Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eluxadoline

Proprietary Product Name: Viberzi

Sponsor: Allergan Australia Pty Ltd

May 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
5-HT3	Serotonin 3 receptor
ACM	Advisory Committee on Medicines
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARCI	Addiction Research Centre Inventory
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the plasma concentration versus time curve between time 0 and 24 hours
$AUC_{0\text{-}7h}$	Area under the plasma concentration versus time curve between time 0 and 7 hours
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve between time 0 and time t
$AUC_{0\text{-}\alpha}$	Area under the plasma concentration versus time curve between time 0 and time alpha
AUC_{last}	Area under the plasma concentration versus time curve from time 0 until last measurable concentration
BCS	Biopharmaceutics Classification System
bd	Twice a day (Latin: bis die)
BSS	Bristol Stool Score The patient-reported BSS consistency score was based on a 1 to 7 scale where 1 corresponded to a hard stool and 7 corresponded to watery diarrhoea.
CB1	Cannabinoid B1 receptor
CB2	Cannabinoid B2 receptor
CCDS	Company Core Data Sheet

Abbreviation	Meaning
CCK	Cholecystokinin
C_{max}	Peak plasma concentration
CMH	Cochran-Mantel-Haenszel Analysis
CMI	Consumer Medicines Information
CNS	Central nervous system
CYP450	Cytochrome P450
DEREK	Deductive estimate of risk from existing knowledge (analysis)
DLP	Data lock point
DOR	Delta-opioid receptor/δ-opioid receptor
ECG	Electrocardiogram
ED_{50}	Half maximal effective dose
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
F1	First filial generation
FAERS	Federal Adverse Events Reporting System
FDA	Food and Drug Administration (United States)
Fe	Fraction of dose excreted in urine
GCP	Good Clinical Practice
GD	Gestation Day
GLP	Good Laboratory Practice
IBS	Irritable bowel syndrome
IBS-c	Irritable bowel syndrome, constipation predominant
IBS-d	Irritable bowel syndrome, diarrhoea predominant
IBS-m	Irritable bowel syndrome, mixed diarrhoea and constipation symptoms

Abbreviation	Meaning
IBS-u	Irritable bowel syndrome, unspecified
ICH	International Conference on Harmonisation
IP	Intraperitoneal
IV	Intravenous/intravenously
KOL	Key Opinion Leader
KOR	Kappa-opioid receptor/k-opioid receptor
LD	Lactation Day
LFT	Liver function test
LLOQ	Lower limit of quantification
M1	Muscarinic 1 receptor
M2	Eluxadoline metabolite
MedDRA	Medical Dictionary for Regulatory Affairs
MOR	Mu-opioid receptor/μ-opioid receptor
MRHD	Maximum recommended human dose
N	Number
NMDA	N-methyl-D-aspartate receptor
NOAEL	No observable adverse effect level
OR	Opioid receptor
PI	Product Information
PIP	Paediatric Investigation Plan
PO	Orally (Latin: per os)
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous/subcutaneously
SO	Sphincter of Oddi

Abbreviation	Meaning
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
T_{max}	Time to peak plasma concentration
ULN	Upper limit of normal
US	United States (of America)
USPI	United States Prescribing Information
w/w	Weight/weight
Xu	Total amount of radioactivity excreted in urine or faeces

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Withdrawn
Date of withdrawal	24 November 2017
Date of entry onto ARTG	Not applicable
Active ingredient:	Eluxadoline
Product name:	Viberzi
Sponsor's name and address:	Allergan Australia Pty Ltd 810 Pacific Highway Gordon NSW 2072
Dose form:	Immediate release film coated tablets
Strengths:	75 mg and 100 mg
Containers:	Aluminium blister packs; plastic bottles closed with child resistant screw caps fitted with induction seal liners
Pack sizes:	28, 56 and 168 tablets plus starter pack of 8 tablets (blisters); 60 tablets (bottles)
Approved therapeutic use:	Not applicable
Route(s) of administration:	Oral (PO)
Dosage:	Not applicable
ARTG number:	Not applicable

Product background

This AusPAR describes the application by the sponsor, Allergan Australia Pty Ltd, to register a new chemical entity, eluxadoline (Viberzi), proposed with the following indications:

> *Eluxadoline (Viberzi) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d).*

2 strengths of the product were proposed as follows:

- 100 mg strength
  - The recommended dosage of Viberzi is 100 mg taken orally twice daily with food.
- 75 mg strength
  - The recommended dosage of Viberzi is 75 mg taken orally twice daily with food in patients who:

- do not have a gallbladder,
- are unable to tolerate the 100 mg dose,
- have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment,
- are receiving concomitant OATP1B1 inhibitors.

Extensive expression of opioid receptors in the gastrointestinal (GI) tract plays a key role in regulating gastrointestinal motility, secretion and visceral sensation.

Irritable bowel syndrome (IBS) is a functional GI disorder that is characterised by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics.[1] Different subtypes of IBS are classified according to predominating bowel symptoms, which include chronic or recurrent: diarrhoea (IBS-d); constipation (IBS-c); a mixture of constipation and diarrhoea (IBS-m); or unspecified (IBS-u). Common to a form of IBS is abdominal pain or discomfort that may be linked to local reflexes within the bowel.[1]

As noted in the European Medicines Agency (EMA) final IBS guideline issued 25 September 2014[2], treatment options for IBS-d are limited, with current pharmacological therapies aimed at treating the individual symptoms with the rationale of modulating intestinal motility, decreasing visceral sensitivity, or treating associated disorders, such as anxiety and/or depression. Pharmacological management of IBS worldwide includes antispasmodic agents, antidepressants including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), and, in patients with IBS-d, anti-motility agents for diarrhoea. However, none of these agents treat all of the important symptoms of IBS-d and none are indicated specifically for IBS-d, and the strength of evidence supporting their use in this condition is variable. Currently, there are no approved IBS-d medicines in the European Union. The selective serotonin 3 receptor (5-HT3) antagonist alosetron is approved for the treatment of chronic IBS-d in the United States (US), but only for women with severe IBS-d and under restricted distribution due to safety concerns. Alosetron is associated with a high incidence rate of constipation (> 20%) in IBS-d patients.

Loperamide, a peripherally restricted μ-opioid receptor (MOR) agonist is approved in the European Union (EU) and the US as an antidiarrheal; however, it shows limited effectiveness in treating the abdominal pain and global symptoms of IBS-d.[3,4,5] Thus, there is a need for new agents with favourable safety and tolerability profiles that are effective in providing sustained relief at the same time for the variety of symptoms such as abdominal pain, abdominal discomfort, diarrhoea, abdominal bloating and bowel urgency associated with IBS-d.

The beneficial effects of eluxadoline in treating IBS-d arise via local action within the GI tract, where the extensive expression of opioid receptors plays a key role in regulating GI motility, secretion, and visceral sensation.[6,7,8] Pharmacological agents with mixed MOR

[1] Drossman D. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006 Apr;130(5):1377-1390.
[2] CPMP/EWP/785/97 Rev. 1 Guideline on the evaluation of medicinal products for 4 the treatment of irritable bowel syndrome
[3] Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol Suppl. 1987;130:81-84.
[4] Lavo B, et al.. Loperamide in treatment of irritable bowel syndrome; a double-blind placebo controlled study. Scand J Gastroenterol Suppl. 1987;130:77-80.
[5] Talley N. Pharmacologic therapy for the irritable bowel syndrome. Am J Gastroenterol. 2003 Apr;98(4):750-758.
[6] Bagnol D, et al. Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. Neuroscience. 1997 Sep 8;81(2):579-591.

agonism/δ (delta) opioid receptor (DOR) antagonism possess increased analgesic potency with different GI effects as compared to pure MOR agonists.[9,10] While centrally acting mixed MOR agonist/DOR antagonist compounds have been investigated for potential analgesic advantages over pure MOR agonists, eluxadoline was developed specifically because of its very low oral bioavailability and its beneficial local GI effects. The low bioavailability of eluxadoline may reduce systemic side effects as well as the potential for abuse and dependence.

In vitro, eluxadoline reduces contractility of intestinal tissue and inhibits neurogenically mediated secretion. In vivo, eluxadoline reduces GI transit and faecal output in stressed and non-stressed mice over a wide dose-range without fully inhibiting GI transit.

Regulatory status

This is an application to register a new chemical entity in Australia.

This product was approved by the US Food and Drug Administration (FDA) on 27 May 2015.The approved indication in the US is '*Viberzi is a mu-opioid receptor agonist, indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d)*'.

Similar applications have also been approved in the EU, Canada, Iceland and Norway (see Table 1, below).

Table 1: International regulatory status

Country/Region	Submission Date	Status (Approved; Review Ongoing; Withdrawn; Rejected)
United States of America	27 June 2014	Approved 27 May 2015
European Union	1 May 2015 (Centralised Procedure)	CHMP positive opinion on 21 Jul 2016, EC Decision 19 September 2016
Iceland	1 May 2015	Approved 7 Oct 2016
Norway	1 May 2015	Approved 13 October 2016
Canada	16 November 2015	26 January 2017

[7] Bitar K, Makhlouf G. Specific opiate receptors on isolated mammalian gastric smooth muscle cells. Nature. 1982 Jun;297(5861):72-74.
[8] Dockray G. Physiology of enteric neuropeptides. In: Johnson LR. Physiology of the gastrointestinal tract. 3rd ed. New York: Raven, 1994; 169-209.
[9] Ananthan S. Opioid ligands with mixed μ/δ opioid receptor interactions: an emerging approach to novel analgesics. AAPS J. 2006 Mar;8(1):E118-E125.
[10] Dietis N, et al. Simultaneous targeting of multiple opioid receptors: a strategy to improve side-effect profile. Br J Anaesth. 2009;103(1):38–49.

II. Registration timeline

Table 2: Registration timeline for Submission PM-2016-02313-1-1

Description	Date
Submission dossier accepted and First round evaluation commenced	30 September 2016
First round evaluation completed	7 March 2017
Sponsor provides responses on questions raised in First round evaluation	4 May 2017
Second round evaluation completed	10 July 2017
Request for Advisory Committee advice and/or Delegate's Overview	4 September 2017
Sponsor's response to Delegate's Overview	19 September 2017
Advisory Committee meeting	5-6 October 2017
Date of application withdrawal	24 November 2017
Entry onto ARTG	Not applicable
Number of TGA working days from commencement of evaluation to registration decision*	213

* Statutory timeframe: 255 working days.

