

Three trials assessed the pharmacokinetics of the M3 metabolite after single (Study SC0411 conducted in the US and Study NA0311, conducted in Japan) and repeated dose (Study NA0611, conducted in Japan) oral administration of 24 mcg lubiprostone in healthy individuals. There appeared to be no major ethnic differences in key pharmacokinetic parameters and systemic exposure to lubiprostone, and its major metabolite M3 was generally low following oral administration.

Pharmacokinetic parameters were also evaluated in the renally impaired in a Phase IV, open-labelled study to investigate the pharmacokinetics and safety of lubiprostone
following oral 24 mcg dose in patients with renal impairment and healthy subjects with normal renal function. There were no clinical differences in observed PK and/or safety parameters between renally impaired and control subjects. Plasma concentrations of M3 were within range of exposure from previous clinical experience with lubiprostone in healthy volunteers; there is no need for dosage adjustment in patients with renal impairment.

A Phase IV, open-labelled study to investigate the pharmacokinetics and safety of a single oral administration of lubiprostone in subjects with hepatic impairment in comparison with healthy subjects with normal hepatic function was conducted following a single oral administration of 24 mcg lubiprostone. The results demonstrated an increase incidence and severity of adverse events in patients with severe hepatic insufficiency and at a higher lubiprostone dose, it is therefore reasonable to suggest that caution should be taken when treating patients with moderately or severely impaired hepatic function with lubiprostone.

2.2 BIOEQUIVALENCE: N/A

2.3 PHARMACODYNAMICS

No human pharmacodynamic studies have been performed

3 CLINICAL EFFICACY

3.1 CHRONIC IDIOPATHIC CONSPIRATION

The clinical efficacy of oral lubiprostone in the treatment of CIC was demonstrated in 5 controlled studies: RTU/0211SC9921 (SC9921), RTU/0211SC0131 (SC0131), SPL/0211CC0721 (CC0721), SPI/0211SC0232 (SC0232) and SPL/0211CC0831 (CC0831) and 4 long term open-label studies: RTU/0211SC01S1 (SC01S1), RTU/0211SC01S2 (SC01S2; Study Period 2 [SP2] only), SPI/0211SC02S3 (SC02S3) and SPL/0211CC0832 (CC0832).

Lubiprostone was also evaluated in 2 Phase I studies (99101 and 99102) performed in healthy volunteers to evaluate dose response and identifying the appropriate dose for evaluation in Phase II in the USA. Two additional Phase I studies (NA0311 and NA0611) were performed in Japanese healthy volunteers to enable conduction of Phase II and III trials in Japan.

Pivotal studies SC0131 and SC0232 were carried out using identical study designs and study CC0831 used a similar study design. Study SC9921 and CC0721 were Phase 2b dose-ranging studies with a design similar to those of the pivotal studies. Studies SC9921, SC0131 and SC0232 (conducted in the USA) were combined for meta-analyses into a grouping called the “Well-controlled Group (WCG) cohort”. SC01S1, SC01S2 SP2, and SC02S3 had similar designs, and these studies were combined in a grouping termed the Long-term Safety (LTS) cohort.

Discussions of efficacy focus on the three individual pivotal trials SC0131, SC0232 and CC0831.

Patient Populations
The mean age was 47.3 years in the WCG cohort, with 57.7% of subjects < 50 years old, 31.8% of subjects ≥ 50 and < 65 years old, and 10.5% of subjects ≥ 65 years old; percentages were similar in the LTS cohort. The majority of subjects in each cohort were female and white. Among subjects for whom irritable bowel syndrome (IBS) status was recorded, 19.0% of WCG subjects and 21.0% of LTS subjects reported having IBS. Paediatric subjects (i.e., those aged less than 18 years) were excluded from all studies.

These demographic characteristics are considered representative of those that could be reasonably expected from the otherwise healthy subjects with constipation for whom treatment with lubiprostone will be recommended.

**Dose-Response Studies**

**SC9921**
This was a multi-centre, parallel-group, double-blind, placebo-controlled, Phase 2b study conducted in the USA to assess the safety and efficacy of different doses and dose regimens of oral lubiprostone on relief of constipation. A total of 127 subjects were enrolled and randomised to receive placebo, lubiprostone 24 mcg/day [24 mcg once daily], lubiprostone 48 mcg/day [24 mcg twice daily] or lubiprostone 72 mcg/day [24 mcg three times a day]. Following a 2 week washout period subjects received 3 weeks of double-blind medication.

**CC0721**
This was a multi-centre parallel-group, double-blind, placebo-controlled, Phase 2b study conducted in Japan. The objectives of this study were to assess the safety and efficacy of different doses of oral lubiprostone compared to placebo on relief of constipation, to verify dose response previously established in non-Japanese patients and to investigate whether, as in Western patients, the 48 mcg/day dose provided in Japanese patients with the most appropriate safe and effective treatment outcome among the doses investigated. A total of 170 subjects were enrolled and randomised to receive placebo (twice a day), lubiprostone 16 mcg/day [8 mcg twice a day], lubiprostone 32 mcg/day [16 mcg twice a day], or lubiprostone 48 mcg/day [24 mcg twice a day]. Following a 2 week washout period, subjects received 2 weeks of double-blind medication.

**Relationship Between Efficacy and Dose**
The Phase 1 study 99101 examined single oral doses of lubiprostone ranging from 6 mcg to 96 mcg; the results of this study demonstrated that increased activity was observed when the lubiprostone dose was increased from 24 mcg to 48 mcg, and the maximum tolerated single dose based on the results of this study was determined to be 96 mcg. The Phase 1 study 99102 examined daily doses of lubiprostone ranging from 72 mcg (24 mcg TID) to 108 mcg (36 mcg TID); the results of this study showed a lack of additional pharmacodynamic effects at doses above 24 mcg TID, suggesting a saturation effect of lubiprostone pharmacodynamics at this dose level. The Phase 2b study SC9921 examined lubiprostone doses of 24 mcg (24 mcg OD), 48 mcg (24 mcg BID), and 72 mcg (24 mcg TID) over a 3-week double-blind treatment period. Results from this study showed that all 3 doses of lubiprostone were more effective than placebo in relieving constipation, with the 48 mcg and 72 mcg doses having similar effects on constipation. The overall tolerability of the 48 mcg dose was considered better than the 72 mcg dose.
In Japan, two Phase I healthy volunteer trials were conducted. Study NA0311 was a single dose trial studying safety and pharmacokinetics of 24, 48 and 72 mcg lubiprostone. Study NA 0611 was a repeated dose study with 24 mcg BID lubiprostone to study the safety and pharmacokinetics of this dose upon administration for one week.

The conclusions of these two Japanese Phase I studies were that safety, tolerability and pharmacokinetics of the 48 mcg (24 mcg BID) dose was similar to what had been observed before in studies conducted in the USA (99101 and 99102).

Comparison of the pharmacokinetic profile of lubiprostone doses applied in studies NA0311 and NA0611 conducted in Japanese subjects with the pharmacokinetic profile of lubiprostone determined in participants of the SC0411 cardiac safety study conducted in healthy subjects in the USA showed that there are no major differences in pharmacokinetic key parameters between the two populations.

**Study Design Considerations**

To eliminate bias in subject selection, each of the 7 Phase 3 studies and in particular each of the three pivotal Phase III studies used the same set of inclusion/exclusion criteria. The inclusion criteria focused primarily on the definition of constipation (< 3 spontaneous bowel movements [SBMs] per week and at least 1 associated symptom), while the exclusion criteria dealt mainly with significant chemical or physiological anomalies or conditions that represented potential confounding factors for the planned statistical analyses.

