ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 75 mg film-coated tablets.

Truberzi 100 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Truberzi 75 mg film-coated tablets
Each film-coated tablet contains 75 mg of eluxadoline.

Truberzi 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of eluxadoline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Truberzi 75 mg film-coated tablets
Modified capsule-shaped, pale yellow to light-tan film-coated tablet of approximately 7 mm x 17 mm, debossed with "FX75" on one side.

Truberzi 100 mg film-coated tablets
Modified capsule-shaped, pink-orange to peach film-coated tablet of approximately 8 mm x 19 mm, debossed with "FX100" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Truberzi is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

4.2 Posology and method of administration

Posology
The treatment should be initiated and supervised by a physician experienced in diagnosis and management of gastrointestinal disorders.

The recommended dose is 200 mg daily (one 100 mg tablet, twice daily).

For patients who are unable to tolerate the 200 mg daily dose (one 100 mg tablet, twice daily), the dose can be lowered to 150 mg daily (one 75 mg tablet twice daily).

Elderly
In principle, general dose recommendations also apply to patients aged 65 years and above. However, given the potential for increased sensitivity to experience undesirable effects, it may be considered to initiate eluxadoline treatment in a dosage of 150 mg daily (one 75 mg tablet twice daily).

If this dosage is well tolerated, but not sufficiently effective, dosage may subsequently be increased to 200 mg daily (one 100 mg tablet twice daily). See section 4.4.

Patients with renal impairment
The safety and pharmacokinetics of eluxadoline in patients with renal impairment have not yet been established. With the renal route being a minor route of elimination for eluxadoline, no dose adjustment based on renal function may be necessary (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of eluxadoline in children aged 0 to18 years have not yet been established. No data are available.
Benefits and risks of the treatment should be periodically assessed in the context of patient symptoms severity.

Method of administration
For oral use.
The tablets should be taken with food in the morning and in the evening (see section 5.2).
Patients should be instructed if they miss a dose (delay of 4 hours) to take the next dose at the regular time and not to take 2 doses at the same time to make up for a missed dose.

4.3 Contraindications

• Hypersensitivity to eluxadoline or to any of the excipients listed in section 6.1.
• Alcoholism, alcohol abuse, alcohol addiction or chronic or acute excessive alcohol use. These patients are at increased risk for acute pancreatitis (see section 4.4).
• Known or suspected biliary tree and/or pancreatic duct obstruction (e.g. gallstones, tumour, periampullary duodenal diverticulum) or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm (see section 4.4).
• Patients without a gallbladder (e.g. due to cholecystectomy or agenesis). These patients are also at increased risk for sphincter of Oddi spasm (see section 4.4).
• Patients on treatment with potent inhibitors of OATP1B1 (e.g. cyclosporine)
• A history of pancreatitis; or known or suspected structural diseases of the pancreas, including pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis (see section 4.4).
• Hepatic impairment (Child-Pugh Class A-C). These patients are at risk for significantly increased plasma concentrations of eluxadoline (see sections 4.4 and 5.2).
• A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.

4.4 Special warnings and precautions for use

Sphincter of Oddi Spasm
Given the mu opioid receptor agonism of eluxadoline, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (eg, biliary-type pain) in patients taking eluxadoline, especially in patients without a gallbladder (see sections 4.3 and 4.8). Patients with known or suspected sphincter of Oddi disease or dysfunction and/or biliary tract or pancreatic disease, including a history of pancreatitis, and those who have had a cholecystectomy or are missing a gallbladder due to other reasons must not receive this medicinal product (see section 4.3).
Patients should be instructed to stop the treatment and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain (e.g. acute epigastric or biliary [i.e., right upper quadrant] pain) that may radiate to the back or shoulder, with or without nausea and vomiting. Eluxadoline should not be restarted in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking eluxadoline (see section 4.3).

Pancreatitis

There is an increased risk of pancreatitis with or without sphincter of Oddi spasm (see section 4.3) in patients taking eluxadoline. Serious cases resulting in hospitalization and death, primarily in patients without a gallbladder have been reported. Truberzi is contraindicated in patients without a gallbladder and other conditions that increase the risk of developing pancreatitis (see section 4.3). Most of the reported cases of serious pancreatitis occurred within a week of starting treatment with eluxadoline and some patients developed symptoms even after one to two doses but cases of pancreatitis after longer duration of treatment have also been reported.

Patients should be informed of and monitored for signs and symptoms suggestive of pancreatitis e.g. abdominal pain, that may radiate to the back or shoulder, nausea and vomiting. Patients should be instructed to stop the medicinal product and seek medical attention if these symptoms develop while taking eluxadoline (see section 4.8).

All patients should be instructed not to use alcohol while on treatment with eluxadoline.

Constipation
There is a potential for increased risk of constipation when taking eluxadoline (see section 4.8). If patients develop severe constipation for a duration of more than 4 days, they should be instructed to stop the treatment and seek medical attention.
Risk of constipation with eluxadoline in patients with other IBS sub-types is unknown, but may be increased. Caution should be exercised when administering eluxadoline in IBS patients whose bowel habits vary over time.

Somnolence and sedation
There is a potential for increased risk of somnolence and sedation when taking eluxadoline (see section 4.8) in patients who may experience increased plasma levels, such as in patients with a genetic predisposition for poor function of OATP1B1 transporter. As patient's genetic disposition may be unknown, it is recommended that patients be monitored for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or using machines (see sections 4.7. and 4.8).