III. Quality findings

Introduction

In the present submission, the sponsor seeks to register immediate release film coated tablets containing eluxadoline 75 mg and 100 mg under the trade name Viberzi to be administered twice a day (bd) with food at a recommended maximum daily dose of 200 mg.

The trade name Viberzi has been accepted by the Delegate.

Drug substance (active ingredient)

Eluxadoline or 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid The absolute configuration of eluxadoline was confirmed by chemical synthesis of all 4 of the possible configurational isomers of the substance, starting with each configuration of the starting materials. The chiral purity is controlled.

The drug substance is manufactured in a 5-step synthesis.

Eluxadoline exhibits stereoisomerism due to the presence of 2 chiral centres possessing S,S configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for the active substance. Polymorph screening studies determined that Form I is the only non-solvated, crystalline form of the active substance. Form I converts to the tri-hydrate at higher humidity. The hydrated form re-converts to Form I as it loses water. No other anhydrous form has been identified.

Eluxadoline is likely to be Biopharmaceutics Classification System (BCS) Class III, (that is, high solubility, low permeability), as defined in US FDA Guidelines.

Because eluxadoline is a BCS Class III drug substance and is soluble in 0.1 N HCl, its particle size distribution was expected to have minimal clinical significance or impact on the dissolution and/or disintegration rates of the finished products.

Only one potential impurity is controlled in the drug substance. The revised limit has been accepted on the advice of the TGA's nonclinical section.

The chiral integrity of the drug substance is assured by the route of synthesis.

A number of issues relating to the quality control of the eluxadoline drug substance were raised with the applicant; all of which have been resolved.

Drug product

Both strength tablets are capsule shaped film-coated tablets. The 75 mg tablets are pale yellow to light tan in colour and are debossed with 'FX75' on one side, whilst the 100 mg tablets are pink-orange to peach in colour and are debossed with 'FX100' on one side. These will be packaged in plastic bottles with polypropylene child-resistant caps (packs of 60 tablets) and in aluminium blisters (packs of 28, 56 and 168 tablets, and a starter pack of 8 tablets).

Since eluxadoline is intended to be a locally acting drug that exerts its intended effect in the GI tract, formulation development concentrated on creating a tablet formulation that dissolved both rapidly and completely.

The suitability of the proposed dose-proportional commercial formulation was demonstrated in the development stage at pilot scale from a low of 25 mg to a high of 100 mg dosage strengths. The Phase III clinical trials (but not the Phase I and II studies) were all conducted using tablets having a formulation proportional to the commercial formulations.

The dissolution method proposed for commercial use was shown to be discriminatory by comparison of the profiles of tablets manufactured with and without disintegrants.

Since eluxadoline is a mixed μ opioid receptor agonist and δ opioid receptor antagonist, an assessment of the abuse potential was undertaken. Although the oral bioavailability is low, this did not preclude the possibility of abuse through alternative routes of administration such as injection or snorting. Four in vitro studies were therefore conducted to determine the ease and feasibility of preparing eluxadoline for such abuse., the salient points of which are summarised below:

- Although eluxadoline was not designed to possess abuse deterrent properties, it presents a unique profile of physicochemical features that may limit its abuse.
- It has limited solubility in solvents commonly used for injection.
- The bulky size of the tablets coupled with low solubility of the drug substance could also limit use by the intranasal route.

- Simulated smoking studies also indicated that the smoking route is not a viable means of administration of the active pharmaceutical ingredient (API) due to thermal decomposition during the process.
- Whilst extraction studies with highly acidic or basic solvents were successful in dissolving API in small volumes that potentially could be injected, these solvents would likely produce significant adverse effects if injected directly, thus requiring additional complex manipulations before the extracted product could be administered.
- No condition, including the combined use of strong acid, near boiling extraction temperature, and extraction of multiple ground tablets, provided any evidence that extraction could produce the necessary concentration of API that would serve as a reinforcement in humans. The maximum achievable concentration under any condition was approximately 30 mg/mL, but most extraction schemes produced considerably lower concentrations. A variety of factors were identified in these laboratory assessments that served to continually limit the concentration of the API in the extractions fluids, with the most important being the low solubility of the API in various solvents; however a number of other factors also limited its extraction, including the inhibiting effect of formulation excipients on extraction of API from ground or intact tablets, physical loss of solution during preparation for intravenous injection ('ability to syringe' studies indicated losses of 30 to 43%), instability of the API to heat, and formation of suspended particles during extraction that produced highly variable results.

Other factors limiting the abuse potential of the tablets were also addressed in the dossier:

- It has a bad flavour which would be predicted to limit intranasal or buccal/sublingual administration.
- The tablet mass (824 mg for the 100 mg tablet) potentially limits the potential for abuse by snorting crushed tablets.
- Whilst high volumes of aqueous solvents can solubilise the majority of the API (albeit not in pure form) from the tablets, production of a drug of abuse would be extremely difficult and time consuming.
- Heating (to speed the drying process) results in a baked on yellow material that cannot be manipulated to produce a powder or any solid for injection, snorting, and so on.
- Thermal decomposition eliminates the potential for smoking administration.

No degradants arising from the finished products were identified. No epimerisation of the stereogenic centres were observed during stability trials of forced degradation studies conducted on the tablets.

The stability data support a shelf life of 24 months stored below 25°C for the tablets packaged in either the bottles or the aluminium blisters proposed for Australia. A number of issues relating to the quality control of the tablets were raised with the sponsor, all of which have been resolved.

Biopharmaceutics

Neither an absolute bioavailability study nor a relative bioavailability (compared with an oral solution or suspension of defined particle size) was provided, as stipulated for a new chemical entity in Section 15.4 of Guidance 15 'Biopharmaceutic Studies' from the Australian Regulatory Guidelines for Prescription Medicines (ARGPM). However, a justification was provided for the omission, clinical and non-clinical aspects of which are acceptable.

2 food effect studies were conducted in support of the submission; Studies EDI-1002 and CPS-1009. Details of these are presented below.

Food effect study (Study EDI-1002)

The study was a single dose, randomised, 2-way crossover study for which the primary objective was to compare the pharmacokinetic profiles of eluxadoline tablets after a high fat/high calorie breakfast versus the fasted state. The secondary objective of the study was safety related. The mean results and the assessment of bioequivalence in respect of eluxadoline peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve between time 0 and time t (AUC_{0-t}) and area under the plasma concentration versus time curve between time 0 and time alpha ($AUC_{0-\alpha}$) are reproduced below.

The sponsor's 90% confidence intervals of the geometric mean ratios for each of the primary pharmacokinetic parameters did not fall within the pre-established range for bioequivalence as defined in the Study Protocol. The Study Report concludes:

- The absorption of eluxadoline (tablet formulation) was rapid under fasting conditions, with a median time to peak plasma concentration (T_{max}) value of 2 h. However, when eluxadoline was administered within 30 minutes of a high fat meal, there was a delay in reaching C_{max} with the resultant median T_{max} value being 4 h.
- The presence of food probably delays gastric emptying, thereby delaying absorption of eluxadoline.
- In general, individual C_{max} values were considerably lower for most subjects in the fed state compared with the fasted state.
- Individual area under the plasma concentration versus time curve from time 0 until last measurable concentration (AUC_{last}) values were lower for most subjects, with mean AUC_{last} being lower in the fed state than in the fasted state.

The sponsor's results were subsequently verified by the evaluator and the conclusions are accepted.

Pivotal food effect study (Study CPS-1009)

The study was a Phase I, single dose, randomised, 2-way crossover study to compare the pharmacokinetic profiles of eluxadoline tablets in the fed state after the high fat/high calorie breakfast versus the fasted state. The secondary objective of the study was safety related.

The summary of pharmacokinetic parameters for fed and fasted states is reproduced below.

The sponsor's 90% confidence intervals of the geometric mean ratios for each of the primary pharmacokinetic parameters (reproduced below) did not fall within the pre-established range for bioequivalence as defined in the Study Protocol.

The statistical analysis of the difference between median T_{max} values indicates that there was no statistically significant difference in T_{max} between the 2 treatment conditions.

The Study Report concluded:

- High fat meal conditions decreased the total and peak exposures of eluxadoline by 60% and 50%, respectively.
- There was no statistically significant difference in T_{max} between fasting and high-fat meal conditions.

The sponsor's results were confirmed by the evaluator.

Quality summary and conclusions

There are no objections to registration from a quality or biopharmaceutics perspective.

IV. Nonclinical findings

Introduction

General comments

2 US FDA reports form the basis of this evaluation. The sponsor's TGA submission also included additional studies not considered by the FDA.

Pharmacology

Primary pharmacology

The sponsor has submitted 12 studies (6 in vitro; 6 in vivo studies), of which 3 new in vitro studies were not evaluated or included in the FDA report. The studies investigated the binding affinity and activity of eluxadoline to the opioid receptor (OR). The in vitro studies demonstrated that eluxadoline could be a potent MOR agonist and DOR antagonist. Studies in mice found that eluxadoline (half maximal effective dose (ED_{50}) was approximately 40.4 mg/kg; orally (PO)) was an inhibitor of propulsive upper GI motility, but compared to loperamide (ED_{50}: approximately 2.3 mg/kg; PO), with eluxadoline being less potent and did not prevent gastric emptying. Furthermore, eluxadoline was shown to be active in reversing the hyperalgesic responses to colorectal distention (rat model of acute, zymosan-induced colitis). In isolated guinea pig ileum, eluxadoline inhibited concentration-dependent contractions. In a stressed mouse model, eluxadoline was able to normalise GI motility. 3 new in vitro studies submitted found that eluxadoline:

- Was inactive of the twitch contraction amplitude in the hamster vas deferens assay, exerting antagonist activity at the DOR;
- Exhibited weak kappa-opioid receptor (KOR) agonist activity;
- Exhibits potency and efficacy in G-protein activity and β-arrestin recruitment assays in cells that expressed only MORs.