Each of the pivotal studies SC0131, SC0232 and CC0831 consisted of a 4-week, randomised, double-blind treatment period. The primary efficacy endpoint in the pivotal studies was the frequency of SBMs at Week 1. No non-inferiority trials were conducted during the development program for lubiprostone in CIC.

**Use of Surrogate Endpoints**

The efficacy of lubiprostone was evaluated through the direct measurement of bowel movement (BM) frequency and symptomatic assessments. No surrogate endpoints were used in the assessment of efficacy.

**Efficacy in Special Populations**

The efficacy of 48 mcg/day lubiprostone is not restricted to a specific group of subjects, nor was its efficacy affected to a noticeable degree by the subject subgroups that were analyzed for the summary of clinical efficacy. These subgroups included analyses by sex, race, age group, and IBS status (i.e., subject did or did not have IBS). Thus, there is no need to extrapolate data from the present subject population in an attempt to justify an efficacy claim for any particular subject group that is not sufficiently represented in the population.

**Plasma Concentration Monitoring**

Because of the very short residence time of lubiprostone in the body (elimination half-life is approximately 1-2 hours, with metabolites eliminated in 7-8 hours) and because lubiprostone is nearly undetectable in human plasma during treatment, the use of plasma concentration monitoring to improve treatment results is not applicable to this application.

**MAIN STUDIES**

**Comparative Efficacy Studies**
Pivotal Studies SC0131 and SC0232 conducted in the USA.
These were multi-centre, parallel group, double-blind placebo-controlled, Phase III studies with identical study designs conducted in the USA. The objective for both studies was to assess the efficacy and safety of oral 48 mcg lubiprostone (24 mcg BID) compared to placebo for the treatment of constipation.

242 and 237 subjects were enrolled and randomized to receive placebo or lubiprostone 48 mcg/day (24 mcg BID). Following a 2-week baseline/washout period, subjects received 4 weeks of double-blind medication. A follow-up telephone interview was conducted 2 weeks after the end of double-blind treatment. No dose escalation was permitted during either study. Subjects were chosen for participation based on their need for relief of constipation, which was defined as, on average, <3 SBMs per week, as documented during the baseline/washout period, and at least 1 protocol-defined associated symptom present for at least 6 months before the screening visit.

Pivotal Study CC0831 conducted in Japan
This was a multi-centre, parallel-group, double-blind, placebo-controlled, Phase III study conducted in Japan, with a similar study design as in previous pivotal trials SC0131 and SC0232. The objective was to assess the efficacy and safety of oral 48 mcg lubiprostone (24 mcg BID) compared to placebo for the treatment of constipation. 124 subjects were enrolled and randomized to receive placebo or lubiprostone 48 mcg/day (24 mcg BID). As in preceding Phase III trials conducted in the United States (SC0131 and SC0232), following a 2-week baseline/washout period, subjects received 4 weeks of double-blind medication. A follow-up visit was conducted 4-14 days after the end of double-blind treatment. No dose escalation was permitted during the study. Subjects were chosen for participation based on their need for relief of constipation, which was defined as, on average, <3 SBMs per week for at least 6 months, as documented during the baseline/washout period, and at least 1 protocol-defined associated symptom present for at least 6 months, again as in preceding pivotal Phase III trials in the United States.

Comparison of Efficacy Results Across all Studies
Studies SC0131, SC0232 and CC0831 compared the efficacy and safety of 48 mcg/day (24 mcg BID) lubiprostone with placebo in subjects with chronic idiopathic constipation over 4 weeks of treatment. In addition, pharmacokinetic information on lubiprostone and its major M3 metabolite, gained from healthy volunteer studies conducted in the United States (SC0411) and Japan (NA0311 and NA0611) did not give evidence for relevant pharmacokinetic ethnic differences between Western and Japanese subjects following oral administration of lubiprostone. This allowed designing and conducting two pivotal trials in the United States (SC0131 and SC0232) and one additional pivotal trial in Japan (CC0831, conducted several years later than SC0131 and SC0232) in a similar manner. Studies SC0131 and SC0232 were powered to detect a difference of 2 SBMs between the placebo and 48 mcg lubiprostone groups after 1 week of treatment. Study CC0831 was powered to detect a statistically significant difference in the mean change from baseline in SBM frequencies between the placebo and 48 mcg lubiprostone groups after the first week of treatment based on results of study CC0721 conducted in Japan. In all studies, following a 2-week baseline/washout period, subjects received 4 weeks of double-blind medication. No dose escalation was permitted during either study. In study CC0831, dose reduction to a single daily administration of 24 mcg lubiprostone was allowed if considered...
appropriate by the investigator; once reduced, the dose could not be increased again. The primary and secondary efficacy endpoints of all three pivotal trials were largely identical, although sometimes data were analyzed in a slightly different manner.

Subjects taking 48 mcg lubiprostone showed a significantly higher (p \leq 0.006) frequency of SBMs at Week 1 than subjects taking placebo. In all three pivotal trials SC0131, SC0232 and CC0831, the overall treatment effect across all weeks was also statistically significant. Results of the secondary efficacy analyses in each of the pivotal studies were similar. Significant improvements for 48 mcg lubiprostone subjects over placebo subjects were observed in the following secondary efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; weekly responder rates (at each week and all weeks); percentage of subjects with an SBM within 24 hours after first dose of study drug; time to first SBM; average stool consistency; average degree of straining; constipation severity; and treatment effectiveness. When considered together, the efficacy results of the pivotal studies SC0131, SC0232 and CC0831 give consistent evidence that a 48 mcg (24 mcg BID) dose of lubiprostone is noticeably, and almost always significantly, more effective than placebo for the relief of constipation and its associated symptoms. The great similarity of the respective results also indicates that the study designs were independent of statistical bias.

Because of sample size limitations in the relevant subgroups at the study level, subgroup analyses were not included in the pivotal studies or the long-term studies. These were performed as meta-analyses in the summary of clinical efficacy.

**Long-term Efficacy**

**SC012S1 (conducted in the USA).**

This was a multi-centre, open-label Phase III safety study with a 2-week baseline/washout period, a 24-week open-label treatment period and follow-up 1 week after the end of treatment conducted in the USA. The objective of this study was to demonstrate the safety of 48 mcg lubiprostone (24 mcg BID) when administrated for 24 weeks on an as needed basis.

Subjects were enrolled and instructed to take 48 mcg lubiprostone (24 mcg BID) daily, as needed. Subjects determined their own need for treatment with lubiprostone; “subject need” was defined as the subject’s perceived severity of constipation and need for relief. When treatment was considered needed, subjects were instructed to take one 24 mcg capsule twice daily. Subjects could remain on daily drug (48 mcg lubiprostone) throughout the entire treatment period if they so chose. A subject could elect to stop study drug if they perceived need for relief had decreased, and the subject could return to the study drug when needed. Subjects who elected to stop and then return to the study drug were to begin dosing again at 48 mcg lubiprostone. Only at the discretion of the investigator, in response to exaggerated pharmacodynamic events (e.g. diarrhoea) or a treatment-related adverse event (e.g. nausea) was the daily dose to be reduced to 24 mcg.

**SC01S2 (conducted in the United States)**

This was a multi-centre, open-label, Phase III safety trial consisting of a 2-week baseline/washout period, a treatment phase made up of 2 study periods, and a follow-up visit 2 weeks after the end of treatment conducted in the United States. The 2 study periods that made up the treatment phase were as follows:
**Study Period 1 (SP1)** consisted of a 4-week active treatment (AT) period, during which all subjects received 48 mcg lubiprostone (24 mcg BID), followed by a 3-week double-blinded, randomized withdrawal (RW) treatment period, during which subjects were randomized to either active (48 mcg lubiprostone) or placebo treatment.