Drug dependence and potential for abuse
Based on the physical-chemical and biopharmaceutical properties (very low oral bioavailability), eluxadoline is expected to have minimal abuse or dependence liability.

Special populations
Elderly
Overall, there was an increased frequency of adverse events reported for patients aged 65 years or greater in the clinical studies. However, patients 65 years of age and older, treated with the 75 mg dose twice daily experienced a reduced rate of serious adverse events as well as adverse events leading to discontinuation compared to patients treated with 100 mg dose twice daily (see section 4.8). Therefore, the 75 mg dose twice daily can be considered for this population, but its benefit risk ratio should be periodically assessed in the context of their symptoms severity (see section 4.2).

Paediatric population
Eluxadoline should not be used in children and adolescents as it has not been studied in this population (see section 4.2).

Renal impairment
No data on the pharmacokinetics of eluxadoline in patients with renal impairment are available (see section 5.2). Due to minimal absorption and the negligible role for renal elimination, an influence of renal impairment on the plasma levels of eluxadoline is not expected.

Hepatic impairment
Eluxadoline must not be used in patients with a history of or known or suspected hepatic impairment (Child-Pugh Class A-C) (see section 4.3).

Effect of OATP1B1 transporter function variability on plasma levels
The plasma levels in patients with a genetic predisposition for poor function of OATP1B1 transporter are increased, and in these patients a higher rate of adverse events, especially with regard to gastrointestinal events, as well as CNS effects might be expected (see section 5.2).

Bile acid malabsorption
A relevant proportion of patients diagnosed with IBS-D may be affected by bile-acid malabsorption as a potential reason for IBS-D symptoms. The safety and efficacy of eluxadoline in this subgroup of IBS-D patients has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that cause constipation
Although no direct drug-drug interactions have been demonstrated, chronic use of loperamide with eluxadoline should be avoided as this may increase the risk of constipation. The use of eluxadoline with other medicinal products that may cause constipation (for example anticholinergics, opioids etc) should also be avoided.

OATP1B1 inhibitors
Co-administration of OATP1B1 inhibitors (cyclosporine, gemfibrozil, antiretrovirals [atazanavir, lopinavir, ritonavir, saquinavir, tipranavir], rifampin) with eluxadoline may increase exposure to eluxadoline (see section 5.2). Eluxadoline should not be administered concomitantly with such medicinal products (see section 4.3).

OATP1B1 substrates
Eluxadoline increases the exposure of the co-administered OATP1B1 substrate; rosuvastatin (see section 5.2) by up to 40% of the total exposure which is usually not considered to be clinically relevant. The effect on other statins which are more sensitive OATP1B1 substrates (e.g. simvastatin and atorvastatin), however, may be more pronounced. Caution should therefore be exercised in patients receiving such medicinal products especially with high doses.
Other substrates potentially affected include e.g. sartans (valasartan, olmesaran).

CYP3A substrates
Eluxadoline may increase the exposure of co-administered medicinal products metabolised by Cytrochrome CYP3A4. Caution should be exercised when administering such products (e.g. midazolam, erythromycin, nifedipine), especially for those with a narrow therapeutic index (e.g. alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus). The concentration of these co-administered medicinal products with a narrow therapeutic index or their other pharmacodynamic markers should be monitored when concomitant use with eluxadoline is initiated or discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited amount of data from the use of eluxadoline in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Truberzi during pregnancy.

Breast-feeding
It is unknown whether eluxadoline is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of eluxadoline in milk (for details see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Truberzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of eluxadoline on fertility are available. In rats, there was no effect on mating, fertility and fecundity indices (see section 5.3).

4.7 Effects on ability to drive and use machines

Eluxadoline has a minor influence on the ability to drive and use machines.
Due to events of somnolence and sedation observed in clinical studies, caution should be exercised (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (incidence of >5%) reported were constipation (7% and 8% of patients receiving 75 mg and 100 mg respectively), nausea (8% and 7% of patients receiving 75 mg and 100 mg respectively) and abdominal pain (6% and 7% of patients receiving 75 mg and 100 mg respectively). Serious adverse reactions of pancreatitis (0.2% and 0.3% of patients receiving 75 mg and 100 mg respectively) and sphincter of Oddi spasm (0.2% of patients receiving 75 mg and 0.8% of patients receiving 100 mg) may also occur.

Tabulated list of adverse reactions
Adverse reactions are presented according to the MedDRA System Organ Classification and frequency convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System organ class	*Common*	*Uncommon*
Nervous system disorders	Dizziness Somnolence[1]	
Gastrointestinal disorders	Constipation Nausea Abdominal pain[2] Vomiting Flatulence Abdominal distention Gastroesophageal reflux disease[4]	Sphincter of Oddi spasm[3] Pancreatitis
Skin and subcutaneous tissue disorders	Rash[5]	
Investigations	Increased ALT Increased AST	

[1]"Somnolence" term includes: somnolence and sedation.
[2]"Abdominal pain" term includes: abdominal pain, abdominal pain lower, and abdominal pain upper.
[3] "Sphincter of Oddi spasm" term includes: manifestation as pancreatitis (terms include alcoholic pancreatitis, pancreatitis, and pancreatitis acute) and hepatic enzyme elevations with abdominal pain (terms include abdominal pain, abdominal pain upper, dyspepsia, and sphincter of Oddi dysfunction).

[4] "Gastrooesophageal reflux disease" term includes gastrooesophageal reflux disease, dyspepsia and gastritis.
[5] "Rash" term includes: dermatitis, dermatitis allergic, rash, rash generalized, rash macula-papular, rash papular, rash pruritic, urticaria, and idiopathic urticarial.