Secondary pharmacodynamics and safety pharmacology

7 secondary pharmacodynamic studies were submitted which were all evaluated in the FDA report. The studies included investigating 50 receptor/ion channel binding screens of eluxadoline and its M2 metabolite (found in all species tested), as well as investigations on the activity of M2 at the OR. However, there was no similar metabolite found in human plasma, with only one glucuronidated metabolite identified in urine from human studies (refer to clinical report). Within the studies submitted for evaluation, the interaction of eluxadoline with receptors associated with abuse was investigated in cannabinoid B1 and B2 (CB1 and CB2); N-methyl-D-aspartate (NMDA); and nicotinic neuronal α4β2, neuronal α7, and muscle-type receptors. Overall, in vitro studies found that eluxadoline did not inhibit or stimulate these receptors associated with abuse potential, and had no significant

agonist or antagonist activity at human muscarinic 1 (M1) receptors. In vitro investigations on the activity of the M2 metabolite on receptor binding indicated that M2 had lower affinity to bind to DOR and MOR than eluxadoline. An in vivo von Frey study in rats induced with pancreatitis was conducted since opiates have a potential to cause spasm of the sphincter of Oddi and the study investigated whether eluxadoline exacerbated the pain associated with pancreatitis. The study found that eluxadoline did not alter the response rate to von Frey stimulation compared to control observations.

17 safety pharmacology studies were submitted and 14 were evaluated by the FDA. In vivo studies following PO administration found that eluxadoline was very well tolerated in animals tested, with observed effects limited to the GI tract. Systemic administration of eluxadoline to animals elicited treatment-related effects consistent with an opioid. Intravenous (IV) infusion of eluxadoline in guinea pigs and dogs showed cardio-haemodynamic effects, which were very pronounced in conscious dogs, but coincided with behavioural findings. A study administering IV eluxadoline (≤ 0.143 mg/kg) in anaesthetised dogs, found no notable effects, with higher exposures observing a slight tendency for aortic diastolic and systolic blood pressure decreases. Another study observed a decrease in arterial blood pressure not associated with an effect on heart rate following subcutaneously (SC) administration (5 to 30 mg/kg from 30 to 300 minutes post-dose) in conscious telemetered monkeys. Overall, studies found that eluxadoline was not a significant agonist or antagonist of off-target receptors and did not elicit notable electrophysiological effects in cardiovascular safety studies (≤ 10 μM).

The 3 new central nervous system (CNS) studies submitted found that eluxadoline:

1. Mice lacked MOR agonist-like withdrawal effects post-dose, indicating that physical dependence does not occur after administration (single PO dose, 300 mg/kg);
2. Rats demonstrated no treatment-related neurobehavioral or clinical signs (single PO dose ≤ 500 mg/kg; hypoactivity at ≥ 1000 mg/kg);
3. Effects observed in Rhesus monkey suggest the likelihood of shared behavioural effects with morphine-like (μ-opioid) agonists, with potentially toxic/lethal effects when IV administered.

Pharmacokinetics

Summary of pharmacokinetics

Absorption

Single oral administration of eluxadoline to mice, rats, and cynomolgus monkeys showed moderate to rapid absorption (T_{max} 0.5 to 7.75 h) with low bioavailability (≤ 0.83%). Studies in animals showed that eluxadoline had a low oral systemic exposure possibly due to limited absorption from the GI tract and a significant first-pass effect.

Distribution

Studies evaluated in the FDA report found that eluxadoline showed moderate plasma protein binding in all species tested (68.5% (dog) to 87.8% (mice) which was similar to results obtained by analysis of plasma samples from humans (82%). The one new distribution study submitted showed that eluxadoline had negligible partitioning into red blood cells. GI tract tissues of rats showed the highest exposure to total radioactivity following PO or SC administration with ^{14}C-eluxadoline, with the greatest proportion of unchanged eluxadoline found in the GI contents. A study in male pigmented Long Evans rats using whole-body autoradiography showed that a single PO dose (50 mg/kg) of eluxadoline was poorly absorbed and hence, was not well distributed to the tissues.

Distribution in blood, plasma and other tissues showed that maximum concentrations were reached at 3 h, with total radioactivity declining rapidly (≤ lower limit of quantification (LLOQ)) by 24 h post-dose. For non-pigmented tissues, the stomach and urinary bladder tissue showed Area under the plasma concentration versus time curve between time 0 and 7 hours (AUC_{0-7h}) values that were ≥ 10 times higher than blood, with adrenal gland, pancreas, kidney cortex, kidney medulla, liver, spleen found to have 2 to 8 times higher repetition time than blood. Pregnant rats administered SC eluxadoline showed, in non-procreative tissues, the highest AUC_{0-7h} values of total radioactivity higher than blood were in the kidney cortex (4 x), kidney medulla (3 x) and liver (2 x). The highest tissue-to-blood AUC_{0-7h} ratios in procreative tissues were noted in the uterine epithelium and lumen (1.6 x).

Metabolism

In vitro metabolism studies using human hepatocytes identified no metabolites. The major metabolite identified in human intestinal microsomal incubations was M11. Two new bioanalytical studies were submitted analysing plasma from rats and monkeys following administration of eluxadoline. The studies found that S,S-eluxadoline was not bio-transformed into S,R-eluxadoline at quantifiable levels (< 0.500 ng/mL for S,S-eluxadoline and < 0.100 ng/mL S,R-eluxadoline) in either species.

Excretion

In vivo studies showed that most of the eluxadoline administered was excreted in faeces unchanged, with the metabolite M11 found to be excreted in the urine of rat, primates and humans, as well as in plasma samples from monkeys. Rats PO or SC administered eluxadoline showed rapid primary excretion in faeces (PO: 97.1%; SC: 90.1%) and urine (PO: 0.54%; SC: 7.29%).

Following PO administration in rats, eluxadoline is excreted in the milk of lactating rats in a less than 1:1 ratio compared to plasma.

Pharmacokinetic drug interactions

The FDA report evaluated studies profiling cytochrome P450 (CYP450) which show that eluxadoline, at clinically relevant concentrations, has low potential for drug-drug interactions based on in vitro results indicating a lack of potential for reversible CYP inhibition (for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP2D6)[11], and/or lack of induction (for CYP1A2, CYP3A4, CYP2C9, CYP2C19), and it also did not induce CYP mRNAs in cryopreserved hepatocytes (≤ 30 μM). A study using the major human CYP450 isozymes showed that eluxadoline had some potential for the mechanism-based inactivation of CYP3A4. In vitro results suggest that eluxadoline has very low passive permeability and does not significantly cross membranes when analysed in drug efflux transporter assays using Madin-Darby canine kidney II (MDCKII) cells.

Eluxadoline was shown to be transported by organic anion transporter 3 (OAT3), organic anion transporting polypeptide 1B1 (OATP1B1) and bile salt export pump (BSEP) at the highest concentration tested (400 ng/mL), but not transported by OAT1, organic cation transporters 1 and 2 (OCT1 and OCT2), OATP1B3, multi-drug resistance 1 (P-gp) or breast cancer resistance protein (BCRP). Furthermore, multi-drug transporter 2 (MRP2) dependent vesicular accumulation of eluxadoline was observed at all concentrations (4 to 400 ng/mL) tested, suggesting that eluxadoline may be a substrate of MRP2. In vitro, eluxadoline (400 ng/mL) did not significantly inhibit BCRP, BSEP, MRP2, OCT1, OCT2, OAT1, OAT3 or OATP1B3 mediated transport of probe substrates, but showed transport

[11] In human liver microsomes, CYP2E1 was moderately inhibited at high eluxadoline concentrations (Study FK5873).

inhibition of probe substrates of OATP1B1 (32.6%) and P-gp (6.25%) in comparison to control.

In summary, eluxadoline at clinical concentrations may have potential for drug interactions through its properties of being a substrate and an inhibitor of OATP1B1 and a substrate of MRP2.

Toxicology

Acute toxicity

The sponsor did not submit any new nonclinical acute toxicity studies for evaluation. The FDA report evaluates and discusses an in vivo study in mice which found that PO administration of 100 mg/kg of eluxadoline produced no treatment-related clinical signs or mortality, and intraperitoneal (IP) administration (≤ 500 mg/kg) of eluxadoline was well tolerated. However, IP administered eluxadoline ≥ 125 mg/kg produced central nervous system (CNS) signs including decreased activity and increased activity with or without circling (≥ 250 mg/kg).

Furthermore, an in vivo study in rats showed decreased faeces in females when administered 2000 mg/kg of eluxadoline PO. Mortality was observed following IP administration (males: ≥ 125 mg/kg; females: 250 mg/kg), with clinical observations noted at all doses, as well as decreased faeces (31.25 mg/kg; ≥ 125 mg/kg), ataxia, decreased activity, and mydriasis (≥ 62.5 mg/kg), and decreases in the depth and rate of respiration (≥ 125 mg/kg).

Repeat-dose toxicity

16 repeat-dose toxicity studies were submitted, which included repeat PO dose studies in mice (non-pivotal: 28 days; and 3 months), rats (5 and 28 days; 3 and 6 months) and monkeys (5, 7 and 28 days; 3, and 9 months) and 14 studies were evaluated by the FDA. 2 new repeat-dose toxicity studies were submitted which included one rat (PO administration; 28 day) and one monkey (IV administration; 7 day) study.

Rats

The investigative tolerance study evaluated in the FDA report found that dose escalating administration of eluxadoline PO (≤ 500 mg/kg) or SC (≤ 75 mg/kg) for 5 consecutive days produced reduced faeces 24 h post-dose with lower mean triglycerides, food filled stomachs and firm faecal matter in the colon. The study showed no meaningful difference in gene expression in the liver tissue after PO (500 mg/kg) or SC (525 or 75 mg/kg) routes, with no induction in CYP mRNAs observed in human hepatocytes (≤ 30 μM).

Intravenously administering eluxadoline in rats for 14 consecutive days (≤ 20 mg/kg/day) was evaluated in the FDA report which showed that eluxadoline was well tolerated with no treatment- related effects on survival, ophthalmology, haematology, coagulation, clinical chemistry, urinalysis parameters, or macroscopic and microscopic pathology. Drug class clinical findings were observed at higher concentrations (10 to 20 mg/kg/day) with administration of eluxadoline showing a lack of any adverse related effects. One new 28 day study in rats showed that doses of ≤ 1000 mg/kg/day PO or ≤ 1000/5 mg/kg/day PO/SC) were well tolerated during the dosing period with slight irritation at the SC injection site, with slight decreases in body weight and food consumption at the higher doses, which were not considered to be adverse.