**Study Period 2 (SP2)** consisted of a 48-week open-label treatment period during which all subjects received 48 mcg lubiprostone (24 mcg BID). The primary objective of this study was to demonstrate the safety of 48 mcg lubiprostone (24 mcg BID) when administered open-label for 48 weeks to subjects with constipation. The secondary objective was to assess post-treatment response in a portion of the study population after 4 weeks of active treatment and 3 weeks of RW treatment. Evidence of constipation (defined as, on average, < 3 SBMs per week and at least 1 protocol-defined associated symptom present for at least 3 months) must have been demonstrated and recorded in the daily diary during the 2-week baseline/washout period for a subject to enter the study. Overall, 248 subjects were enrolled and treated during the study; of these, 128 subjects were randomized and treated during SP1. During SP1, eligible subjects were enrolled and instructed to administer 48 mcg lubiprostone (24 mcg BID) daily during the 4-week AT period. These subjects then entered the 3-week double-blinded RW treatment period and administered either 24 mcg lubiprostone or placebo BID, based on a prospectively defined randomization schedule prior to entering SP2. During SP2, all subjects took 24 mcg lubiprostone BID as needed based on the subject’s perceived severity of constipation and need for relief. During this period, investigators could adjust the daily dose in response to exaggerated pharmacodynamic events (e.g., diarrhea), or treatment-related AEs (e.g., nausea).

**SC02S3 (conducted in the United States)**
This was a multi-centre, open-label, Phase III safety study with a screening visit (during which constipation, based on BM frequency and at least 1 protocol-defined associated symptom, both being present for at least 3 months, was confirmed via subject medical history), a 48-week open-label treatment period, and follow-up 2 weeks after the end of treatment conducted in the United States. The primary objective of this study was to demonstrate the safety of 48 mcg lubiprostone (24 mcg BID) when administered open-label for 48 weeks to subjects with constipation. The secondary objective of this study was to collect additional evidence of the efficacy of lubiprostone. Three hundred twenty-four (324) subjects were enrolled and treated in this study. Eligible subjects were enrolled and instructed to administer 48 mcg lubiprostone (24 mcg BID) daily, as needed. Subjects determined their own need for treatment with lubiprostone; “subject need” was defined as the subject’s perceived severity of constipation and need for relief. When treatment was considered necessary, subjects were instructed to take one 24-mcg capsule BID. Subjects could remain on daily drug (48 mcg lubiprostone) throughout the entire treatment period if they so chose. A subject could elect to stop study drug if the perceived need for relief had decreased, and the subject could return to study drug when needed. Subjects who elected to stop and then return to study drug were to begin dosing again at 48 mcg lubiprostone. Only at the discretion of the investigator, in response to exaggerated pharmacodynamic events (e.g., diarrhea) or treatment-related AEs (e.g., nausea), was the daily dose to be reduced to 24 mcg.

**CC0832 (conducted in Japan)**
This was a multi-centre, open-label, Phase III safety and efficacy study with a screening visit (during which constipation, based on BM frequency and at least 1 protocol-defined associated symptom, both being present for at least 6 months, was confirmed via subject medical history), a 48-week open-label treatment period, and follow-up within a period of 4 days to 2 weeks after the end of treatment conducted in Japan. The objective of this study was to demonstrate the safety of 48 mcg lubiprostone (24 mcg BID) when...
administered open-label for up to 48 weeks to subjects with constipation. Additional evidence of the efficacy of lubiprostone was to be collected as well.

Two-hundred nine (209) subjects were enrolled and treated in this study. Eligible subjects were enrolled and instructed to administer 48 mcg lubiprostone (24 mcg BID) daily for up to 48 weeks. During the treatment period, if required due to occurrence of adverse events and at the discretion of the investigator, dose adjustment (dose reduction or drug holiday) was allowed; if the constipation symptom(s) recurred after the dose adjustment and the AE disappeared, the dose could be returned to 24 mcg BID or restarted from 24 mcg once a day depending on patient’s and investigator’s discretion. Also, in case of lack of sufficient bowel movement for 3 continuous days, additional administration of a rescue medication was allowed during the treatment period.

Applicability of Data Generated in Other Regions
With the exception of the Phase I studies 99101 and 99102, which were conducted in Belfast, Northern Ireland, all studies were conducted within the United States or Japan. The studies in Northern Ireland enrolled mainly Caucasian subjects, which mirrors the ethnic makeup of the studies conducted in the United States and of the regions of application (UK). Although sample sizes were small, subgroup analyses by race did not indicate any notable differences in efficacy or safety among different racial groups, so it is expected that the clinical trial data is applicable to the regions of application. Data generated in the Japanese development program were very similar to those generated in the USA, further assuring that no large inter-racial difference are to be expected when treating CIC patients with 48 mcg/day lubiprostone.

Long Term-Efficacy Results
Long-term efficacy evaluations of 48 mcg lubiprostone performed during the conduct of SC01S1 (24-week open-label period), SC01S2 (SP2 only; 48-week open-label period), and SC02S3 (48-week open-label period) and CC0832 (48-week open-label) did not provide a comparison with placebo; rather, they provided a comparison with the results of the same assessments (specifically severity of constipation, treatment effectiveness, abdominal bloating, and abdominal discomfort) as performed in the double blind, randomised studies. Side-by-side comparison of efficacy parameters assessed in the three 48-week trials (SC01S2(SP2), SC02S3 and CC0832) demonstrated that SBM frequency as well as all accompanying symptoms showed clear improvements post baseline in all trials.

Because the WCG and LTS populations were defined differently, direct comparison of the efficacy results for these groups was not performed. However, side-by-side comparisons of the efficacy results from WCG and LTS subjects showed not only that lubiprostone was effective in treating constipation for periods up to 48 weeks but also that the LTS efficacy results represented noticeable numerical improvements over the results reported for WCG lubiprostone 48 mcg subjects, which themselves were nearly always significantly better than those for WCG placebo subjects.

In summary, the efficacy findings relating to treatment with 48 mcg/day lubiprostone for CIC are not only almost always significantly better than those observed among placebo subjects, but they are also representative of important improvements in subject regularity with respect to SBM frequency and several subjective assessments that contribute to overall quality of life.
Statistical Assessment of Efficacy of Amitiza (lubiprostone)

Two Phase III pivotal studies (SC0131 and SC0232) have been submitted to provide evidence of efficacy in this indication and are included in the statistical assessment below.

Design of studies

The two pivotal studies, of identical design, were multi-centre randomised double-blind placebo-controlled parallel-group studies with a 4-week treatment period conducted within the United States. After a 2-week washout period, eligible subjects were randomised in approximately equal numbers to receive either lubiprostone 24mcg twice daily or placebo. Rescue medication was not allowed during the first week of randomised treatment or within 48 hours of the first dose but was allowed during the remaining three weeks of the treatment period and during the washout period.

The primary efficacy variable was defined as the frequency rate of spontaneous bowel movements (SBM) during Week 1 where an SBM was defined as a bowel movement that does not occur within 24 hours after rescue medication use. Secondary efficacy variables included the frequency rate of SBMs during Weeks 2, 3 and 4 as well as weekly responder rates.

With respect to study CC0831, the study design is consistent with the previous 2 pivotal studies, with the primary end point at Week 1, but data generated up to Week 4.

Statistical analysis

Four populations were defined for the analysis of efficacy: Intent-to-treat (ITT) subjects with LOCF (last observation carried forward) which was considered to be the primary population with supportive populations of ITT subjects without LOCF, ITT completers and Per Protocol (PP) subjects. An analysis of the primary efficacy variable was to be performed on PP subjects only if more than 5% of the subjects were protocol violators during Week 1.