Description of selected adverse reactions

Constipation

Approximately 50% of constipation events occurred within the first 2 weeks of treatment.
Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg eluxadoline and there were no serious complications of constipation related to eluxadoline use in pivotal studies. 1% of patients receiving 75 mg and 2% of patients receiving 100 mg discontinued treatment or temporarily suspended dosing secondary to constipation, respectively, compared to <1% of patients treated with placebo. Patients should be instructed to stop the medicinal product and seek medical attention if they develop severe constipation for more than 4 days (see section 4.4).

Sphincter of Oddi spasm

In clinical studies, events of sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain in 8 patients, pancreatitis in 1 patient and abdominal pain with lipase elevation less than 3 times the upper limit of normal in 1 patient. 80% (8/10) of sphincter of Oddi spasm events presented within the first week of treatment. All events resolved upon discontinuation of Truberzi, with symptoms typically improved by the following day. All events of sphincter of Oddi spasm occurred in patients without a gallbladder. Therefore, eluxadoline is contraindicated in this population as well as in those with previous biliary tract problems (see sections 4.2, 4.3 and 4.4). The occurrence of such events in patients with an intact biliary tract cannot be excluded.

Pancreatitis

Additional cases of pancreatitis not associated with sphincter of Oddi spasm were reported in clinical studies. Of the 5 cases reported, 3 were associated with excessive alcohol intake, 1 was associated with biliary sludge, and in one case the patient discontinued eluxadoline 2 weeks prior to the onset of symptoms.
All pancreatic events, whether or not associated with sphincter of Oddi spasm, were retrospectively evaluated as mild, indicating an absence of organ failure and local or systemic complications. All pancreatic events resolved with lipase normalization upon discontinuation of eluxadoline, with 80% (4/5) resolving within 1 week of treatment discontinuation (see section 4.4).

Elderly

Of 1,795 IBS-D patients who were enrolled in clinical studies of eluxadoline and assigned to 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old.
There was an overall increased frequency of adverse events in the older population compared to patients <65 years which was comparable across all treatment groups, including placebo.
The frequency of serious adverse events, gastrointestinal events, and events leading to discontinuation tended to be lower for the 75 mg dose compared to the 100 mg dose. Therefore, in this population, the 75 mg dose twice daily can be used. (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Single supratherapeutic oral doses of eluxadoline up to 1,000 mg and single intranasal doses up to 200 mg were associated with a higher incidence of adverse events than a 100 mg single dose,

especially gastrointestinal and central nervous system events. An overdose of eluxadoline may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product.

Management
In the event of acute overdose, the patient should be carefully observed and given standard supportive treatment as required. Gastric lavage or charcoal administration should be considered. Given eluxadoline's action at opioid receptors, administration of a narcotic mu opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, subjects should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {not yet assigned}, ATC code: {not yet assigned}

Mechanism of action
Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist. Eluxadoline is also an agonist at the kappa opioid receptor (κOR). The binding affinities (Ki) of eluxadoline for human μOR and δOR are 1.8 nM and 430 nM, respectively. The binding affinity (Ki) of eluxadoline for human κOR has not been determined; however, the Ki for guinea pig cerebellum κOR is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut. Eluxadoline has demonstrated efficacy in normalizing GI transit and defecation in several models of stress induced or post GI inflammation-altered GI function in animals. Eluxadoline has very low oral bioavailability and exerts no detectable central nervous system (CNS)-mediated effects when administered orally to animals at effective doses. Eluxadoline also reverses hyperalgesic responses in an animal model of acute colitis-induced visceral pain.

Pharmacodynamic effects
Since bioavailability is limited, the pharmacodynamic activity of eluxadoline is based predominantly on local action within the GI tract. Supporting the lack of systemic pharmacodynamic effects are results from an oral abuse liability study in recreational opioid users that showed oral doses up to 1,000 mg did not produce significant pupillary constriction or significant drug liking. An abuse liability study with 100 mg and 200 mg intranasal doses of eluxadoline resulted in higher systemic concentrations of eluxadoline that produced changes in pupil diameter but were associated with drug disliking. In patients with IBS-D, no signal for central nervous system-mediated adverse events was identified. Taken together these results suggest that when using the medicinal product as directed at therapeutic doses patients will not experience significant central nervous system effects or adverse events consistent with a drug of abuse.

Clinical efficacy and safety
The efficacy and safety of eluxadoline in IBS-D patients was established in two randomized, multi-center, multi-national, double-blind, placebo-controlled studies (Studies 1 & 2). A total of 1,282 patients in Study 1 (IBS-3001) and 1,146 patients in Study 2 (IBS-3002) were enrolled and received treatment with Truberzi 75 mg, Truberzi 100 mg or placebo twice daily. Overall, patients had a mean age of 45 years (range 18-80 years with 10% at least 65 years of age or older), 66% female, 86% white, 12% black, and 27% Hispanic.
All patients met Rome III criteria for IBS and were required to meet the following criteria:
- an average of worst abdominal pain (WAP) scores in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization.
- an average daily stool consistency score (BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization.

• an average global symptom score >2.0 on a 0-4 scale (0 corresponds to no symptoms, 1 corresponds to mild symptoms, 2 corresponds to moderate symptoms, 3 corresponds to severe symptoms and 4 corresponds to very severe symptoms) over the week prior to randomization

The study designs were identical through the first 26 weeks. Study1 (IBS-3001) continued double-blinded for an additional 26 weeks for long-term safety (total of 52 weeks of treatment), followed by a 2-week follow-up. Study 2 (IBS-3002) included a 4-week single-blinded, placebo-withdrawal period upon completion of the 26-week treatment period.

