Part VI: Summary of the risk management plan

Summary of risk management plan for Truberzi

This is a summary of the risk management plan (RMP) for Truberzi. The RMP details important risks of Truberzi, how these risks can be minimised, and how more information will be obtained about Truberzi's risks and uncertainties (missing information).
Truberzi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Truberzi should be used.
This summary of the RMP for Truberzi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Truberzi's RMP.

I. The medicine and what it is used for

Truberzi is authorised for treatment of IBS-D in adults (see SmPC for the full indication). It contains eluxadoline as the active substance and it is given by oral administration.
Further information about the evaluation of Truberzi's benefits can be found in Truberzi's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/medicines/human/EPAR/truberzi

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Truberzi, together with measures to minimise such risks and the proposed studies for learning more about Truberzi's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety updated report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Truberzi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Truberzi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Truberzi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs

further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Decreased GI motility shown as constipation SO spasm (SOD) Pancreatitis
Important potential risks	Potential complications of decreased GI motility (e.g. serious FI, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, or TM) Asthma exacerbation Abuse Use in patients ≥65 years of age CNS effects as a result of extended systemic exposure in patients with hepatic impairment or concomitant treatment with OATP1B1 inhibitors
Missing information	Use in pregnancy and lactation Use in patients of ethnic origin other than whites Use in patients with impaired intestinal barriers (IBD and Coeliac Disease)

II.B Summary of important risks

Important identified risk 1: Decreased GI motility shown as constipation	
Evidence for linking the risk to the medicine	Truberzi can induce constipation by stimulating opioid receptors along the gut that play a key role in regulating the movement of the gut. Clinical trials showed elevated incidence rate of constipation compared to placebo with 50% of the constipation events occurring within the first 2 weeks of treatment. Constipation is considered an important identified risk as severe constipation for a prolonged duration can be a serious condition that if left untreated may lead to further complications and hospitalisation.
Risk factors and risk groups	Constipation is a heterogeneous disorder, with multiple causes, including an inadequate diet, medication use, concurrent diseases, and disorders of bowel structure or function. ***Patient factors*** Female gender, pregnancy, increasing age, history of chronic or severe constipation, multiple sclerosis, Parkinsonism, and dementia were found to be the most strongly associated with statistically independent elevations in risk of chronic constipation. In addition, important risk factor for mechanical small bowel obstruction is prior abdominal surgery causing postoperative adhesions. Patients with a history of prior abdominal or pelvic surgery, and particularly colorectal surgery, appendectomy, gynaecologic surgery, prior adhesiolysis, and resection of malignancy are prone to adhesive small bowel obstruction. For patients with a history of prior bowel obstruction, whether managed medically or surgically, the likelihood of recurrent obstruction increases with an increasing number of episodes. Adhesive small bowel obstruction can occur in the absence of prior surgery due to prior intestinal inflammation, such as with prior bouts of diverticulitis or Crohn's disease. Other pathologies that can cause extrinsic compression leading to small bowel obstruction include hernia and volvulus. Diseases intrinsic to the wall of the small intestine (eg, tumour, stricture, intramural hematoma) can cause small bowel

Important identified risk 1: Decreased GI motility shown as constipation	
	obstruction by encroaching on the lumen of the bowel because of oedema, infiltration of the bowel wall, or from progressive stricture formation. Processes that block an otherwise normal bowel lumen (e.g., intussusception, gallstones, foreign body) can also cause mechanical bowel obstruction (Bordeianou & Yeh, 2016). ***Risk period*** In clinical trials, constipation AEs were commonly reported early in the course of treatment (within the first 13 weeks of initial treatment). Approximately 50% of constipation events occurred within the first 2 weeks of treatment. ***Additive or synergistic factors*** Many medications, particularly aluminium-containing antacids, diuretics, opioids, antidepressants, antispasmodics, and anticonvulsants were associated with a higher risk of chronic constipation (Talley et al., 2003).
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section:4.3, 4.4, 4.5 and 4.8* *PL section: 2 and 4* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Important identified risk 2: SO spasm (SOD)	
Evidence for linking the risk to the medicine	The SO, a small round muscle in the upper intestine, normally lets the digestive juices flow from the liver and pancreas into the intestines. Truberzi may induce spasm of this muscle which in turn can prevent the flow of digestive juices leading to pancreatitis and liver enzyme elevations associated with pain in the upper abdomen near the stomach. In clinical trials, 13 cases (0.51%) that were adjudicated as SO spasm were reported. SO spasm is considered an important identified risk that if left untreated may lead to complications such as pancreatitis and hospitalisation.
Risk factors and risk groups	***Patient factors*** Patients with known or suspected biliary tree and/or pancreatic duct obstruction (e.g. gallstones, tumour, periampullary duodenal diverticulum) or SO disease or dysfunction are at increased risk of SO spasm.In addition, prior cholecystectomy (or the absence of a gall bladder) was a highly predictive risk factor for cases of SO spasm during the clinical trial programme.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section:4.3, 4.4 and 4.8* *PL section: 2 and 4* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: *DUS*