A 13-week study in rats evaluated in the FDA report found that eluxadoline was well tolerated when orally administered (≤ 1000 mg/kg; No observable adverse effect level (NOAEL)), as well as when administered in a combination of oral and SC administrations

(≤ 200/5 mg/kg; NOAEL), with slight local irritation at the SC injection site. Furthermore, rats administered eluxadoline PO daily for 26 weeks showed it was well tolerated and found no test article-related effects on mortality, body weight, food consumption, ophthalmological findings, clinical observations, haematology, coagulation, clinical chemistry, or urinalysis parameters, or in macroscopic, organ weight, and microscopic evaluations in either sex.

Monkeys

One new 7 day study in cynomolgus monkeys IV administered eluxadoline showed no observable treatment related clinical signs (≤ 5 mg/kg/day). The highest dose, 40 then 30 mg/kg/day, (dose reduced from 40 to 30 on Day 2) was associated with clinical signs in both sexes (decreased activity, ataxia, eyelids partially/completely closed, pupil constriction, inappetence and difficult/shallow breathing), with no treatment-related changes in clinical pathology and no treatment-related macroscopic findings observed post-mortem. A study evaluated in the FDA report IV administered eluxadoline in cynomolgus monkeys for 14 consecutive days (≤ 20 mg/kg/day) found no treatment-related effects on survival, body weights, ophthalmology, haematology, coagulation, clinical chemistry, urinalysis, macroscopic, organ weights or microscopic evaluations.

Alterations in electrocardiogram (ECG) parameters were observed in treated animals including a reversible slowing of the heart rate in all doses post-dose but were not considered adverse.

Additionally, a 3 month cynomolgus monkey study evaluated in the FDA report found that eluxadoline was well tolerated when administered via PO (≤ 200 mg/kg/day) or PO/SC (≤ 200/25 mg/kg/day). Study results showed no treatment–related clinical signs or changes in food consumption, body weight, clinical pathology findings, ophthalmology findings or electrocardiogram parameters. Furthermore, the 39 week study using cynomolgus monkeys showed that PO eluxadoline (≤ 200 mg/kg/day) had no adverse treatment-related effects on mortality, clinical findings, body weight, ophthalmological findings, urinalysis parameters, electrocardiographic examinations or any macro- and microscopic findings in either gender.

Relative exposure

The 13 week study in rats achieved very high systemic levels with SC boosts (200/5 mg/kg; C_{max}: 654 ng/mL; area under the plasma concentration versus time curve between time 0 and 24 hours (AUC_{0-24h}): 3495 ng.h/mL) which were greater than 216 and 74 fold the values (C_{max}: 3.03 ng/mL and AUC_{0-24h}: 47.08 ng.h/mL respectively) of the human therapeutic dose (100 mg bd; Clinical Study CPS-1008) (see Table 3, below). The 9 month study in cynomolgus monkeys achieved adequate levels of eluxadoline exposure at the highest concentration used compared to the maximal human therapeutic dose.

Table 3: Relative exposure in pivotal repeat-dose toxicity and carcinogenicity studies

Species	Study duration (Study ID)	Dose (mg/kg/day PO/SC)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
Mouse (CD-1)	3 months (Study 1808-006)	500	142.9	3.0
		1000	228.6	4.9
		1500	252.7	5.4
	2 years (Carcinogenicity; Study 1808-009)	150	68.9	1.5
		500	129.8	2.8
		1500	325.1	6.9

Species	Study duration (Study ID)	Dose (mg/kg/day PO/SC)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
Rat (SD)	3 months (Study TOX8677)	200/0	95.6	2.0
		200/5	3495.0	74
		1000/0	425.5	9.0
	2 years (Carcinogenicity; Study 1808-008)	150	360.8	7.7
		500	620.4	13.2
		1500	872.5	18.5
Monkey (cynomolgus)	9 months (Study 1808-004)	50	126.2	2.7
		100	189.3	4.0
		200	328.1	7.0
Human (healthy volunteers)	Steady state (Study EDI-1001) (Study CPS-1008)	100 mg (100 mg bd)	23.54[a] (47.08)[a]	–

= animal: human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling occasion;
a) Derived from results from clinical Study CPS-1008 (Day 1: 23.54 ng.h/mL; Healthy volunteers; n = 59), following a 100 mg dose; for the MRHD (200 mg/day), $2 \times AUC_{0-\infty}$ = 47.08 ng.h/mL.

Major toxicities

There were no major toxicities noted when assessing the studies that have already been evaluated in the FDA report, as well as the new studies submitted. Studies showed that eluxadoline was well tolerated in mice, rats and monkeys at exposures ≥ 10 fold greater than the anticipated clinical exposure at the maximum recommended human dose (MRHD). Administration via SC or IV, in all animals tested, revealed slight to moderate local irritation at the injection site which may be due to either the vehicle or eluxadoline. However, since the proposed clinical administration route is oral, these observations at the injection site have little relevance for the current submission. Observations of slight decreases in body weight and food consumption at the high doses of eluxadoline (rats: PO and PO/SC administration), as well as alterations in ECG parameters (monkeys: PO administration) were not considered to be adverse and most observations were reversible after a designated recovery period. Overall, eluxadoline was well tolerated in the animals used for experimentation with minimal and reversible treatment-related observations.

Genotoxicity

No new genotoxicity studies were submitted. 5 genotoxicity studies (4 in vitro; 1 in vivo) were evaluated in the FDA report which showed that eluxadoline was not genotoxic in the in vitro bacterial/microsomal assay, the mouse lymphoma assay, human peripheral lymphocyte assay or in the in vivo mouse bone marrow micronucleus assay. A DEREK (deductive estimate of risk from existing knowledge) analysis showed no potential genotoxic impurities in the synthesis of eluxadoline.

Carcinogenicity

No new carcinogenicity studies were submitted. Two 104 week studies were evaluated in the FDA report and were in accordance to International Conference on Harmonisation (ICH) Guidelines S1, S1A, S1B and S1C (R2).[12]

Mice were PO administered 150, 500 and 1500 mg/kg/day of eluxadoline daily for 104 weeks with no treatment-related mortalities throughout the experimental period, and no adverse clinical or mass findings related to treatment. Furthermore, treatment with eluxadoline showed no significant effects on survival, body weights, food consumption, ophthalmology, haematology, gross pathology, or histopathology, indicating that daily PO administration of eluxadoline had no oncogenic effect.

Similarly, a study of rats and daily PO administered 150, 500 and 1500 mg/kg/day eluxadoline for 104 weeks showed no significant adverse treatment-related clinical or mass findings, or effects on survival, body weights, food consumption, ophthalmology, haematology, gross pathology or histopathology. Administration of eluxadoline in rats did not produce any statistically significant increase in the incidence of tumour progression or any gender differentiation.

Overall, the 2 carcinogenicity studies evaluated by the FDA provided no evidence of carcinogenic potential.

Reproductive toxicity

6 reproductive toxicity studies were submitted with 4 evaluated in the FDA report (fertility: 1 rat study; embryofetal: 1 rat and 1 rabbit study; postnatal development: 1 rat study). 2 new non-pivotal embryofetal development studies were submitted, 1 in rats and 1 using rabbits.

Fertility

The rat study evaluated in the FDA report administered eluxadoline (≤ 1000 mg/kg/day) for 28 days (males) or 14 days (females) prior to pairing to both sexes and through to Gestation Day (GD) 7 in females.

Results showed no significant treatment related findings on any of the parameters measured in both sexes. Toxicokinetic measurements were not conducted in this study.

The study indicates that treatment with eluxadoline in rats has no significant effects on fertility.

Embryofetal development

A new dose-ranging rat study investigating embryofetal development which daily administered eluxadoline to dams (GD 6 to GD 7; PO: ≤ 1000 mg/kg/day; PO/SC: ≤ 1000/5 mg/kg/day) found that there was considerable inter- and intragroup variation with maternal body weight gain, with the corrected mean maternal weight gain found to be significantly lower in the groups receiving the higher doses compared to control. Furthermore, dams administered eluxadoline had reduced food consumption compared to control with no dose related pattern observed. Administration of eluxadoline to dams had no observed effects on litter values or fetal observations. The FDA report evaluated a study investigating rats administered eluxadoline (PO: ≤ 1000 mg/kg/day; PO/SC: 1000/5 mg/kg/day) during GD 6 to GD 7. Results showed no significant treatment related on parameters measured, except for an increase in the incidence of the skeletal variant 'wavy ribs' in fetuses of dams administered eluxadoline. However, the skeletal

[12] ICH Harmonised Tripartite Guidelines; S1: Rodent Carcinogenicity Studies for Human Pharmaceuticals; S1A: Need for Carcinogenicity Studies of Pharmaceuticals; S1B: Testing for Carcinogenicity of Pharmaceuticals; and S1C (R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals.

variant observation in fetuses did not persist postnatally and was considered to be a non-specific response unrelated to treatment.

A new dose ranging study was submitted which administered eluxadoline (PO: ≤ 1000 mg/kg/day; PO/SC: ≤ 1000/5 mg/kg/day) to rabbits on GD 6 to GD 19. The study showed that maternal body weight gain was variable between groups with most animals exhibiting reduced faecal output. The dams administered eluxadoline during gestation showed no significant effects on litter values or fetal observations. Another study in pregnant rabbits daily administered eluxadoline (GD 6 to GD 19; PO: ≤ 1000 mg/kg/day; PO/SC: 1000/5 mg/kg/day) evaluated by the FDA, found no significant treatment-related effects on any of the parameters examined, which included fetal parameters. However, the study showed an increase in the incidence of additional ribs and lumbar vertebrae (PO: 300 mg/kg/day; SC: 1000/5 mg/kg/day) which was considered to be related to maternal toxicity.

Overall, the studies indicate that treatment with eluxadoline in rats or rabbits has no significant effects on embryofetal development.