Efficacy of eluxadoline was assessed using an overall responder analyses as defined by the simultaneous improvement in the daily WAP score by ≥30% as compared to the baseline weekly average AND a reduction in the BSS to <5 on at least 50% of the days within a time interval. Improvements in global symptoms of IBS were assessed based on an adequate relief response endpoint defined as achieving adequate relief of IBS symptoms on at least 50% of weeks and on a global symptom response endpoint defined by a daily rating of global symptoms of none or mild on at least 50% of days. Results for endpoints were based on electronic daily diary entries by patients. The efficacy results for ≥50% of responder days (primary composite endpoint) over 6 months are shown in Table 2. In both studies, the proportion of patients who were composite responders to Truberzi 100 mg twice daily was statistically significantly higher than placebo. The proportion of patients who were adequate relief responders was statistically significantly higher than placebo for Truberzi 100 mg twice daily over 6 month interval in both studies. The proportion of patients who were global symptom responders was statistically significantly higher than placebo for Truberzi 100 mg twice daily over 6 month interval in Study 2 and numerically higher than placebo in Study 1. There were no efficacy differences according to gender.

Table 2: Efficacy Results in Randomized Clinical Studies

	Study 1 (IBS 3001)			**Study 2 (IBS 3002)**		
	Truberzi 100 mg n=426	**Truberzi 75 mg n=427**	**Placebo n=427**	**Truberzi 100 mg n=382**	**Truberzi 75 mg n=381**	**Placebo n=382**
Composite Response						
Responder rates	29%	23%	19%	33%	30%	20%
P values	<0.001	0.112		<0.001	0.001	
Abdominal Pain Response						
Responder rates	47%	45%	43%	50%	48%	45%
P values	0.355	0.852		0.148	0.448	
BSS <5 Response						
Responder rates	34%	28%	24%	40%	34%	24%
P values	0.001	0.186		<0.001	<0.001	
Adequate Relief Response						
Responder rates	49.5%	45.7%	40.0%	53.7%	52.8%	43.7%
P values	0.005	0.097		0.006	0.013	
Global Symptom Response						
Responder rates	34.7%	35.1%	28.8%	43.2%	45.1%	34.3%
P values	0.063	0.048		0.012	0.002	

For the daily composite response, eluxadoline began to separate from placebo shortly after initiating treatment with a maximal effect seen at 4-6 weeks that was maintained throughout the course of

treatment. Additionally, the proportion of patients who were composite responders to eluxadoline at each 4-week interval for months 1 through 6 was higher than placebo for both doses in both Phase 3 studies demonstrating that efficacy is maintained with continuous eluxadoline treatment.
Treatment with eluxadoline also resulted in significant improvements in patients whose IBS-D symptoms were not adequately controlled with use of loperamide prior to enrolment.
When the threshold for abdominal pain response was increased to ≥40% or ≥50% improvement from baseline in daily worst abdominal pain, the proportion of abdominal pain responders was 6%-7% higher for eluxadoline 100 mg twice daily compared to placebo which was statistically significant ($P \leq 0.009$) for the pooled (Study 1 and Study 2) data. Patients receiving eluxadoline also reported significant reductions in bowel movement frequency and abdominal bloating compared to placebo as demonstrated by changes from baseline in daily bowel movements and bloating score at Weeks 12 and 26. Patients receiving eluxadoline reported significant increases in urgency-free days both for ≥50% urgency-free days as well as ≥75% urgency free days. Also, eluxadoline significantly improves patients quality of life as demonstrated by change from baseline score in the IBS-QOL questionnaire at weeks 12 and 26.

During the 4 week single-blind withdrawal period in Study 2 (IBS-3002), no evidence of rebound diarrhoea or abdominal pain was demonstrated.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of clinical studies with Truberzi in one or more subsets of the paediatric population in IBS-D (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Eluxadoline's systemic exposure following oral administration is low and is consistent with its local action in the GI tract. The active substance has linear pharmacokinetics with no accumulation upon repeated twice daily dosing. Mean plasma elimination half-life is 5 hours with high inter-subject variability. Eluxadoline is primarily cleared as such via the biliary system with the kidney playing a minimal role in elimination. Eluxadoline is not an inducer/inhibitor of major CYP enzymes, however, eluxadoline has some potential for the metabolism based inactivation of CYP3A4. It is a substrate and an inhibitor of the hepatic uptake transporter OATP1B1; and a substrate for the hepatic efflux transporter MRP2. Hepatic impairment or coadministration with cysclosporine results in significant increases in plasma concentrations of eluxadoline.

Absorption
The absolute bioavailability of eluxadoline has not been determined but is estimated to be low due to limited absorption and first pass effects. The absorption of eluxadoline was rapid under fasting conditions, with a median T_{max} value of 2 hours. The administration of eluxadoline with a high fat meal significantly decreased both C_{max} (50%) and AUC (60%) without any effect on T_{max}. Upon administration of multiple oral doses twice daily, there was no accumulation of active substance.

Distribution
In a population pharmacokinetic analysis, the estimated apparent volume of distribution of eluxadoline was 27,100 L. In healthy subjects, eluxadoline was moderately (81%) bound to plasma proteins.