The primary efficacy analysis was conducted using van Elteren’s test stratified by centre. As outliers are commonly observed in these data, parametric models might not be robust. In order to adjust for early withdrawals during the week of treatment, weekly SBM frequency rates were calculated as:

\[
7 \times \frac{\text{Number of SBMs}}{\text{Number of days}}
\]

using the number of days during the week that the subject remained in the study. If the number of days was less than 4, the rate was considered to be missing.

LOCF was defined as the general method of handling missing data. No adjustment was made for baseline although improvement from baseline was assessed using the Wilcoxon signed-rank test for each treatment group. No adjustment for multiplicity was considered necessary. Small centres with 8 or fewer ITT subjects were pooled according to a pre-defined specification.

For each week the number of non-responders, moderate responders and full responders were calculated and analysed using van Elteren’s test stratified by centre to assess treatment response and to account for study drop-out and rescue medication use.
All tests for treatment effects were two-sided at a significance level of 5%.

The distribution of values observed for the weekly SBM frequency rates from baseline to Week 4 of the study confirm the applicant’s assumption that outliers will be ‘commonly observed’ in the data. Therefore the use of nonparametric methods is considered to be appropriate.

The lack of adjustment for baseline is accepted as the slight imbalance in baseline data, which reached statistical significance in Study SC0232 although not in Study SC0131, was in favour of the placebo group.

Although LOCF has been defined as the method of handling missing data, this will not be applied to the primary efficacy endpoint which is based on data from the first week of treatment only. Therefore there is no earlier value to carry forward in the case of a missing SBM rate in the primary analysis. Subjects discontinuing within the first week will have a weekly rate estimated providing at least four days of data were provided. Assuming the primary variable is missing for a small number of subjects, the handling of missing data should be adequate.

Disposition of subjects
Study SC0131

The disposition of the 242 subjects who were randomised and treated in this study is presented in the table below. Considerably more subjects discontinued from the lubiprostone arm than from placebo, 14 (12%) compared to 6 (5%), mainly due to adverse events.

<table>
<thead>
<tr>
<th>Summary of Subject Disposition</th>
<th>Placebo (N = 124)</th>
<th>RS-0211 40 µg (N = 120)</th>
<th>Total (N = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Number of Subjects Randomized</td>
<td>124 (100.0)</td>
<td>120 (100.0)</td>
<td>244 (100.0)</td>
</tr>
<tr>
<td>Number of Subjects Randomized But Not Treated</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Number of Subjects Treated</td>
<td>122 (98.4)</td>
<td>120 (100.0)</td>
<td>242 (99.2)</td>
</tr>
<tr>
<td>Number of Subjects Completed</td>
<td>118 (95.2)</td>
<td>106 (88.3)</td>
<td>224 (91.8)</td>
</tr>
<tr>
<td>Number of Subjects Discontinued</td>
<td>6 (4.8)</td>
<td>14 (11.7)</td>
<td>20 (8.2)</td>
</tr>
<tr>
<td>Reason for Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>1 (0.8)</td>
<td>5 (7.5)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Subject Voluntary Withdrawal</td>
<td>1 (0.8)</td>
<td>3 (2.5)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Did Not Meet Entry Criteria</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Missing</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Timing of Drug Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>4 (3.2)</td>
<td>5 (4.2)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Week 2</td>
<td>1 (0.8)</td>
<td>5 (4.2)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Week 3</td>
<td>0 (0.0)</td>
<td>4 (3.3)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Week 4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>After Week 4</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Number of Days on Study Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>124</td>
<td>120</td>
<td>244</td>
</tr>
<tr>
<td>Mean (Std)</td>
<td>27.8 ( 5.32)</td>
<td>26.5 ( 7.50)</td>
<td>27.1 (6.50)</td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>(Min,Max)</td>
<td>( 0, 33)</td>
<td>( 1, 38)</td>
<td>( 0, 39)</td>
</tr>
</tbody>
</table>

A slight imbalance in the numbers of subjects in the two treatment groups was seen for the per protocol population with 119 subjects treated with placebo and 111 with active.
Subjects were excluded from the PP population mainly because of violations concerning prohibited concomitant medication, poor study drug compliance and inappropriate use of rescue medication before the first dose of study medication.

**Study SC0232**

The disposition of the 237 subjects who were randomised and treated in this study is presented in the table below. As in the other pivotal study, more subjects discontinued from the active treatment than the placebo (20, 17% compared to 11, 9%) mainly due to adverse events.

**Table 10-1. Summary of Subject Disposition (All Randomized Subjects)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 118)</th>
<th>RU-0211 48 µg (N = 119)</th>
<th>Total (N = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Treated Subjects</td>
<td>118 (100.0)</td>
<td>119 (100.0)</td>
<td>237 (100.0)</td>
</tr>
<tr>
<td>Number of Completed Subjects</td>
<td>107 (90.7)</td>
<td>99 (83.2)</td>
<td>206 (86.9)</td>
</tr>
<tr>
<td>Number of Discontinued Subjects</td>
<td>11 (9.3)</td>
<td>20 (16.8)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Discontinuation Reasons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>1 (0.8)</td>
<td>15 (12.6)</td>
<td>16 (6.8)</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Subject Voluntary Withdrawal</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>6 (5.1)</td>
<td>1 (0.8)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>1 (0.8)</td>
<td>4 (3.4)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.7)</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Timing of Early Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>2 (1.7)</td>
<td>11 (9.2)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Week 2</td>
<td>2 (1.7)</td>
<td>7 (5.9)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>Week 3</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Week 4</td>
<td>3 (2.5)</td>
<td>0 (0.0)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Week &gt;=5</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Number of Days on Study Drug</td>
<td>117</td>
<td>118</td>
<td>235</td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>28.1 (4.78)</td>
<td>25.4 (8.65)</td>
<td>26.8 (7.12)</td>
</tr>
<tr>
<td>Median</td>
<td>29.0</td>
<td>29.0</td>
<td>29.0</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(5, 75)</td>
<td>(1, 39)</td>
<td>(1, 39)</td>
</tr>
</tbody>
</table>
Study CC0831

The Applicant has adequately described the patient disposition and there is very little missing data. The decision to exclude missing data from the analysis set is not supported, but given how little is missing, previous concerns with respect to analyses populations e.g. concerns with the ITT/per-protocol differences will not be a concern, unless the results are extremely borderline.

Results

For study SC0131, the analysis of the primary efficacy variable demonstrated that lubiprostone was statistically superior to placebo for all four analysis populations. This finding was supported by the analyses of the secondary endpoints, the weekly SBM rate at Weeks 2, 3 and 4 which showed superiority of lubiprostone to placebo at all subsequent timepoints.

For study SC0232 the results of the analysis of the primary efficacy variable confirmed that lubiprostone provided statistically superior relief of constipation compared to placebo for all four analysis populations, despite the fact that lubiprostone subjects were significantly more constipated at baseline. Treatment with lubiprostone resulted in improvements over placebo in SBM frequency at Weeks 2, 3 and 4 with the difference demonstrating statistical significance in favour of active treatment at Weeks 3 and 4 in all four populations (p<0.045 in all cases). At Week 2 the difference was significant only for ITT subjects with LOCF (p=0.0487) and not for the other three analysis populations.
The results of the analysis of the primary efficacy variable and the corresponding variable analysed at the later timepoints are presented in the table below for both pivotal studies, SC0131 and SCO232.