Pre/postnatal development

The sponsor conducted one study investigating pre/postnatal development in rats administered 100, 300 and 1000 mg/kg/day PO (GD 6 to Lacation Day (LD) 20), which was discussed in the FDA report. Administration of eluxadoline (≤ 1000 mg/kg/day) showed no significant treatment-related effects on survival or any of the parameters measured in parental females. Similarly, no treatment-related effects were observed from parturition, first filial generation (F1) litter size data, and F1 pups pre- or post-weaning. Macroscopic evaluations of the parental females or F1 animals showed no significant treatment-related effects. Eluxadoline was found to be excreted in the milk of the lactating rats at all doses, at concentrations (LD 12) of 2.78, 5.49 and 44 ng/mL, respectively. Toxicokinetic measurements were not conducted in this study.

Overall, administration of eluxadoline to parental females indicates no significant treatment-related effects on F1 pups.

Relative exposure

Table 4: Relative exposure in pivotal reproductive toxicity studies

Species	Study (Study ID)	Dose (mg/kg/day PO/SC)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
Rat (SD)	Embryofetal development (Study TOX8398)	100	43.9	0.9
		300	71.8	1.5
		1000/5	1230.0	26
Rabbit (NZW)	Embryofetal development (Study TOX8376)	100	124.0	2.6
		300	369.0	7.8
		1000/5	2750.0	58
Human (healthy volunteers)	Steady state (Study EDI-1001) (Study CPS-1008)	100 mg (100 mg bd)	23.54[a] (47.08)[a]	

= animal: human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling occasion;
a) Derived from results from Clinical Study: (Day 1: 23.54 ng.h/mL; Healthy volunteers; n = 59), following a 100 mg dose; for the MRHD (200 mg/day), 2 × $AUC_{0-\infty}$ = 47.08 ng.h/mL (from sponsor's response).

Pregnancy classification

The proposed pregnancy classification is Pregnancy Category B1.[13] The proposed pregnancy category is appropriate based on the animal findings.

Juvenile studies

2 juvenile animal studies were submitted (≤ 4 weeks in rats) with the 4 week study evaluated by the FDA. A new, non-pivotal 2 week study using juvenile rats was submitted and found that daily PO administration of eluxadoline had no effects in any of the parameters examined.

Administration of eluxadoline to juvenile animals achieved moderate systemic levels ($AUC_{0\text{-}last}$: approximately 260 ng.h/mL) with the margin greater than 10 fold of the human therapeutic dose (100 mg bd; $AUC_{0\text{-}24h}$: 22.8 ng.h/mL).

The 4 weeks study evaluated in the FDA report similarly found no treatment-related effects on mortality, clinical observations, body weights, Functional Observational Battery evaluations, haematology, coagulation, clinical chemistry, or urinalysis parameters, or in organ weights, macroscopic and microscopic evaluations, and bone length measurements in either sex with only minor treatment-related changes in food consumption for both sexes. No gender based differences were observed with the toxicokinetic parameters calculated (Days 1, 28). The increase in dose administered (500 to 1500 mg/kg/day; Days 1, 28) was proportional to the increase in $AUC_{0\text{-}24}$ and C_{max} values calculated with the combined mean T_{max} (0.25 to 12.10 h) not varying with dose or duration of treatment.

Overall, the 2 studies submitted showed that daily administration of eluxadoline of ≤ 4 weeks had no statistically significant treatment-related effects on juvenile animals.

Phototoxicity

One phototoxicity study was submitted and evaluated in the FDA report. A neutral red uptake phototoxicity assay of eluxadoline was conducted in Balb/c 3T3 mouse fibroblasts. The study showed that eluxadoline (1% dimethyl sulfoxide in Dulbecco's phosphate buffered saline) had no treatment-related cytotoxicity or phototoxicity.

All OECD 432 recommended cell survival;[14] OD540 criteria;[15] and promethazine cytotoxicity and phototoxicity criteria were met according to testing facility historical control data.

Other toxicity studies

2 further toxicity studies were submitted by the sponsor, which were evaluated in the FDA report. One study topically-administered eluxadoline to the auricular lymph nodes of CBA/J mice once daily for 4 consecutive days. The study recorded mortality, abnormalities, as well as any signs of pain or distress. Overall, results found that eluxadoline had no significant treatment- related clinical observations and was not a contact sensitiser. An in vitro bovine corneal opacity-permeability assay assessed the ocular irritation potential of eluxadoline using isolated bovine corneas, found no treatment-related increase in corneal opacity and no relevant increase in permeability. Overall, the 20% (weight/weight (w/w)) formulation of eluxadoline used in this study was classified as a non-eye irritant.

[13] Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[14] OECD 432 Guideline for testing of chemicals. In vitro testing 3T3 NRU phototoxicity test
[15] Optical Density at 540 nm

In conclusion, based on the two studies submitted, eluxadoline is shown not to be a contact sensitiser or eye irritant.

Paediatric use

Eluxadoline is not proposed for paediatric use.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of a pharmaceutical.[16] The overall quality of the nonclinical dossier was high, and all pivotal safety-related studies were Good Laboratory Practice (GLP) compliant.
- In vitro studies indicated that eluxadoline was a potent MOR agonist and DOR antagonist, an inhibitor of propulsive upper GI motility and did not prevent gastric emptying. In vivo, eluxadoline was active in reversing the hyperalgesic responses to colorectal distention, inhibited concentration-dependent contractions and could normalise GI motility. The nonclinical pharmacology studies submitted support the proposed clinical indication.
- In vitro pharmacology studies found that eluxadoline did not inhibit or stimulate receptors associated with abuse potential, and showed no significant agonist or antagonist activity at human M1 receptors. In vivo studies showed that eluxadoline did not alter the response rate to von Frey stimulation compared to control observations.
- In vivo safety pharmacology studies found that eluxadoline was very well tolerated in animals tested, with observed effects mainly limited to the GI tract. Systemic administration of eluxadoline to animals elicited treatment related effects consistent with an opioid. IV infusion of eluxadoline in guinea pigs and dogs showed cardio-haemodynamic effects, which were very pronounced in conscious dogs, but coincided with behavioural findings. IV administration to anesthetised dogs showed no notable effects, with higher exposures showing a slight tendency for aortic diastolic and systolic blood pressure decreases. In vivo studies found that eluxadoline was not a significant agonist or antagonist at off-target receptors and did not elicit notable electrophysiological effects in cardiovascular safety studies. Furthermore, eluxadoline lacked μOR agonist like withdrawal effects post-dose in mice, indicating that physical dependence does not occur after PO administration. No treatment related neurobehavioral or clinical signs were observed after PO administration in rats and effects in monkeys after IV administration suggest the likelihood of shared behavioural effects with morphine-like (MOR) agonists.
- Pharmacokinetics: In vivo, eluxadoline had a low oral systemic exposure, likely due to limited absorption from the GI tract and a significant first-pass effect. Eluxadoline had moderate plasma protein binding in all species tested, including humans. In vitro metabolism studies using human hepatocytes identified no significant metabolites with one metabolite identified in human intestinal microsomal incubations being M11. In vivo, eluxadoline was found to be primarily excreted in faeces and urine, with M11 excreted in the urine of rat, primates and humans, as well as present in monkey plasma samples. Eluxadoline was shown to be excreted in the milk of lactating rats in a less than 1:1 ratio compared to plasma.

[16] CPMP/ICH/286/95 ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

- Eluxadoline has low potential for drug-drug interaction based on CYP inhibition and/or induction. In vitro results suggest that eluxadoline has very low passive permeability and does not significantly cross membranes when analysed in drug efflux transporter assays using MDCKII cells. Eluxadoline was shown to be transported by OAT3, OATP1B1 and BSEP, but not transported by OAT1, OCT1, OCT2, OATP1B3, P-gp or BCR, with studies showing that eluxadoline is a substrate of MRP2. In vitro, eluxadoline did not significantly inhibit BCRP-, BSEP-, MRP2-, OCT1-, OCT2-, OAT1-, OAT3 or OATP1B3 mediated transport of probe substrates but showed transport inhibition of probe substrates of OATP1B1 and P-gp.
- Administration (PO, intraperitoneal (IP)) of eluxadoline in mice was well tolerated and produced few treatment related clinical signs and no mortality. IP administration produced CNS signs including decreased activity and increased activity with or without circling. Administration (PO) elicited decreased faeces in female rats and some rat mortality (IP) was observed. Clinical observations were noted at all doses and administration routes, as well as decreased faeces, ataxia, decreased activity, mydriasis, decreases in the depth and rate of respiration.
- Repeat-dose PO toxicity studies were conducted in mice (≤ 3 months), rats (≤ 3 months) and cynomolgus monkeys (≤ 9 months). No major toxicities were observed with minimal and reversible treatment related observations. Eluxadoline was well tolerated in all animals tested at systemic (AUC) exposures ≥ 10 fold greater than that at the MRHD.
- Eluxadoline was not genotoxic in the in vitro bacterial/microsomal assay, the mouse lymphoma assay, human peripheral lymphocyte assay or in the in vivo mouse bone marrow micronucleus assay. A DEREK analysis showed no potential genotoxic impurities in the synthesis of eluxadoline.
- There was no evidence for carcinogenicity in 2 in vivo 2 year PO carcinogenicity studies in mice and rats.
- In vivo, eluxadoline was found not to have any effect on the fertility of rats. Embryofetal development studies in rats and rabbits found that administration of eluxadoline to dams had no observed effects on litter values or fetal observations. A pre/postnatal development study PO administering eluxadoline to rats showed no significant effect on survival or any of the parameters measured in parental females, or on parturition, F1 litter size data, and F1 pups pre- or post-weaning. Exposures (achieved or estimated) in the reproductive toxicity studies were adequate.
- Daily administration of eluxadoline of ≤ 4 weeks had no statistically significant treatment related effects on juvenile rats. A neutral red uptake phototoxicity assay of eluxadoline was conducted in Balb/c 3T3 mouse fibroblasts and found no treatment-related cytotoxicity or phototoxicity.
- The proposed specification limits for impurities and residual solvents in the drug substance have been qualified/are acceptable.