Biotransformation
Eluxadoline is primarily excreted in the feces, either as unabsorbed active substance or via the biliary system with the kidney playing a minimal role in elimination.
In vitro studies demonstrated that eluxadoline was stable in human hepatocytes, liver and intestinal microsomes, and that the only minor and inactive metabolite of eluxadoline detected was the acyl glucuronide metabolite (M11) formed through glucuronidation of the methoxybenzoic acid moiety. Following a 1,000 mg oral dose in healthy male volunteers, M11 was detected in urine but not in systemic circulation.

Eluxadoline exists predominantly as the (S,S)-diastereomer (>99%) and undergoes little or no chiral conversion *in vivo*.
Eluxadoline has a low potential for drug-drug interactions based on limited in vitro CYP inhibition/induction and given that eluxadoline is not a substrate for CYPs at clinically meaningful concentrations.

OATP1B1 inhibitors
Eluxadoline is a substrate of the hepatic uptake transporter OATP1B1. Co-administration of eluxadoline with cyclosporine (an OATP1B1 inhibitor) increased eluxadoline exposure by approximately 5-fold (see sections 4.3 and 4.5).

MRP2 inhibitors
Eluxadoline is a substrate of the hepatic efflux transporter MRP2. Co-administration of eluxadoline with probenecid (MRP2 inhibitor) resulted in approximately 1.4-fold increase in exposure to eluxadoline. No dose adjustment is necessary.

OATP1B1 substrates
Eluxadoline is an inhibitor of the hepatic uptake transporter OATP1B1. Co-administration of eluxadoline with rosuvastatin (an OATP1B1 substrate) resulted in an up to 1.4-fold increase in exposure of rosuvastatin and the major active metabolite, n-desmethyl rosuvastatin compared to administration of rosuvastatin alone. No dose adjustment is necessary for co-administered OATP1B1 substrates. However, caution should be exercised in patients receiving high doses of OATP1B1 substrates (see section 4.5).

In vitro assessment of drug interactions
In vitro studies indicate that eluxadoline is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 at clinically relevant concentrations. CYP2E1 was slightly inhibited (50% inhibitory concentration [IC50] of approximately 20 µM [11 µg/mL]), although this is not expected to result in any clinically meaningful interactions. *In vitro* studies in liver microsomes showed that eluxadoline is not an inhibitor of CYP3A4 at clinically relevant concentrations, but in intestinal microsomes, eluxadoline inhibited CYP3A4 with a Ki of 450 µM (256 µg/mL). Potentially high (up to 700 µM) eluxadoline concentrations in gut may affect the pharmacokinetic of concomitantly administered CYP3A4 substrates (see section 4.5).
In vitro studies indicated that eluxadoline is a substrate and an inhibitor of the hepatic uptake transporter OATP1B1; a substrate for the hepatic efflux transporter MRP2 and is not a substrate or inhibitor of the P-gp and BCRP transporters.

Elimination
Following a single oral dose of 300 mg [^{14}C] eluxadoline in healthy male subjects, 82.2% of the total [^{14}C] eluxadoline was recovered in faeces in 336 hours and less than 1% was recovered in urine in 192 hours.

Specific populations
Age and gender
Given eluxadoline's local action in the GI tract, low F_{oral} and lack of metabolism, prospective clinical studies regarding differences in age, body mass index (BMI), ethnicity, and gender were deemed unnecessary. Pharmacokinetic data for healthy volunteers pooled across Phase 1 studies (using the 100 mg single oral dose) and analyzed for potential differences based on sex, age, race, and BMI demonstrated no significant differences.

Renal Impairment
Eluxadoline has not been specifically studied in patients who have renal impairment. Given the low estimated oral bioavailability (F_{oral} 1.34%) of eluxadoline and limited renal elimination, renal impairment is not expected to affect clearance of eluxadoline.

Hepatic impairment
The apparent clearance of eluxadoline is markedly reduced and half-life increases in hepatic-impaired patients (see sections 4.3 and 4.4). Following single oral 100 mg dose in subjects with varying degrees of liver impairment and healthy subjects, eluxadoline plasma levels were on average 6-fold, 4-fold, and 16-fold elevated in mild, moderate, and severe hepaticimpaired subjects (Child Pugh Class A, B, C), respectively, while half-life increased 3-5 fold (see sections 4.3 and 4.4).

OATP1B1 poor function haplotypes
The plasma levels in patients with a genetic predisposition for poor function of OATP1B1 transporter are increased and in these patients a higher rate of adverse events, especially with regard to gastrointestinal events, as well as CNS effects might be expected (see section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. In rat, eluxadoline was excreted into milk in an approximately dose proportional manner with maximal concentrations less than plasma concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicified microcrystalline cellulose (E460);
Colloidal anhydrous silica (E551);
Crospovidone, type B (E1202);
Mannitol (E421);
Magnesium stearate (E572);
Polyvinyl alcohol (E1203);
Titanium dioxide (E171);
Macrogol 3350 (E1521);
Talc (E553b);
Iron oxide yellow (E172);
Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PCTFE/PVC/Al-blister containing 14 film-coated tablets. Pack sizes of 28, 56 and a multipack containing 168 (3 packs of 56) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Warner Chilcott Deutschland GmbH
Dr.-Otto-Roehm-Strasse 2-4,
64331 Weiterstadt,
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 75 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/001 56 film-coated tablets
EU/1/16/1126/002 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX – MULTIPACK ONLY) – 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 75 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/005 168 film-coated tablets (3packs of 56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (WITHOUT BLUE BOX – MULTIPACK ONLY) – 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 75 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/005 168 film-coated tablets (3 packs of 56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 100 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
28 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/003 56 film-coated tablets
EU/1/16/1126/004 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX – MULTIPACK ONLY) – 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 100 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/006 168 film-coated tablets (3 packs of 56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (WITHOUT BLUE BOX – MULTIPACK ONLY) – 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 100 mg film-coated tablets.
eluxadoline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of eluxadoline.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1126/006 168 film-coated tablets (3 packs of 56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