### Table 2.7.3.2-4. Summary of SBMs at Weeks 1-4 for SC0131 and SC0232 (ITT with LOCF)

<table>
<thead>
<tr>
<th></th>
<th>SC0131</th>
<th>LBP 48 mcg</th>
<th>Placebo (N = 122)</th>
<th>LBP 48 mcg (N = 120)</th>
<th>Placebo (N = 118)</th>
<th>LBP 48 mcg (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (n)</strong></td>
<td>119</td>
<td>120</td>
<td>118</td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>1.47 (1.326)</td>
<td>1.37 (0.873)</td>
<td>1.52 (0.801)</td>
<td>1.28 (0.881)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-values&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.612</td>
<td></td>
<td></td>
<td></td>
<td>0.0126</td>
<td></td>
</tr>
<tr>
<td><strong>Week 1 (n)&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td>122</td>
<td>116</td>
<td>116</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>3.46 (2.285)</td>
<td>5.69 (4.417)</td>
<td>3.99 (2.706)</td>
<td>5.89 (4.022)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>5.0</td>
<td>3.5</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-values&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Week 2 (n)</strong></td>
<td>122</td>
<td>116</td>
<td>116</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>3.18 (2.530)</td>
<td>5.06 (4.076)</td>
<td>3.55 (2.670)</td>
<td>4.96 (4.208)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>4.0</td>
<td>3.0</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-values&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.0017</td>
<td></td>
<td></td>
<td></td>
<td>0.0487</td>
<td></td>
</tr>
<tr>
<td><strong>Week 3 (n)</strong></td>
<td>122</td>
<td>116</td>
<td>116</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>2.84 (2.231)</td>
<td>5.25 (4.875)</td>
<td>3.36 (2.755)</td>
<td>5.56 (4.560)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>5.0</td>
<td>3.0</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-values&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td><strong>Week 4 (n)</strong></td>
<td>122</td>
<td>116</td>
<td>116</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Std Dev)</td>
<td>2.91 (2.357)</td>
<td>5.30 (4.735)</td>
<td>3.46 (2.861)</td>
<td>5.37 (4.804)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.3</td>
<td>4.0</td>
<td>3.0</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-values&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
<td>0.0068</td>
<td></td>
</tr>
</tbody>
</table>

LBP = lubiprostone; SBM = spontaneous bowel movement

1. Week 1 SBM frequency was the primary efficacy endpoint in each study. The overall p-value for the difference between the treatments was < 0.0001 in both studies (based on final mixed model testing for overall treatment effect).

2. Based on van Elteren tests adjusted for pooled centre.

The following tables present the percentage of full responders defined as those subjects with at least 4 SBMs per week. For both studies the difference in responder rates was statistically significantly different in favour of lubiprostone across all four weeks of treatment.
### Study SC0131

**Summary of Weekly Responder Status**

**Intent-To-Treat Subjects**

<table>
<thead>
<tr>
<th>Week</th>
<th>Responder Status*</th>
<th>Placebo (N = 122)</th>
<th>RU-0211 48 µg (N = 116)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>num/denom+ (%)</td>
<td>num/denom+ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>Full Responder</td>
<td>53/122 (43.4)</td>
<td>75/116 (64.7)</td>
<td>0.0023</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>19/122 (15.6)</td>
<td>14/116 (12.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>50/122 (41.0)</td>
<td>27/116 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Full Responder</td>
<td>44/120 (36.7)</td>
<td>66/114 (57.9)</td>
<td>0.0054</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>17/120 (14.2)</td>
<td>10/114 (8.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>59/120 (49.2)</td>
<td>38/114 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Full Responder</td>
<td>35/119 (29.4)</td>
<td>62/108 (57.4)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>16/119 (13.4)</td>
<td>8/104 (7.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>68/119 (57.1)</td>
<td>38/108 (35.2)</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Full Responder</td>
<td>34/118 (28.8)</td>
<td>62/104 (59.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>20/118 (16.9)</td>
<td>10/104 (9.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>64/118 (54.2)</td>
<td>32/104 (30.8)</td>
<td></td>
</tr>
</tbody>
</table>

Program/Output (Date): T_RESP_SAS/T_RESP2.LST (14NOV2003)

* Full Responder was defined as responder with >= 4 SBMs per week.
  Moderate Responder was defined as responder with >= 3 but < 4 SBMs per week.
  Non-Responder was defined as subjects with < 3 SBMs for a given week, who dropped out during
  or prior to the given week due to lack of efficacy, or any subject who used rescue medication
during or within 24 hours prior to the given week.
* The denominator represents the number of subjects in the study during the given week.
* P-values are based on van Elteren tests adjusted for pooled center.

### Study SC0232

**Table 11-6. Summary of Weekly Responder [1] Status (Intent-to-Treat Subjects with LOCF)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>num/denom+ (%)</td>
<td>num/denom+ (%)</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>Full Responder</td>
<td>57/117 (48.7)</td>
<td>80/111 (72.1)</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>14/117 (12.0)</td>
<td>16/111 (14.4)</td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>46/117 (39.3)</td>
<td>15/111 (13.5)</td>
</tr>
<tr>
<td>Week 2</td>
<td>Full Responder</td>
<td>50/117 (42.7)</td>
<td>64/111 (57.7)</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>13/117 (11.1)</td>
<td>13/111 (11.7)</td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>54/117 (46.2)</td>
<td>34/111 (30.6)</td>
</tr>
<tr>
<td>Week 3</td>
<td>Full Responder</td>
<td>42/117 (35.9)</td>
<td>68/111 (61.3)</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>15/117 (12.8)</td>
<td>11/111 (9.8)</td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>60/117 (51.3)</td>
<td>32/111 (28.0)</td>
</tr>
<tr>
<td>Week 4</td>
<td>Full Responder</td>
<td>45/117 (39.5)</td>
<td>66/111 (59.5)</td>
</tr>
<tr>
<td></td>
<td>Moderate Responder</td>
<td>17/117 (14.5)</td>
<td>13/111 (11.7)</td>
</tr>
<tr>
<td></td>
<td>Non-Responder</td>
<td>55/117 (47.0)</td>
<td>32/111 (28.0)</td>
</tr>
</tbody>
</table>

LOCF: Missing values were imputed by the last observation carried forward.

[1] Full Responder was defined as responder with >= 4 SBMs per week.
  Moderate Responder was defined as responder with >= 3 but < 4 SBMs per week.
  Non-Responder was defined as subjects with < 3 SBMs for a given week, who dropped out
during or prior to the given week due to lack of efficacy, or any subject who used rescue
medication during or within 24 hours prior to the given week.

[2] The denominator represents the number of subjects with a non-missing responder status
during the given week.

[3] P-values are based on van Elteren tests adjusted for pooled center.

Other secondary efficacy variables associated with constipation such as stool consistency, degree of straining and severity of constipation showed statistically significant superiority for lubiprostone for both studies.
Statistical Assessor’s comment:
The consistency of the findings for secondary endpoints provides supporting evidence of efficacy of lubiprostone in terms of the improvement of symptoms of constipation as well as frequency of bowel movements.