Important identified risk 3: Pancreatitis

Evidence for linking the risk to the medicine	There were three cases of pancreatitis that were secondary to SO spasm and additional 6 cases of pancreatitis that were independent of SO spasm in the overall development programme. All of the cases (9) were rated as mild based on the Atlanta criteria. Pancreatitis can be serious and is likely to lead to hospitalisation and hence is an important identified risk. Further evaluation of frequency, severity, seriousness and outcome of this risk in the post-marketing period is warranted.
Risk factors and risk groups	***Patient factors*** In most series, the vast majority of patients have gallstones- or alcohol-induced pancreatitis (Vidarsdottir et al., 2013). The following groups of patients are considered to be at risk for acute pancreatitis: - patients suffering from alcoholism, alcohol abuse or alcohol addiction or patients with chronic or acute excessive alcohol use; - patients with a history of pancreatitis; - patients having structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. ***Additive or synergistic factors*** Drug-induced pancreatitis is relatively rare; however, 525 different drugs are listed in the WHO database suspected to cause acute pancreatitis as a side effect. Many of them are widely used to treat highly prevalent diseases. The true incidence is not entirely clear since only few systematic population-based studies exist. In a recent cohort study, 3.4% of the patients had drug-induced pancreatitis. Some drugs have pancreatitis documented as a side effect such as azathioprine, and opiates have also been shown to lead to pancreatitis in most series investigating this (Vidarsdottir et al., 2013).
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.3, 4.4 and 4.8* *PL section: 2 and 4* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*
Additional pharmacovigilance activities	*DUS*

Important potential risk 1: Potential complications of decreased GI motility (e.g. serious FI, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, or TM)	
Evidence for linking the risk to the medicine	Truberzi can induce decreased GI motility by stimulating opioid receptors along the gut that play a key role in regulating the movement of the gut. During the clinical development programme there were two events suggestive of complications of decreased GI motility in patients exposed to eluxadoline; one case of faecaloma and one case of serious ileus that required hospitalisation. Potential complications of decreased GI motility is considered an important potential risk as due to the paucity of cases there is currently insufficient evidence to conclude that these cases are associated with eluxadoline use. These complications can be serious and if left untreated may lead to hospitalisation.
Risk factors and risk groups	***Patient factors***

Important potential risk 1: Potential complications of decreased GI motility (e.g. serious FI, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, or TM)	
	Patients with chronic constipation, IBS-C, or mechanical GI obstruction are at special risk of developing severe complications of bowel obstruction. The aetiology of chronic constipation that could lead to chronic constipation is associated with low fibre intake, inadequate hydration, reduced mobility as the result of general functional decline and institutionalisation, reduced sensation of thirst, electrolyte disturbances (hypercalcemia, hypokalaemia, hypermagnesaemia), endocrine and metabolic disorders (eg, diabetes mellitus, hyperparathyroidism, hypothyroidism, chronic renal failure), neurological disorders (eg, dementia, Parkinson disease, neuropathies, multiple sclerosis, spinal cord injuries, cauda equine syndrome), and psychological comorbidities (eg, depression, distress, personality disorders, or history of abuse) (Chang et al., 2010; Leung et al., 2011; Palmer et al., 2008). Children, incapacitated patients, and the institutionalised elderly are considered the highest at-risk populations for experiencing FI (Hussain et al., 2014). Processes that block an otherwise normal bowel lumen (e.g., intussusception, gallstones, foreign body) can also cause mechanical bowel obstruction (Bordeianou & Yeh, 2016). ***Additive or synergistic factors*** Patients receiving concomitant medication that may cause constipation are at increased risk of developing complications of decreased GI motility (eg, anticholinergics, diuretics, b-blockers, opiates, iron supplements, calcium channel blockers, antidepressants, antipsychotics, acetaminophen, aspirin and NSAIDs all are said to contribute to chronic constipation, especially in the elderly (Chang et al., 2010; Leung et al., 2011; Palmer et al., 2008).
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.3, 4.4, 4.5 and 4.8* *PL section: 2 and 4* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Important potential risk 2: Asthma exacerbation	
Evidence for linking the risk to the medicine	Cases of asthma exacerbation were reported in clinical trials. Most of the cases were evaluated as mild to moderate. However, there is the potential for these to be serious.
Risk factors and risk groups	***Patient factors*** Analysis of the European Community Respiratory Health Survey cohort (18,156 subjects; age: 0 to 44) showed that a family history of asthma or allergy was associated with a higher risk of developing asthma (HR, 1.89; 95% CI, 1.67-2.13). Early, acute respiratory infections were associated with an increased lifelong risk of asthma onset (pooled HR, 3.19; 95% CI, 2.75-3.69) (de Marco et al., 2004). Anto and colleagues reported that the following risk factors were found to increase the risk of new-onset asthma: female gender (OR: 1.97; 95% CI: 1.38,2.81), bronchial hyper-responsiveness (3.25; 2.19,4.83), atopy (1.55;1.08,2.21), FEV_1 < 100 % predicted (1.87;1.34,2.62), nasal allergy (1.98;1.39,2.84) and maternal