TRUBERZI 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 75 mg film-coated tablets.
eluxadoline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Truberzi 100 mg film-coated tablets.
eluxadoline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals International Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Truberzi 75 mg film-coated tablets
Eluxadoline

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Truberzi is and what it is used for

Truberzi is a medicine that contains the active substance eluxadoline. It is used to treat irritable bowel syndrome (‘IBS’) with diarrhoea (IBS-D) in adults.

IBS is a common gut disorder. The main symptoms of IBS-D include:
- stomach ache;
- stomach discomfort;
- diarrhoea;
- urgent bowel movements.

Truberzi acts on the surface of your gut to restore the normal function of your bowels and block the sensation of pain and discomfort in IBS-D patients.

2. What you need to know before you take Truberzi

Do not take Truberzi:
- if you are allergic to eluxadoline or any of the other ingredients of this medicine (listed in section 6);
- if you have, or have had, pancreatitis (inflammation of the pancreas);
- if you don’t have a gallbladder by birth or your gallbladder has been surgically removed;
- if you have, or have had, problems with alcohol abuse, alcohol addiction, or if you drink alcohol;
- if you have, or have had, any blockage in your gallbladder, bile ducts, or pancreas (such as gallstones, tumour, duodenal diverticulum);
- if you have, or have had, disease or dysfunction of the sphincter of Oddi (a small round muscle in your upper belly that controls the flow of bile and pancreatic fluids into your upper intestine);
- if you have liver disease with decreased liver function;

- if you have had constipation for a while or if constipation is the main symptom of your IBS (called 'IBS with constipation' [IBS-C]);
- if you have, or may have, a blockage in your intestine/bowels;
- If you take medicines that may increase the level of the concentration of eluxadoline in the blood (so-called OATP1B1 inhibitor, e.g. ciclosporin).

Talk to your doctor or pharmacist if you are unsure if any of the above apply to you.

Warnings and precautions
Stop taking Truberzi and seek medical attention immediately if you develop any of the following while taking this medicine:
- new or worsening pain in the belly, with or without nausea and vomiting;
    - pain may begin soon after you start Truberzi. You may feel pain on the right side of your belly or the upper area of the belly, right below the ribs. The pain may feel like it is moving through to your back or shoulder;
    - these symptoms are uncommon and may indicate pancreas or bile duct system problems (i.e. inflammation of the pancreas or spasm of the sphincter of Oddi);
        - your risk of developing pancreas or bile duct system problems may be higher if you drink alcohol in excess,
        - the spasm of the sphincter of Oddi usually goes away when you stop Truberzi.
- constipation lasting longer than 4 days.

Please report to your doctor:
- how much alcohol you drink (e.g. daily number of drinks);
- if you experience any effects, such as dizziness and sleepiness.

Take special care if you are 65 years of age or older, as there is a higher risk that you may have certain side effects (see section 4).

Children and adolescents
Truberzi should not be given to children and adolescents less than 18 years old as there is no information about its use in this age group.

Other medicines and Truberzi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Avoid frequent use of loperamide (a medicine used to treat diarrhoea) if you are taking Truberzi as this may increase the risk of constipation. Avoid taking Truberzi with any other medicines that may cause constipation such as opioids (e.g. fentanyl [used to treat pain]) or anticholinergics (e.g. atropine [used to treat cardiac disorders among other indications]).

Some medicines may increase the level of Truberzi in the blood. These medicines can include:
- ciclosporin (immunosuppressant used to reduce inflammation);
- gemfibrozil (used to lower lipid levels);
- atazanavir, lopinavir, ritonavir, saquinavir, tipranavir (antiretrovirals used to treat HIV);
- rifampicin (antibiotic used to treat infections).
Do not take Truberzi with any of these medicines.

Truberzi may increase the level of some medicines in the blood. These medicines can include**:**
- rosuvastatin (statin used to treat high cholesterol and to prevent cardiovascular disease);
- valsartan and olmesartan (used to treat high blood pressure);
- erythromycin (used to treat infections);
- midazolam (a medicine to sedate you when you e.g.undergo endoscopic procedures);
- nifedipine (used to treat high blood pressure);
- alfentanil, fentanyl (opioid analgesic used to treat pain);
- dihydroergotamine, ergotamine (used to treat migraine);

- pimozide (used to treat mental disorders) ;
- quinidine (used to treat heart diseases);
- sirolimus, tacrolimus (immunosuppressant used for the control of body's immune response).
If any of the above applies to you, tell your doctor or pharmacist before taking Truberzi. Check with your doctor or pharmacist if you are not sure.

Pregnancy and breast-feeding
Truberzi should not be taken whilst pregnant or breast-feeding. If you are pregnant or breast-feeding or you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
It is unlikely that Truberzi will affect your ability to drive or use tools or machines. However, you may experience side effects such as sleepiness or dizziness while taking Truberzi which might affect your ability to drive or use machines. Do not drive or use machines while taking this medicine until you know how it affects you.