Study CC0831
Changes in spontaneous bowel movement frequency at Week 1 of treatment

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>Min.</th>
<th>Median</th>
<th>Max.</th>
<th>2-Sample t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubiprostone group</td>
<td>60</td>
<td>3.56</td>
<td>2.79</td>
<td>-1.5</td>
<td>3.42</td>
<td>13.0</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Placebo group</td>
<td>62</td>
<td>1.26</td>
<td>1.82</td>
<td>-2.5</td>
<td>1.00</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

Spontaneous bowel movement frequency (FAS)

<table>
<thead>
<tr>
<th>Week</th>
<th>Treatment group</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>Min.</th>
<th>Median</th>
<th>Max.</th>
<th>2-Sample t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation phase</td>
<td>Lubiprostone group</td>
<td>61</td>
<td>1.65</td>
<td>0.78</td>
<td>0.0</td>
<td>2.00</td>
<td>2.7</td>
<td>P=0.873</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>62</td>
<td>1.68</td>
<td>0.77</td>
<td>0.0</td>
<td>2.00</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>Lubiprostone group</td>
<td>61</td>
<td>5.37</td>
<td>2.78</td>
<td>0.0</td>
<td>5.00</td>
<td>15.0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>62</td>
<td>2.93</td>
<td>1.82</td>
<td>0.0</td>
<td>2.75</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Lubiprostone group</td>
<td>58</td>
<td>4.44</td>
<td>2.45</td>
<td>0.0</td>
<td>4.11</td>
<td>10.0</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>60</td>
<td>2.98</td>
<td>2.02</td>
<td>0.0</td>
<td>3.00</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Lubiprostone group</td>
<td>57</td>
<td>4.43</td>
<td>2.56</td>
<td>0.0</td>
<td>4.00</td>
<td>13.0</td>
<td>P=0.005</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>51</td>
<td>3.18</td>
<td>2.20</td>
<td>0.0</td>
<td>3.00</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Lubiprostone group</td>
<td>59</td>
<td>4.32</td>
<td>2.88</td>
<td>0.0</td>
<td>4.00</td>
<td>11.0</td>
<td>P=0.044</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>50</td>
<td>3.31</td>
<td>2.52</td>
<td>0.0</td>
<td>3.00</td>
<td>13.0</td>
<td></td>
</tr>
</tbody>
</table>

The results clearly demonstrate that statistically results have been attained. There is a concern that the number of patients in the FAS is different for the lubiprostone group, but as this is only 1 patient it is unlikely in the extreme to affect the results. The magnitude of effect (difference between placebo and lubiprostone at Week 1) is 2.4, in line with previous results. As the results are comfortably less than p=0.05, the effect of 1 or 2 missing patients is negligible.
**Rescue Medication use:**
Below are tables of the rescue medication use per 7-day period.

<table>
<thead>
<tr>
<th>Number of additional Treatment days</th>
<th>Week</th>
<th>Treatment group</th>
<th>Number of patients</th>
<th>Mean</th>
<th>SD</th>
<th>Min.</th>
<th>Median</th>
<th>Max.</th>
<th>2-Sample t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation phase</td>
<td></td>
<td>Lubiprostone group</td>
<td>62</td>
<td>0.55</td>
<td>0.82</td>
<td>0.0</td>
<td>0.00</td>
<td>3.5</td>
<td>P=0.526</td>
</tr>
<tr>
<td>Placebo groups</td>
<td>62</td>
<td>0.46</td>
<td>0.73</td>
<td>0.0</td>
<td>0.00</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td></td>
<td>Lubiprostone group</td>
<td>62</td>
<td>0.22</td>
<td>0.57</td>
<td>0.0</td>
<td>0.00</td>
<td>3.0</td>
<td>P=0.796</td>
</tr>
<tr>
<td>Placebo groups</td>
<td>62</td>
<td>0.24</td>
<td>0.53</td>
<td>0.0</td>
<td>0.00</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td>Lubiprostone group</td>
<td>60</td>
<td>0.28</td>
<td>0.85</td>
<td>0.0</td>
<td>0.00</td>
<td>5.0</td>
<td>P=0.481</td>
</tr>
<tr>
<td>Placebo groups</td>
<td>62</td>
<td>0.30</td>
<td>0.78</td>
<td>0.0</td>
<td>0.00</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td>Lubiprostone group</td>
<td>59</td>
<td>0.36</td>
<td>0.94</td>
<td>0.0</td>
<td>0.00</td>
<td>5.0</td>
<td>P=0.847</td>
</tr>
<tr>
<td>Placebo groups</td>
<td>61</td>
<td>0.33</td>
<td>0.63</td>
<td>0.0</td>
<td>0.00</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td>Lubiprostone group</td>
<td>59</td>
<td>0.27</td>
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The use of rescue medication follows a broadly similar pattern to study SC0232 and thus there are no new concerns with respect to efficacy.

The main difference with this study is that it has been conducted in Japanese patients. In all other respects, it provides consistency with previous studies and raises no new efficacy concerns.

**CLINICAL SAFETY**

The safety data presented for the lubiprostone program in chronic idiopathic constipation (CIC) is based on a total of 16 Phase I to III clinical trials, including safety data from seven Phase I, two Phase II, and seven Phase III studies [three pivotal and four safety studies] conducted in Western and Japanese populations. All Phase II and III trials were conducted in either the United States or Japan. Additionally, three Phase IV trials in special populations were conducted: in paediatric constipation patients, in subjects with renal impairment, and in subjects with hepatic impairment together with a review of available post-marketing safety data. No class-related risk for prostones has been identified to date based on comparison of the safety profile of these two compounds. Clinical studies for lubiprostone indicate that a majority of adverse events (AEs) occurring secondary to treatment with lubiprostone are gastrointestinal in nature. During the clinical development programme for CIC, four safety risks for patients treated with lubiprostone were identified: nausea, diarrhoea, dyspnoea and chest discomfort/chest pain.

**Patient Population and Extent of Exposure**

In the Overall Safety (OS) cohort for the CIC studies (which comprises all 11 Phase I-III studies conducted in a Western population), median subject age was 47 years, 57% of subjects were < 50 years old, 29% of subjects were ≥ 50 and < 65 years old, and 14% of subjects were ≥ 65 years old; the majority of subjects were female; the majority of subjects were white; and subjects across studies had similar baseline constipation status and medical history.
Comparison of demographic data between the pivotal studies conducted in the United States and Japan indicates that patients in Japanese trials were a few years younger in average with a median subject age of 38.5 years in lubiprostone-treated group of the Japanese pivotal study CC0831. However, the age range covered in Japanese trials was very similar to US trials and the majority of subjects were female as well. In total, 13% of patients in the pivotal Japanese study CC0831 were ≥ 65 years old. Patients in trial CC0831 were slightly less severely constipated at baseline than in the two pivotal US trials SC0131 and SC0232 (median SBM number at baseline 2.0 vs. 1.5, respectively).

For the OS cohort, mean percent compliance was 90.7% and 87.3% of subjects were at least 70% compliant. Compliance was generally similar in the placebo group and across lubiprostone dose groups. Compliance appeared to be lower in the 48 mcg lubiprostone dose group, but this result was influenced by the long-term studies, which were open-label in nature and allowed subjects to administer study drug on an as-needed basis. The median average daily exposure was 24.00 mcg for subjects in the < 48 mcg dose group, 43.35 mcg for subjects in the 48 mcg dose group, and 72.00 mcg for subjects in the > 48 mcg dose group. Amongst the three pivotal Phase 3 studies that together made up the PSG cohort, the median average daily exposure in the lubiprostone 48 mcg groups was similar, at approximately 46 mcg in both US studies and 48 mcg in the Japanese study. The mean percent compliance was also similar in these studies, being >92% across all treatment groups, with >94% of patients across treatment groups being compliant at least 70% of the time. Exposure across the three long-term open label 12-months safety trials that together made up the UJ-LTS cohort was comparable, with a higher percentage of completers in the Japanese trial CC0832, due to higher patient compliance and the protocol requirement for continuous rather than as-needed treatment during the study period. Reasons for early withdrawal were identical in nature with similar frequency across all trials.

SERIOUS ADVERSE EVENTS

Deaths, Serious Adverse Events, and Other Significant Adverse Events

No subjects died during the treatment or follow-up periods of any of the 16 studies in the CIC development program; no case of death occurred in the complementary trials in paediatric constipation, or renal and hepatic impairment.