Nonclinical Conclusions and recommendation

- The nonclinical dossier had no major deficiencies.
- Primary pharmacology in vitro studies showed that eluxadoline was a potent MOR agonist and DOR antagonist, an inhibitor of propulsive upper GI motility and did not prevent gastric emptying. Overall, the in vitro and in vivo nonclinical studies submitted support the drug's use for the proposed indication.

- Secondary pharmacodynamics and safety pharmacology studies indicate that eluxadoline does not inhibit or stimulate receptors associated with abuse potential. Overall, based on the nonclinical studies submitted, there are no clinically relevant hazards identified.
- Repeat-dose toxicity studies by the oral route showed no major toxicities with minimal and reversible treatment-related observations. Based on the nonclinical studies submitted, there are no clinically relevant effects which may be expected in patients.
- Eluxadoline is not considered to pose a genotoxic or carcinogenic hazard.
- The proposed pregnancy Category is B1, which is appropriate based on the animal findings.[13]
- There are no nonclinical objections to registration.
- Amendments to the draft PI were also recommended to the Delegate.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Pharmacological agents with mixed MOR agonism/DOR antagonism possess increased analgesic potency with different GI effects as compared to pure MOR agonists. The low bioavailability of eluxadoline may reduce systemic side effects as well as the potential for abuse and dependence.

In vitro, eluxadoline reduces contractility of intestinal tissue and inhibits neurogenically mediated secretion. In vivo, eluxadoline reduces GI transit and faecal output in stressed and non-stressed mice over a wide dose-range without fully inhibiting GI transit.

The sponsor here argues for this being a different class from loperamide being both MOR agonist/DOR antagonist however in relation to treatment related adverse events (AEs) the sponsor only considers selected AEs based on known class effects of MOR agonists and opioids.

Guidance

- CPMP/EWP/785/97 Rev. 1: Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome; effective: 25 May 2015.
- 15.3 Medicines that do not require Biopharmaceutic Data: 'We do not require biopharmaceutic data or a justification for not providing this data. Note: A study or justification may be required if there is doubt as to whether absorption occurs.' pp. 127-132 of Rules 1998 (3C)-3CC6a Clinical Investigation of Medicinal Products for Long-Term Use Replaces: pp. 163-165 of Rules 1989.
- CHMP/ICH/2/04 ICH Topic E14: Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.
- CPMP/EWP/560/95/Rev. 1 Corr.: Guideline on the Investigation of Drug Interactions Replaces: CPMP/EWP/560/95 (Adopted by TGA 19 April 2001); and EMEA/CHMP/EWP/297931/2008: Concept Paper on this topic.

- CPMP/EWP/908/99: Points to Consider on Multiplicity Issues in Clinical Trials.
- CPMP/ICH/363/96 ICH Topic E9: Note for Guidance on Statistical Principles for Clinical Trials.
- CPMP/EWP/2339/02: Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Bioavailability Study Reports:
  - Study CPS-1009: A Phase I, open label, single dose crossover study to determine the effects of a high-fat meal on the pharmacokinetics of eluxadoline in healthy normal volunteers.
  - Study EDl-1002: An open label, randomised study to compare the pharmacokinetic profiles of eluxadoline in the fed state after the high fat/high calorie breakfast versus the fasted state following the oral administration of a single 500 mg dose in tablet form to healthy adult subjects.
- Metabolism:
  - Study FK6533: In vivo metabolism of eluxadoline in humans.
  - Study FK5826: In vitro metabolism of eluxadoline in cryopreserved rat, dog, monkey and human hepatocytes.
- Healthy subject pharmacokinetic and initial tolerability Study Reports:
  - Study EDl-1001: A double blind, placebo controlled, randomised, single and multiple ascending dose study to investigate the safety, tolerability and pharmacokinetics of eluxadoline.
  - Study EDl-1003: A single centre study to evaluate the mass balance and metabolic disposition of eluxadoline in healthy male subjects.
- Intrinsic factor pharmacokinetic Study Reports:
  - Study CPS-1005: An open label evaluation of the single dose pharmacokinetics of eluxadoline in subjects with and without hepatic impairment (Study meta-anal-intrins): a meta-analysis of pooled Phase I pharmacokinetics by intrinsic factors: gender, age, race, and BMI.
- Extrinsic factor pharmacokinetic Study Reports:
  - Study CPS-1007: An open label study to evaluate the pharmacokinetics and pharmacodynamics of an oral contraceptive containing norethindrone and ethinyl estradiol when co-administered with eluxadoline in healthy adult female subjects.
  - Study CPS-1011: A Phase I, open label, single dose crossover study to determine the effects of cyclosporine and probenecid on the pharmacokinetics of eluxadoline in healthy normal volunteers.
  - Study CPS-1012: An open label, crossover study to determine the effects of multiple doses of eluxadoline on the pharmacokinetics of a single dose of rosuvastatin in healthy normal volunteers.
- Drug interactions in vitro:

  - Study FK5731: The potential effects of eluxadoline in the induction of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 cryopreserved human hepatocytes.
  - Study FK5873: An in vitro study of the potential of eluxadoline to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 CYP2E1 and CYP3A4.
- Reports of human pharmacodynamic studies:
  - Healthy subject pharmacodynamic and pharmacokinetic/pharmacodynamic Study Reports.
  - Study CPS-1006: A randomised, double blind, placebo and active controlled study to evaluate the relative abuse potential and safety of orally administered eluxadoline in non-dependent recreational opioid users.
  - Study CPS-1008: A randomised, evaluator blinded, placebo and positive controlled 4 period crossover study to evaluate the effect of single, oral doses of eluxadoline on cardiac repolarisation in healthy male and female adult subjects.
  - Study CPS-1010: A randomised, blinded, placebo and active-controlled study to evaluate the relative abuse potential and safety of intra-nasally administered eluxadoline in non-dependent recreational opioid users.
- Reports of efficacy and safety studies:
  - Study Reports of controlled clinical studies pertinent to the claimed indication
  - Study IBS-2001: A randomised, double blind, placebo controlled, parallel group, dose-ranging, multicentre study to evaluate the efficacy, safety, and tolerability of eluxadoline in the treatment of patients with irritable bowel syndrome with diarrhoea.
  - Study IBS-3001: A randomised, double blind, placebo controlled, Phase III study to evaluate the efficacy safely, and tolerability of eluxadoline in the treatment of patients with diarrhoea-predominant irritable bowel syndrome.
  - Study IBS-3002. A randomised, double blind, placebo controlled Phase III study to evaluate the efficacy safety, and tolerability of eluxadoline in the treatment in patients with diarrhoea predominant irritable bowel syndrome.
- Reports of analyses of data from more than one study:
  - Hepatobiliary and pancreatitis Adjudication Committee Summary of Findings
  - Integrated Summary of Efficacy
  - Integrated Summary of Safety
- Meta-analysis of pooled Phase I eluxadoline adverse events by mean systemic exposure
- Literature References

Paediatric data

The EMA Paediatric Committee agreed to grant a waiver for paediatric population from birth to less than 6 years as well as a deferral for paediatric population above 6 years.

The FDA in addition to the 2 clinical studies approved in the Paediatric Investigation Plan (PIP), requested an open label extension safety study.

Good clinical practice

All clinical trials were conducted in compliance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Studies providing pharmacokinetic information are listed in Table 5, below.

Table 5: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK (single dose)	CPS-1009	
		EDl-1002	
		EDl-1001	
	General PK (multi-dose)	EDl-1001	*
	Mass Balance Study	EDl-1003	*
	Food effect	CPS-1009	*
		EDl-1002	*
PK in special populations	Target population § (multi-dose)	IBS-2001	
	Hepatic impairment	CPS-1005	*
	Abuse potential	CPS-1006	*
Genetic/gender related PK	Males versus females	EDl-1001	
PK interactions	Norethindrone and ethinyl estradiol	CPS-1007	*
	Cyclosporine	CPS-1011	*
	Probenecid	CPS-1011	*
	Rosuvastatin	CPS-1012	*
Population PK analyses	Healthy subjects: gender, age, race, BMI	meta-anal-intrins	*
	Target population	IBS-2001	

PK = pharmacokinetic(s); * Indicates the primary PK aim of the study; § indicated studies in subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The submission does not contain a full review of pharmacokinetics, the sponsor justifying this based on the low oral bioavailability. Hepatic metabolism is minimal but sufficient occurs for genetic effects to be demonstrated by slow metabolisers (numbers too small for statistical significance) and hepatic impairment results in greater exposure (mean eluxadoline plasma exposure was 6 fold, 4 fold and 16 fold higher in mild, moderate, and severe hepatically impaired subjects (Child Pugh Class A, B, C) respectively).

Pharmacodynamics

Studies providing pharmacodynamic data

The relationship between the systemic exposure and beneficial effects of eluxadoline are not entirely clear. Eluxadoline has a very low oral bioavailability and works locally within the GI tract. Despite a suggested correlation between systemic exposure and clinical response in a post-hoc pharmacokinetic/pharmacodynamic model using data from the Phase II Study IBS-2001, overall the data demonstrated no true pharmacokinetic/pharmacodynamic relationship. This is especially true when considering that increasing exposures above those achieved with 100 mg bd did not produce corresponding increases in efficacy. This further supports the hypothesis that the beneficial effects of eluxadoline are mediated through local action in the GI tract.

Studies providing pharmacodynamic information are listed in Table 6, below.

Table 6: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on bowel function	EDI-1001	*
Secondary Pharmacology	Effect on cardiac repolarisation	CPS-1008	*
	Effect on pupillometry	EDI-1001	
	Abuse potential	CPS-1006 CPS-1010	*
Population PD and PK-PD analyses **Target population**	PK/PD effect on bowel function	IBS-2001	
	PK/PD effect on pain score	IBS-2001	

PD = pharmacodynamic(s); PK = pharmacokinetic(s); * Indicates the primary PD aim of the study.

Evaluator's conclusions on pharmacodynamics

The sponsor attempted to show a separate relationship between pharmacokinetics and pain score or bowel function (Bristol Stool Score (BSS));[17] but failed to do so. Only in a post hoc analysis of both combined could a relationship to AUC be shown.

The sponsor proposes to insert under the 'Pharmacodynamics' section in the PI only statements on the mechanism of action and the statements being derived from animal and in vitro studies.