3. How to take Truberzi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The usual recommended dose is one 100 mg tablet twice a day.
Your doctor may prescribe you a lower dose of one 75 mg tablet twice a day if you:
- are 65 years of age or older;
- are unable to tolerate the 100 mg dose;
The tablets should be taken orally with food in the morning and in the evening.

If you take more Truberzi than you should
If you have taken more Truberzi than you should, tell your doctor or seek urgent medical assistance.

If you forget to take Truberzi
Do not take a double dose to make up for a forgotten dose. Take the next dose at the next scheduled time and continue as normal.

If you stop taking Truberzi
Do not stop taking Truberzi without first talking to your doctor as your symptoms may worsen.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious
Stop taking Truberzi, and seek medical attention immediately if you have new or worsening stomach pain, with or without nausea and vomiting, while taking Truberzi. These symptoms occur uncommonly (may affect up to 1 in 100 people) and may indicate pancreas or bile duct system problems (e.g. inflammation of the pancreas or spasm of the sphincter of Oddi).

Other side effects can include
Common: may affect up to 1 in 10 people
- dizziness;
- sleepiness;
- constipation;

- feeling sick (nausea);
- stomach ache;
- being sick (vomiting);
- gas (flatulence);
- feeling bloated;
- heartburn or acid reflux;
- rash;
- abnormal blood test results (increased levels of certain liver enzymes).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Truberzi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Truberzi contains
- The active substance is eluxadoline. Each tablet contains 75 mg of eluxadoline.
- The other ingredients are:
  Core tablet: silicified microcrystalline cellulose (E460); colloidal anhydrous silica (E551); crospovidone, type B (E1202); mannitol (E421) and magnesium stearate (E572).
  Film-coating: polyvinyl alcohol (E1203); titanium dioxide (E171); macrogol 3350 (E1521); talc (E553b); iron oxide yellow (E172) and iron oxide red (E172).

What Truberzi looks like and contents of the pack
The film-coated tablets are modified capsule-shaped, pale yellow to light-tan and debossed with ‘FX75’ on one side.
The tablets are packed in PCTFE/PVC/Al-blisters. Truberzi is available in packs containing 28 or 56 film-coated tablets and in a multipack of 168 film-coated tablets comprising 3 cartons, each containing 56 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Allergan Pharmaceuticals International Limited
Clonshaugh Industrial Estate
Coolock
Dublin 17
Ireland

Manufacturer
Warner Chilcott Deutschland GmbH
Dr.-Otto-Roehm-Strasse 2-4,
64331 Weiterstadt,
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Sverige
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Suomi/Finland
Allergan Norden AB

Tel: + 39 06 509 562 90

Latvija
Allergan Baltics UAB
Tel: + 371 676 60 831

Puh/Tel: + 358 800 115 003

United Kingdom/Malta/Ireland
Allergan Ltd
Tel: + 44 (0) 1628 494026

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Truberzi 100 mg film-coated tablets
Eluxadoline

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Truberzi is and what it is used for

Truberzi is a medicine that contains the active substance eluxadoline. It is used to treat irritable bowel syndrome (‘IBS’) with diarrhoea (IBS-D) in adults.

IBS is a common gut disorder. The main symptoms of IBS-D include:
- stomach ache;
- stomach discomfort;
- diarrhoea;
- urgent bowel movements.

Truberzi acts on the surface of your gut to restore the normal function of your bowels and block the sensation of pain and discomfort in IBS-D patients.

2. What you need to know before you take Truberzi

Do not take Truberzi:
- if you are allergic to eluxadoline or any of the other ingredients of this medicine (listed in section 6);
- if you have, or have had, pancreatitis (inflammation of the pancreas);
- if you don’t have a gallbladder by birth or your gallbladder has been surgically removed;
- if you have, or have had, problems with alcohol abuse, alcohol addiction, or if you drink alcohol;
- if you have, or have had, any blockage in your gallbladder, bile ducts, or pancreas (such as gallstones, tumour, duodenal diverticulum);
- if you have, or have had, disease or dysfunction of the sphincter of Oddi (a small round muscle in your upper belly that controls the flow of bile and pancreatic fluids into your upper intestine);
- if you have liver disease with decreased liver function;

- if you have had constipation for a while or if constipation is the main symptom of your IBS (called 'IBS with constipation' [IBS-C]);
- if you have, or may have, a blockage in your intestine/bowels;
- If you take medicines that may increase the level of the concentration of eluxadoline in the blood (so-called OATP1B1 inhibitor, e.g. ciclosporin).

Talk to your doctor or pharmacist if you are unsure if any of the above apply to you.

Warnings and precautions
Stop taking Truberzi and seek medical attention immediately if you develop any of the following while taking this medicine:
- new or worsening pain in the belly, with or without nausea and vomiting;
    - pain may begin soon after you start Truberzi. You may feel pain on the right side of your belly or the upper area of the belly, right below the ribs. The pain may feel like it is moving through to your back or shoulder;
    - these symptoms are uncommon and may indicate pancreas or bile duct system problems (i.e. inflammation of the pancreas or spasm of the sphincter of Oddi);
        - your risk of developing pancreas or bile duct system problems may be higher if you drink alcohol in excess,
        - the spasm of the sphincter of Oddi usually goes away when you stop Truberzi.
- constipation lasting longer than 4 days.

Please report to your doctor:
- how much alcohol you drink (e.g. daily number of drinks);
- if you experience any effects, such as dizziness and sleepiness.