In CIC studies conducted in the Western population, 4 placebo subjects (1.3%) reported 6 SAEs, no SAE preferred term was reported by more than 1 subject, and all events were considered unrelated to study drug.

Thirty-two subjects taking 48 mcg lubiprostone (2.9%) reported 45 treatment-emergent SAEs. Most reported SAE preferred terms were reported by only a single subject. Appendicitis, diverticulitis, syncope, chest pain, and dehydration, all of which were considered unrelated to study drug, were the only SAE preferred terms reported by more than 1 subject.

There was 1 SAE of diarrhoea that was considered possibly related to treatment.

One subject who became pregnant while taking lubiprostone gave birth to a child with talipes, and this was also considered possibly treatment-related. The subject was taking other concomitant medications at the time she became pregnant.

No SAEs were reported in the two Japanese Phase I studies. In the three Japanese studies three SAEs were reported by two patients treated with 48mcg/day lubiprostone:
In Study CC0831, one patient on lubiprostone 48 mcg had a spontaneous abortion. As this abortion occurred more than three months after treatment with lubiprostone had been discontinued and the patient had a history of a previous spontaneous abortion, the investigator considered the event as unrelated to lubiprostone.

In study CC0832, one patient on lubiprostone 48 mcg experienced rotary vertigo and hypoesthesia. Both events were considered possibly treatment related by the investigator because the pre-existing vertigo that increased in intensity and the newly developed mild hypoesthesia of one hand led to hospitalisation of the patients. Symptoms in this patient were first reported on Day 11 after treatment initiation. Lubiprostone was discontinued a few days later. The patient fully recovered.

In the WCG cohort, comprising trials that were conducted as randomised, double-blind, placebo controlled trials in the United States, including the two pivotal US trials SC0131 and SC0232, the frequency of withdrawal for 48 mcg lubiprostone subjects was significantly higher than for placebo subjects for gastrointestinal disorders and respiratory, thoracic and mediastinal disorders. Most of the AEs in the Medical Dictionary for Regulatory Activities (MedDRA) system/organ/classes (SOCs) led to withdrawal for < 1% of subjects.

Nausea (4.8%), diarrhoea (1.5%), abdominal pain (1.5%), flatulence (1.2%), and dyspnoea (1.5%) were the only exceptions. No AEs leading to withdrawal were reported in the two Japanese Phase I studies. In the Phase II Japanese study, only one patient withdrew due to AEs; a patient on lubiprostone 48 mcg/day who experienced palpitations, headache and nausea, all considered treatment-related.

In the pivotal Japanese Phase III trial CC0831 one subject was withdrawn from treatment with lubiprostone due to moderate chest discomfort; the patient had fully recovered from the event one day later.

In the pooled pivotal study group (PSG) cohort overall, 0.7% of placebo subjects and 8.0% of 48 mcg lubiprostone subjects withdrew because of an AE, and this difference was statistically significant (p<0.0001.

For gastrointestinal disorders, 0.3% of placebo subjects and 6.0% of 48 mcg lubiprostone subjects withdrew because of an AE. Gastrointestinal AEs that led to withdrawal for at least 1% of lubiprostone 48 mcg subjects were nausea (4.0%), abdominal pain (1.3%), diarrhoea (1.3%), and flatulence (1.3%).

There was also a significant difference between the treatment groups in the respiratory, thoracic and mediastinal disorders and general disorders and administration site conditions SOCs: 2.3% and 1.7% of lubiprostone subjects withdrew due to AEs, respectively, vs. no placebo subjects (p=0.0075 and 0.0305, respectively).

Dyspnoea (1.7%) was the only event in these SOCs that led to withdrawal in the 48 mcg lubiprostone group with an incidence rate ≥1%. Headache (1.3%) and dizziness (1.0%) were the only other AEs that led to discontinuation ≥1% of lubiprostone-treated patients in the PSG cohort.

Frequencies were generally similar when subjects were exposed to 48 mcg lubiprostone for up to 48 weeks, i.e., in the UJ-LTS cohort. Gastrointestinal disorders were the most common SOC for AEs leading to withdrawal. Adverse events in the pooled UJ-LTS
group that led to withdrawal for at least 1% of subjects were nausea (6.8%), diarrhoea (1.5%), abdominal distension (1.3%), abdominal pain (1.2%), vomiting (1%), headache (2.2%). Dyspnoea withdrawals accounted for 0.8% of lubiprostone subjects in the UJ-LTS cohort.

COMMON ADVERSE EVENTS
In the General Safety (GS) cohort for the CIC studies, most AE preferred terms were reported by ≤ 1% of subjects that took any dose of lubiprostone.

Nausea (31.1%), diarrhoea (16.6%), abdominal distension (7.1%), abdominal pain (6.7%), flatulence (6.1%), and headache (13.2%) were the only AEs reported by more than 5% of subjects.

In the pivotal study group (PSG) cohort, nausea (26.9%), diarrhoea (9.6%), headache (9.0%), and abdominal pain (6.0%) were reported by at least 5% of subjects taking 48 mcg lubiprostone and, with the exception of headache, the frequency for these AEs in the 48 mcg lubiprostone group was at least twice that in the placebo group. Other common AEs that were at least twice as frequent among lubiprostone 48 mcg subjects as among placebo subjects were flatulence, vomiting, abdominal discomfort, dizziness, peripheral oedema, and chest discomfort. Across the pivotal studies, the pattern of AEs was similar.

In the open label long-term (12-month) Safety (“UJ-LTS”; US+JP) cohort, adverse events reported by more than 5% of patients over the entire period comprised nausea (27.7%), diarrhoea (26.1%), abdominal distension (7.8%), abdominal pain (7.0%), nasopharyngitis (11.3%) and headache (11.1%) (Table 2.7.4.2-3). Across the three pivotal trials the most common treatment-related AE was nausea, which occurred in 14.5–31.7% of patients on lubiprostone, compared with 1.6–4.2% of those on placebo. Nausea is generally a mild to moderate event that occurs early during treatment (nearly half the risk for first experiencing nausea is within the first day of treatment) and generally does not persist during long-term treatment or result in frequent subject withdrawal. The other AEs reported by more than 5% of subjects were either known and expected adverse effects of lubiprostone treatment based on its mechanism of action (diarrhoea, abdominal distension, abdominal pain, and flatulence) or the frequency was not inconsistent with that in an otherwise healthy population of subjects (e.g. for headache).

Amongst treatment-related AEs, in both pivotal US studies, diarrhoea, abdominal pain, flatulence and dizziness were generally more than twice as common in lubiprostone treated groups (but with incidences <10%) as in placebo groups; headache was more than twice as common in lubiprostone groups (with an incidence up to 15%) as in placebo groups. Amongst the same treatment-related AEs, in the pivotal Japanese study, diarrhoea, abdominal pain and dizziness were all at least twice as common in the lubiprostone group as in the placebo group. Diarrhoea was as common as nausea in patients on lubiprostone in the pivotal Japanese study (16.1 of patients compared with none on placebo, while the other AEs had incidences <5% with lubiprostone, and dizziness was only reported in one patient on lubiprostone. Treatment-related flatulence and headache was not reported at all with lubiprostone in the Japanese pivotal trial. Thus, there is some evidence for differences in the gastrointestinal safety profile of lubiprostone between Western (mostly Caucasian) patients and Japanese patients. These differences could be due to ethnic or cultural reporting differences, or both. The higher incidence of diarrhoea in Japanese patients may be related to their comparably
lower body weight.