Dosage selection for the pivotal studies

Study IBS-2001: A 12 week, double blind, placebo controlled, dose-ranging, Phase II study showed no improvement in response seen between 100 and 200 mg doses and had a

[17] Bristol Stool Score (BSS): The patient-reported BSS consistency score is based on a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponded to watery diarrhoea.

higher incidence of adverse events seen at the 200 mg dose. This led to the decision to use the 100 mg dose as the maximum clinically relevant dose.

Although the efficacy of 75 mg bd was not specifically explored in the Phase II study, this dose was included based on efficacy trends and the favourable safety profile of doses up to 100 mg bd.

Efficacy

Studies providing efficacy data

- Study IBS-3001: A randomised, double blind, placebo controlled Phase III study to evaluate the efficacy safely, and tolerability of eluxadoline in the treatment of patients with diarrhoea-predominant irritable bowel syndrome.
- Study IBS-3002: A randomised, double blind, placebo controlled Phase III study to evaluate the efficacy safety, and tolerability of eluxadoline in the treatment in patients with diarrhoea-predominant irritable bowel syndrome.
- Study IBS-2001: A randomised, double blind, placebo controlled, parallel group, dose ranging, multicentre study to evaluate the efficacy, safety, and tolerability of eluxadoline in the treatment of patients with irritable bowel syndrome with diarrhoea.

Evaluator's conclusions on efficacy

In Study 3001, while both the 75 and 100 mg groups showed statistically superiority to placebo in the percentage of composite responders at 12 weeks, only the 100 mg dose did so at 26 weeks.

In Study 3002, the primary endpoint, the proportion of composite responders for the 75 mg and 100 mg treatment groups, was statistically superior to placebo for Weeks 1 to 12 ($P < 0.001$) and Weeks 1 to 26 ($P \leq 0.001$).

The absolute responder rates results for the placebo group were similar in both Studies 3001 and 3002, the difference between the studies reflecting a difference in absolute responder rates results for the eluxadoline groups.

In Study 2001, at Week 4, primary response rates were statistically superior to that of placebo only for the 25 mg and 200 mg treatment groups. While at Week 12 only the 100 mg treatment group was statistically superior to placebo. The response rates both for eluxadoline and placebo were less than used in the population calculations.

In the meta-analysis, both 75 mg and 100 mg showed statistical superiority at Weeks 12 and 26.

Thus, evidence for efficacy based on statistical superiority of the primary endpoints favours eluxadoline 100 mg bd.

Among those on 100 mg bd with baseline pain scores < 5 (67/250) only 36.2% achieved a 30% (that is, < 2) reduction in their score, in those with scores of 5 to < 8 (159/250) 30.4% achieved a reduction in their score of 30% (1.7 or more) and of those with scores of ≥ 8 (24/250) 24.5% achieved a reduction in their score of 30% (2.7 or more).

'Decreases in individuals' pain intensity of approximately 1 cm (or 1.0 point) or 15% to 20% represent 'minimal' or 'little' change, whereas decreases of 2.0 to 2.7 points or 30% to 41% have more meaning to patients, for example, being associated with not requesting rescue medication or ratings of 'much' or 'some' change. This research also supports the importance of taking baseline pain into account when evaluating these change scores.

The sponsor attempted to assess use of acetaminophen (Tylenol, Panadol, paracetamol) as rescue medication in Study 2001.[18]

The original protocol dated 29 March 2010 had: 'If rescue medication for pain is required, the following may be taken by the patient after randomisation: During Weeks 1 through 12: Tylenol with a recommended maximum dose of 2400 mg/day. The use of Tylenol should be recorded by the patients in their daily telephone diary'.

The study report said the use of Tylenol as rescue for abdominal pain, was rarely reported by patients in any treatment group.

Table 7: Number (%) of patients taking Tylenol Concomitant Medications Safety Set 2001

	100 mg bd (N=165)	Placebo bd (N=159)
Paracetamol	18 (10.9%)	19 (11.9%)
Tylenol PM	1 (0.6%)	3 (1.9%)

Patients may have more than one medication per preferred term. A patient was counted once if the patient reported one or more medications. Concomitant medications are medications that are ongoing or that start on or after the date of the first dose of study drug and until the end of treatment date (Week 12 visit). Tylenol is a registered tradename for a paracetamol and diphenhydramine containing product.

Similar to Study 3001 a variety of concomitant analgesics/opiates was seen.

The use of Tylenol was reported as the number of days in a week used giving a consistently low result.

Pain rescue was not defined in the protocol for Study 3001. The following extract from the list of used concomitant medicine's shows the variety of opiates alone and compounded and paracetamol alone and compounded.

The study report, in commenting on concomitant medication said:

- Study 2001: The use of the ibuprofen, paracetamol, and acetylsalicylic acid, all of which could impact the efficacy endpoint of worst abdominal pain, was similar across all treatment groups.
- Study 3001: The proportion of patients taking omeprazole, ibuprofen, paracetamol, and acetylsalicylic acid was similar across treatment groups.

Table 8: Number (%) of patients taking Concomitant Medications Enrolled Set 3001

	75 mg bd (N = 429)	100 mg bd (N = 426)	Placebo bd (N = 427)	Total (N = 1282)
Co-Tylenol	0	0	1 (0.2%)	1 (0.1%)
Cough and cold preparations	5 (1.2%)	6 (1.4%)	5 (1.2%)	16 (1.2%)
Codeine phosphate	0	0	1 (0.2%)	1 (0.1%)

[18] Acetaminophen is United Stated Adopted Name (USAN) and Japanese Accepted Name (JAN), whereas paracetamol is the Australian Approved Name (AAN), British Approved Name (BAN) and International Nonproprietary Name (INN) for the same drug. Tylenol and Panadol are registered tradenames for paracetamol containing products.

	75 mg bd (N = 429)	100 mg bd (N = 426)	Placebo bd (N = 427)	Total (N = 1282)
Dextromethorphan	0	4 (0.9%)	1 (0.2%)	5 (0.4%)
Dextromethorphan hydrobromide	0	3 (0.7%)	1 (0.2%)	4 (0.3%)
Dihydrocodeine	0	0	1 (0.2%)	1 (0.1%)
Dozol	2 (0.5%)	1 (0.2%)	3 (0.7%)	6 (0.5%)
Fentanyl	3 (0.7%)	5 (1.2%)	6 (1.4%)	14 (1.1%)
Fentanyl Citrate	0	1 (0.2%)	0	1 (0.1%)
Gabapentin	20 (4.7%)	16 (3.8%)	19 (4.4%)	55 (4.3%)
Hydrocodone	6 (1.4%)	2 (0.5%)	2 (0.5%)	10 (0.8%)
Hydromorphone	1 (0.2%)	4 (0.9%)	2 (0.5%)	7 (0.5%)
Hydromorphone hydrochloride	5 (1.2%)	9 (2.1%)	3 (0.7%)	17 (1.3%)
Lomotil	0	3 (0.7%)	1 (0.2%)	4 (0.3%)
Loperamide hydrochloride	4 (0.9%)	5 (1.2%)	8 (1.9%)	17 (1.3%)
Loperamide with simethicone	0	1 (0.2%)	0	1 (0.1%)
Morphine	3 (0.7%)	11 (2.6%)	5 (1.2%)	19 (1.5%)
Morphine sulphate	3 (0.7%)	3 (0.7%)	0	6 (0.5%)
Nite-Time Cold Medicine	2 (0.5%)	0	1 (0.2%)	3 (0.2%)
Opium and belladonna	0	1 (0.2%)	0	1 (0.1%)
Oxycodone	0	1 (0.2%)	2 (0.5%)	3 (0.2%)
Oxycodone Hydrochloride	0	2 (0.5%)	0	2 (0.2%
Panadeine Co	2 (0.5%)	2 (0.5%)	5 (1.2%)	9 (0.7%)
Paracetamol	45 (10.5%)	60 (14.1%)	56 (13.1%)	161 (12.6%)
Pethidine	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
Pethidine hydrochloride	0	2 (0.5%)	1 (0.2%)	3 (0.2%)
Solpadeine	0	0	1 (0.2%)	1 (0.1%)
Tramadol	6 (1.4%)	3 (0.7%)	5 (1.2%)	14 (1.1%)

	75 mg bd (N = 429)	100 mg bd (N = 426)	Placebo bd (N = 427)	Total (N = 1282)
Tramadol hydrochloride	1 (0.2%)	0	0	1 (0.1%)
Tussin Dm	3 (0.7%)	2 (0.5%)	0	5 (0.4%)
Tussionex	0	1 (0.2%)	0	1 (0.1%)
Tussionex Pennkinetic	0	2 (0.5%)	1 (0.2%)	3 (0.2%)
Tylenol Sinus Medication	0	2 (0.5%)	2 (0.5%)	4 (0.3%)

Patients may have more than one medication per preferred term. At each level of patient summarization, a patient was counted once if the patient reported one or more medications. Concomitant medications presented are medications that are ongoing or that start on or after the date of first dose of study drug and up to and including 7 days after the date of the last study medication. Percentages are of the number of patient in that treatment group.

The improvement in some outcomes was modest compared with placebo, however for the patients whose problems are not going to spontaneously resolve, it may be considered an efficacy option.

The sponsor in an overview of clinical efficacy has stated the following:

> *'While the locally acting μ-opioid receptor agonist loperamide is effective in treating diarrhoea, it has limited effectiveness in IBS-d due to lack of effect on abdominal pain and global symptoms and the possibility for excessive constipation. By contrast, the mixed opioid pharmacology of eluxadoline appears to confer on it the ability to effectively improve abdominal pain and stool consistency in IBS-d patients while mitigating the risk of constipation'.*

However:

> *'While the proportion of abdominal pain responders for the active treatment groups was higher than placebo over both intervals, the differences were not statistically significant (P > 0.05) for the individual studies or the pooled analyses'.*

Thus, the modestly effective combined endpoint relies on the results on stool consistency and the sponsor's claim of pain relief appears not to be statistically supported.

The primary results for other secondary outcomes are modest but generally supportive, although without statistical allowance for multiplicity.

It is noted that the IMMPACT statement;[19] in relation to chronic pain recommends (as well as assessment of pain scores) the assessment of:

- usage of rescue analgesics;
- physical functioning;
- emotional functioning; and
- participant ratings of global improvement and satisfaction with treatment.