Take special care if you are 65 years of age or older, as there is a higher risk that you may have certain side effects (see section 4).

Children and adolescents
Truberzi should not be given to children and adolescents less than 18 years old as there is no information about its use in this age group.

Other medicines and Truberzi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Avoid frequent use of loperamide (a medicine used to treat diarrhoea) if you are taking Truberzi as this may increase the risk of constipation. Avoid taking Truberzi with any other medicines that may cause constipation such as opioids (e.g. fentanyl [used to treat pain]) or anticholinergics (e.g. atropine [used to treat cardiac disorders among other indications]).

Some medicines may increase the level of Truberzi in the blood. These medicines can include:
- ciclosporin (immunosuppressant used to reduce inflammation);
- gemfibrozil (used to lower lipid levels);
- atazanavir, lopinavir, ritonavir, saquinavir, tipranavir (antiretrovirals used to treat HIV);
- rifampicin (antibiotic used to treat infections).
Do not take Truberzi with any of these medicines.

Truberzi may increase the level of some medicines in the blood. These medicines can include**:**
- rosuvastatin (statin used to treat high cholesterol and to prevent cardiovascular disease);
- valsartan and olmesartan (used to treat high blood pressure);
- erythromycin (used to treat infections);
- midazolam (a medicine to sedate you when you e.g. undergo endoscopic procedures);
- nifedipine (used to treat high blood pressure);
- alfentanil, fentanyl (opioid analgesic used to treat pain);
- dihydroergotamine, ergotamine (used to treat migraine);

- pimozide (used to treat mental disorders) ;
- quinidine (used to treat heart diseases);
- sirolimus, tacrolimus (immunosuppressant used for the control of body's immune response).
If any of the above applies to you, tell your doctor or pharmacist before taking Truberzi. Check with your doctor or pharmacist if you are not sure.

Pregnancy and breast-feeding
Truberzi should not be taken whilst pregnant or breast-feeding. If you are pregnant or breast-feeding or you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
It is unlikely that Truberzi will affect your ability to drive or use tools or machines. However, you may experience side effects such as sleepiness or dizziness while taking Truberzi which might affect your ability to drive or use machines. Do not drive or use machines while taking this medicine until you know how it affects you.

3. How to take Truberzi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is one 100 mg tablet twice a day.
The tablets should be taken orally with food in the morning and in the evening.

If you take more Truberzi than you should
If you have taken more Truberzi than you should, tell your doctor or seek urgent medical assistance.

If you forget to take Truberzi
Do not take a double dose to make up for a forgotten dose. Take the next dose at the next scheduled time and continue as normal.

If you stop taking Truberzi
Do not stop taking Truberzi without first talking to your doctor as your symptoms may worsen.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious
Stop taking Truberzi, and seek medical attention immediately if you have new or worsening stomach pain, with or without nausea and vomiting, while taking Truberzi. These symptoms occur uncommonly (may affect up to 1 in 100 people) and may indicate pancreas or bile duct system problems (e.g. inflammation of the pancreas or spasm of the sphincter of Oddi).

Other side effects can include
Common: may affect up to 1 in 10 people
- dizziness;
- sleepiness;
- constipation;
- feeling sick (nausea);
- stomach ache;
- being sick (vomiting);

- gas (flatulence);
- feeling bloated;
- heartburn or acid reflux;
- rash;
- abnormal blood test results (increased levels of certain liver enzymes).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Truberzi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Truberzi contains
- The active substance is eluxadoline. Each tablet contains 100 mg of eluxadoline.
- The other ingredients are:
  Core tablet: silicified microcrystalline cellulose (E460); colloidal anhydrous silica (E551); crospovidone, type B (E1202); mannitol (E421) and magnesium stearate (E572).
  Film-coating: polyvinyl alcohol (E1203); titanium dioxide (E171); macrogol 3350 (E1521); talc (E553b); iron oxide yellow (E172) and iron oxide red (E172).

What Truberzi looks like and contents of the pack
The film-coated tablets are modified capsule-shaped, pink-orange to peach and debossed with 'FX100' on one side.
The tablets are packed in PCTFE/PVC/Al-blisters. Truberzi is available in packs containing 28 or 56 film-coated tablets and in a multipack of 168 film-coated tablets comprising 3 cartons, each containing 56 film-coated tablets.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV
Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for eluxadoline, the scientific conclusions of CHMP are as follows:

During the period under review, there were cases of pancreatitis in patients treated with eluxadoline. Eluxadoline is currently contraindicated in patients without gallbladder and in patients with known or suspected biliary duct obstruction. There was a case of pancreatitis in an 80-year old female patient with gallstones. As a consequence, PRAC proposes to provide more precise information in section 4.3 of SmPC to add list of conditions that predispose to the obstruction of the biliary tree and/or pancreatic duct (gallstones, tumour, periampullary duodenal diverticulum). In section 4.4 subheading *pancreatitis*, the PRAC proposes to revise the information to reflect current data on pancreatitis related to eluxadoline gathered during the reporting period. Two cases were fatal. On the other hand, the majority of cases of pancreatitis occurred within one week, after the first doses. The proposed warning will better reflect characteristics of pancreatitis cases reported. It is also proposed to amend section 4.2 by adding a recommendation that the product should be initiated and used under supervision of physician experienced in management of gastrointestinal disorders in order to minimise the risk of pancreatitis related to eluxadoline use.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing eluxadoline, Annex IIB and a Direct Health Care Communication (DHPC) were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for eluxadoline the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing eluxadoline is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.