LABORATORY FINDINGS
Biochemistry: N/A

Haematology: N/A

ECG and QTc
In the CIC development program, ECG monitoring was performed in the two Japanese Phase I studies. No clinically significant changes in ECGs were observed in these trials. The safety of lubiprostone with respect to cardiac repolarization was studied in a Phase I QTc trial. This study comprised 4 treatment arms: 1) placebo; 2) 24 mcg lubiprostone (single dose; equivalent to the recommended therapeutic dosage of 48 mcg administered as 24 mcg BID 3) 144 mcg lubiprostone (single dose of 6 lubiprostone 24 mcg capsules); and 4) moxifloxacin 400 mg (single dose) as a positive control. There was no evidence of an effect on cardiac conduction or cardiac repolarization and only a small (non-clinically significant) increase in heart rate at the 144 mcg dose level.

SAFETY IN SPECIAL POPULATIONS
Subgroup analyses of AE frequencies in the CIC trials were performed with subject results stratified by the intrinsic factors of age, sex and race. For the studies conducted in the Western population there were few observable patterns when comparing results for overall populations with those of the subgroups for most AE preferred terms. CIC study adverse events were as follows: nausea and dry mouth were more common among female subjects than among male subjects in all cohorts; and peripheral oedema showed a monotonic increase in frequency with increasing age in each of the 3 cohorts. Overall, the subgroup analyses do not give evidence of any clinically relevant findings to indicate that subjects in a specific age, sex, or race in the Western populations are placed at an undue risk for experiencing any AEs or specific AEs by taking lubiprostone. Within the pivotal study group, the incidence of AEs appeared to be greater in younger patients taking active treatment, whereas at the preferred term level, there were few differences across age groups. Within the lubiprostone group of the PSG cohort, a higher proportion of female than male patients reported at least 1 AE (65.2% vs 44.1%), whereas AE frequencies were generally similar across sex subpopulations for preferred terms, except that nausea occurred substantially more frequently among females than among males (29.6% vs. 6.0%). In the PSG lubiprostone group, the proportion of subjects reporting at least 1 AE was comparable for white and non-white subjects (62.6% vs. 63.2%). Despite these overall similarities, the following AEs were reported notably more commonly with lubiprostone in white compared with non-white subjects: nausea (31.3% vs 18.9%), and headache (12.3% vs 2.8%).

Similarly, there is some evidence of differences in the safety profile of lubiprostone between Western (mostly Caucasian) patients in the US pivotal studies and Japanese patients in the pivotal study conducted in Japan. In Western patients, the most common type of treatment-related AE was gastrointestinal, particularly nausea (in up to approximately one third of patients), but also diarrhoea, abdominal pain and flatulence (all in <10% of patients). Treatment-related headache occurred in up to 15% of patients, and another notable treatment-related AEs (occurring in <10% of patients) was dizziness. In Japanese patients, the most common type of treatment-related AE was also gastrointestinal, but most commonly diarrhoea as well as nausea, both occurring in approximately 15% of patients; other treatment-related gastrointestinal AEs were each reported in less than 5% of patients.
SAFETY RELATED TO INTERACTIONS
Proposals for post marketing surveillance.
The applicant has not proposed any specific postmarketing pharmacovigilance studies.

OVERALL CONCLUSIONS ON CLINICAL SAFETY
Frequencies of reported AEs were similar across all clinical studies included in the summary of clinical safety. Any AE preferred terms reported exclusively in a single study of subjects were at very low frequencies (typically < 1% within a given study).

In both the Western and Japanese study population, gastrointestinal adverse events represent the clear majority of reported AEs. There was a generally consistent safety profile across both US pivotal studies and also across all-causality and treatment-related analyses.

The most common type of treatment-related AE was gastrointestinal, particularly nausea, which occurred in up to approximately one third of patients. The risk of nausea was highest in the first few days of treatment. Treatment-related headache occurred in up to 15% of patients in these studies, and other notable treatment-related AEs (occurring in <10% of patients) were diarrhoea, abdominal pain, flatulence and dizziness.

In Japanese patients, the most common type of treatment-related AE was also gastrointestinal, but most commonly diarrhoea as well as nausea, both occurring in approximately 15% of patients; other treatment related gastrointestinal AEs were each reported in less than 5% of patients. Treatment-related headache and dizziness were rarely reported in Japanese patients. Dyspnoea, chest discomfort and peripheral oedema were reported in the pivotal studies.

All of these AEs occurred in approximately 2% of patients on lubiprostone in the pivotal studies, but in virtually no patients on placebo. The majority of these cases were considered treatment-related but mild to moderate in severity. None was an SAE, but some did lead to treatment withdrawal, particularly in the case of dyspnoea.

Clinical Assessor’s conclusions
The applicant has demonstrated acceptable profiles for safety and efficacy of lubiprostone and has proposed an acceptable risk:benefit evaluation in the indications and doses recommended.

The apparent tapering in efficacy after 4 weeks treatment is sufficiently clinically relevant to necessitate a change in posology and the patient information. (Please see section on Commission on Human Medicines).

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The SmPC was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

Patient Information Leaflet (PIL)
The PIL was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

Labelling
The labelling was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

Clinical Overview
A satisfactory clinical overview was provided and prepared by an appropriately qualified expert. The CV of the clinical expert was supplied.
The application was referred to Commission on Human Medicines (CHM) on 12th July 2012.

The Commission were asked to consider the proposed posology based on the clinical efficacy data as the efficacy diminishes after 4 weeks treatment without other safety concerns in the treatment of chronic idiopathic constipation.

The applicant was advised to amend the posology for the treatment of the indication for chronic idiopathic constipation to be limited to 2 weeks.

Approval is recommended on the condition this question is satisfactorily resolved.

The Applicant amended the posology to limit treatment duration to 2 weeks.

CONCLUSIONS

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was therefore recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of AMITIZA 24 micrograms Soft Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
Pharmacokinetic studies of orally administered lubiprostone were performed in several in vivo models. The species utilised were also used to assess the safety and toxicokinetic profiles of lubiprostone.

An extensive battery of GLP non-clinical studies designed to assess the toxicity of lubiprostone and its metabolites have been conducted. All repeat toxicity studies also evaluated systemic exposure by utilizing analytical methods. In addition, a full battery of genetic and reproductive toxicity and carcinogenicity studies were conducted. All studies conducted were conducted in compliance with GLP standards.

EFFICACY
Clinical studies include 7 Phase I studies, 2 Phase II studies and 7 Phase III studies (3 pivotal and 4 long-term safety studies). Three separate clinical studies were conducted in subjects with renal or hepatic impairment, as well as paediatric patients diagnosed with chronic constipation.

The applicant has demonstrated acceptable profiles for safety and efficacy of lubiprostone. Any efficacy issues arising from this application have been fully resolved.

PRODUCT LITERATURE
The approved SmPC and PIL are acceptable. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling is satisfactory and fulfils the statutory requirements for Braille.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and any non-clinical or clinical safety concerns have been fully resolved. The risk benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<th>No.</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 8 September 2011.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 29 September 2011.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality and clinical dossiers on 8 March 2012.</td>
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<td>The application was referred to the Commission on Human Medicine on 12 July 2012.</td>
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<td>6</td>
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AMITIZA 24 MICROGRAM SOFT CAPSULES
PL 21341/0003

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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UKPAR –AMITIZA 24 Micrograms Soft Capsules

PL 21341/0003
AMITIZA 24 MICROGRAM SOFT CAPSULES
PL 21341/0003

SUMMARY OF PRODUCT CHARACTERISTICS
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
AMITIZA 24 MICROGRAM SOFT CAPSULES

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PATIENT INFORMATION LEAFLET
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
AMITIZA 24 MICROGRAM SOFT CAPSULES

PL 21341/0003

LABELLING

CARTON