	asthma (1.91;1.13;3.21) (Anto et al., 2010). A later study from the same cohort further confirmed that female sex is an independent risk factor for non-allergic asthma (Leynaert et al., 2012). ***Additive or synergistic factors*** The role of infection in asthma is complex and still not fully understood. Although viral infections, and especially those caused by rhinovirus are now well established as being associated with acute asthma exacerbations (Kurai et al., 2013; Saraya et al., 2014), there is increasing evidence from controlled studies to support an association between atypical bacterial infection, particularly with *C. pneumoniae* and *M. pneumonia*, and both chronic stable asthma and acute exacerbations of asthma (Johnston & Martin, 2005).
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC: Not applicable* *PL section: Not applicable* *Treatment should be initiated and supervised e by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Important potential risk 3: Abuse	
Evidence for linking the risk to the medicine	There were no reports of drug abuse and dependence during clinical development.
Risk factors and risk groups	There are a number of subject factors, which are thought to be risk factors for drug abuse. These include a positive family history, male gender, concomitant mental health disorders including anxiety and depression, social and family difficulties, peer pressure, abuse starting at an early age. The risk of abuse of eluxadoline is considered to be low based upon the following factors: • It is not a selective μOR but a mixed μOR and κOR agonist and δOR antagonist • Its structure is dissimilar to marketed opioids • It has limited solubility in small volumes • IV or intranasal insufflations administration is difficult and unlikely • Oral bioavailability is low (estimated at < 2%) • Eluxadoline is not an immediate precursor of another controlled substance The results of a clinical oral abuse potential study in nondependent recreational opioid users confirmed that eluxadoline was liked similarly to placebo even at doses of 1000 mg (10 times the recommended therapeutic dose) and demonstrated that pupil diameter was not affected. In an intranasal abuse potential study where higher systemic exposures were achieved and central effects were confirmed by pupillary constriction, eluxadoline was disliked compared to placebo and also associated with dysphoric feelings. A review of the AEs in the pooled Phase 2 and 3 studies revealed a low incidence of AEs potentially related to abuse. Additionally, in the Phase 3 studies, no evidence of withdrawal from eluxadoline was detected based on the SOWS. Median overall SOWS total scores were very low and similar across the 75-mg, 100-mg, and placebo treatment groups (3.0, 4.0, and 4.0, respectively) indicating no evidence of withdrawal.

Important potential risk 3: Abuse	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.4 and 5.1* *PL section: Not applicable* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Important potential risk 4: Use in patients ≥65 years of age	
Evidence for linking the risk to the medicine	Clinical studies showed an increased incidence of AEs in patients aged ≥65 years compared to those <65 years however it is not clear if the increased incidence of AEs simply reflects a poorer health status among elderly patients. A higher proportions of older patients experienced SAEs compared to the younger patients in the 75mg group (6.2% and 4.0%) that was more notable in the 100mg group (10.7% vs. 3.4).
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.2, 4.4, 4.8 and 5.2* *PL section: 2* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Important potential risk 5: CNS effects as a result of extended systemic exposure in patients with hepatic impairment or concomitant treatment with OATP1B1 inhibitors	
Evidence for linking the risk to the medicine	Studies in hepatic impaired patients or concomitant use with cyclosporine (OATP1B1 inhibitor) did not show elevated risk of CNS effects. However, data from the clinical studies suggested a trend towards an increase in CNS effects, especially dizziness and somnolence with increasing doses. CNS effects as a result of extended systemic exposure in patients with hepatic impairment or concomitant treatment with OATP1B1 inhibitors is considered an important potential risk but due to the paucity of cases, there is currently insufficient evidence to conclude that these cases are associated with eluxadoline use. Impaired mental or physical abilities can be dangerous while performing activities such as driving a car or using machines.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.3, 4.4, 4.5 and 5.2* *PL section: 2 and 4* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Missing information 1: Use in pregnancy and lactation

Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: 4.6 and 5.3* *PL section: 2* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Missing information 2: Use in patients of ethnic origin other than whites	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: Not applicable* *PL section: Not applicable* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

Missing information 3: Use in patients with impaired intestinal barriers (IBD and Coeliac Disease)	
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section: Not applicable* *PL section: Not applicable* *Treatment should be initiated and supervised by a physician experienced in diagnosis and management of GI disorders* **Additional risk minimisation measures**: *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of marketing authorisation or specific obligation of Truberzi.

II.C.2 Other studies in post-authorisation development plan

Study name	**Rationale and study objectives**
DUS	Define the compliance of health care providers to eluxadoline contraindications (i.e., history of cholecystectomy, pancreatitis or SOD) over time and the number of subjects diagnosed with pancreatitis after eluxadoline treatment.