[19] IMMPACT = Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Dworkin R et al., Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005 Jan; 113 (2005) 9–19.

Safety

Studies providing safety data

Pivotal and/or main efficacy studies:

- Study 3001 was extended beyond the 6 months for efficacy, to provide a further 6 months of safety data.
- Study 3002 likewise had an extension; a 4 week single blinded withdrawal period.

Patient exposure

Study drug was received for at least one year for 245 and 243 patients in the 75 mg and 100 mg eluxadoline groups respectively.

Table 9: Disposition, pooled analysis of Phase II and Phase III studies

	Eluxadoline dose (BID)					Placebo (BID)
	5 mg	25 mg	75 mg	100 mg	200 mg	
n (%)						
Enrolled	111	174	810	985	174	981
Completed study	50 (45.0)	131 (75.3)	507 (62.6)	644 (65.4)	103 (59.2)	660 (67.3)
Discontinued study	61 (55.0)	43 (24.7)	303 (37.4)	340 (34.5)	71 (40.8)	321 (32.7)
Adverse event	2 (1.8)	5 (2.9)	68 (8.4)	79 (8.0)	22 (12.6)	42 (4.3)
Other	59 (53.2)	38 (21.8)	235 (29.0)	261 (26.5)	49 (28.2)	279 (28.4)

Patient base: Enrolled subjects

Table 10: Total exposure (Safety set); Pooled analysis Phase I (oral administration), Phase II, and Phase III studies; Number of patients with any eluxadoline exposure[a]

Phase I oral administration studies[b]	330
Phase II	617
Phase III	1615
Overall	2562

a) Subjects/patients who received at least 1 dose of eluxadoline were counted. Any individual who was randomised more than once was counted only in the first study to which they were randomised. Any individual who was randomised to placebo but received eluxadoline as a misallocated treatment was also counted. Individuals were counted within the phase of study they first received eluxadoline. If an individual was randomised in both Phase II and III studies and only received eluxadoline for the first time during Phase III then this individual was counted only in Phase III. Similarly, if an individual received eluxadoline in both Phase II and III they were counted only in Phase II since they first received eluxadoline during that phase; b) The Phase I row included data from 10 Phase I oral administration studies. Study CPS-1010 was an intranasal administration study and, therefore, was not included.

Table 11: Duration of exposure (days) by demographic Factors (Enrolled set); pooled analysis of Phase II and III studies

		Eluxadoline dose (BID)					Placebo (BID)
		5 mg (N=111)	25 mg (N=174)	75 mg (N=810)	100 mg (N=985)	200 mg (N=174)	N=981
By age group							
< 65 years	n	107	171	740	902	170	869
	mean ± SD	65.1 ± 25.3	72.7 ± 25.1	210.8 ± 122.1	185.3 ± 122.9	63.6 ± 31.7	187.2 ± 121.0
≥ 65 years	n	2	1	63	74	0	103
	mean ± SD	82.5 ± 0.71	85.0	224.4 ± 118.8	195.0 ± 130.5	0	222.6 ± 119.7
By gender							
Male	n	32	53	268	320	52	332
	mean ± SD	66.9 ± 28.0	71.0 ± 26.8	219.7 ± 121.7	192.4 ± 125.0	68.6 ± 27.1	198.8 ± 121.4
Female	n	77	119	535	656	118	640
	mean ± SD	64.9 ± 24.1	73.6 ± 24.3	207.9 ± 121.8	182.9 ± 122.6	61.4 ± 33.4	186.8 ± 121.11

Patient base: Patients in the Enrolled Set who received at least 1 dose of study drug; the treatment group is based on the treatment to which the patient was randomised. For any nonrandomised patients who received study drug, it was based on the treatment received at Day 1.

Table 12: Duration of exposure (Safety set); pooled analysis of Phase II and III studies

	Eluxadoline 5 mg BID[a] (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807[b])	Eluxadoline 100 mg BID (N=1032[b])	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975[b])	Total (N=3202)
Overall duration of exposure (days)							
n[c]	109	172	803	976	170	972	3202
Mean (SD)	65.5 (25.19)	72.8 (25.06)	211.9 (121.80)	186.0 (123.42)	63.6 (31.66)	190.9 (121.28)	177.3 (122.49)
Median	78.0	85.0	183.0	183.0	84.0	183.0	181.0
Min, Max	4, 97	1, 95	1, 384	1, 399	1, 103	1, 390	1, 399

Patient base: Safety analysis set (all patients who received at least 1 dose of study drug; based on the treatment actually received at the time the measurement was taken, regardless of assigned treatment according to the planned randomisation) IVRS = interactive voice response system; IWRS = interactive web response system; NA = not applicable; a) After the interim analysis for Study IBS-2001, the 5-mg treatment group was deselected for lack of efficacy and patients subsequently enrolled were randomly assigned to 1 of the 4 remaining treatment groups (25 mg, 100 mg, or 200 mg eluxadoline or placebo); b) N reflects the safety set and includes all patients who received at least 1 dose of study drug (i.e., number of patients randomised + number of patients who received the treatment due to IVRS/IWRS misallocation or site misallocation; c) used in the determination of overall duration of exposure does not include patients who received study drug due to IVRS/IWRS misallocation or site misallocation. Exposure was defined as the total days the patient was exposed to study drug, excluding any days where it was recorded that an interruption had occurred. If the last dose date was missing or incomplete, the following steps were implemented to impute the exposure duration: (1) If the latest kit dispensed had a complete return date, the return date to calculate exposure was used; (2) If the partial information on the last dose date was UK-MMM-YYYY, the last day of the appropriate month as the end date was assumed. (3) Otherwise, the latest kit dispensed date and the number of tablets was used to impute an end date assuming the patient took the tablets with 100% compliance, that is, divided the total tablets by 4 to determine the number of days and added this to the dispensed date.

Safety issues with the potential for major regulatory impact

Rather than reviewing all treatment related AEs the sponsor considered selected AEs that were considered class related.

The sponsor argues for this being a different class from loperamide being both MOR agonist and DOR antagonist however in relation to treatment related AEs the sponsor only

considers selected AEs based on known class effects of MOR agonists and opioids in the initial section relating to 'Pharmacologic Class' but under 'Other Significant Adverse Events' says the sponsor has:

> *'identified certain AEs of special interest related to the pharmacological class of eluxadoline (mixed opioid agonist)*.'

and lists the following:

- AEs consistent with Sphincter of Oddi spasm;
- other and hepatic events;
- constipation events;
- events of fall, syncope;
- road traffic accident;
- cardiac and chest pain events; and
- events of rash and pruritus.

Sphincter of Oddi spasm

Of 11 pancreatitis cases on the eluxadoline database, 9 were felt to be pancreatitis of which 3 were felt associated with sphincter of Oddi spasm. All 3 patients had prior cholecystectomy, events, were transient and occurred during the first day of treatment.

There were 9 cases of acute hepatobiliary events with all having sphincter of Oddi spasm associated. All had absent gall bladders. All events were transient and rapidly resolved on stopping therapy however 1 patient was hospitalised briefly for control of nausea and vomiting. Patients presented with either epigastric/abdominal or biliary type pain, often with symptoms of nausea. 7 patients reported their first onset of symptoms within the first week of treatment.

Pancreatitis

Among the above 9 adjudicated cases, there were 6 cases of pancreatitis that were felt not consistent with sphincter of Oddi spasm. 4 of these AEs involved patients with known alcohol abuse or increased alcohol intake.

Liver function and liver toxicity

Four additional patients, (all having had cholecystectomy), had elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels and experienced symptoms of an acute biliary type syndrome having some of the characteristics of the sphincter of Oddi spasm.

The sponsor presented considerable analysis of liver function tests (LFT) including the effect of prior cholecystectomy.

Table 13: Post-randomisation increase in parameter ALT (Safety analysis set); Pooled analysis of Phase II and III studies (All studies)

Highest Post-Baseline Value	Eluxadoline 75mg BID (N=807) n (%)	Eluxadoline 100mg BID (N=1032) n (%)	Placebo BID (N=975) n (%)
Highest Prescreen or Baseline ALT <= ULN			
>1xULN - 3xULN	114 (14.1%)	126 (12.2%)	128 (13.1%)
>3xULN - 5xULN	5 (0.6%)	4 (0.4%)	4 (0.4%)
>5xULN - 10xULN	4 (0.5%)	5 (0.5%)	1 (0.1%)
>10xULN - 20xULN	1 (0.1%)	1 (0.1%)	0
>20xULN	1 (0.1%)	0	0
Highest Prescreen or Baseline ALT > ULN			
>1xULN - 3xULN	82 (10.2%)	120 (11.6%)	108 (11.1%)
>3xULN - 5xULN	9 (1.1%)	8 (0.8%)	11 (1.1%)
>5xULN - 10xULN	6 (0.7%)	2 (0.2%)	4 (0.4%)
>10xULN - 20xULN	0	2 (0.2%)	0
>20xULN	0	0	0

Percentages are calculated using the safety analysis set as denominator. Subjects were eligible for study entry with ALT up to 3 x upper limit of normal (ULN). Incidence rates of ALT elevations are presented separately for those subjects with baseline values below ULN and those with baseline values above ULN. Subject [information redacted] unscheduled pre-treatment ALT measurement has been used and is summarised within the > ULN category for this integrated safety summary.

Table 14: Post-randomisation increase in parameter alkaline phosphatase (ALP) (Safety analysis set); pooled analysis of Phase II and III studies (All studies)

Highest Post-Baseline Value	Eluxadoline 75mg BID (N=807) n (%)	Eluxadoline 100mg BID (N=1032) n (%)	Placebo BID (N=975) n (%)
Highest Prescreen or Baseline Alkaline Phosphatase <= ULN			
>=1.5xULN	3 (0.4%)	4 (0.4%)	1 (0.1%)
Highest Prescreen or Baseline Alkaline Phosphatase > ULN			
>=1.5xULN	4 (0.5%)	4 (0.4%)	3 (0.3%)

Percentages are calculated using the safety analysis set as denominator. Incidence rates of alkaline phosphatase elevations are presented separately for those subjects with baseline values below ULN and those with baseline values above ULN

Table 15: Post-randomisation increase in parameter total bilirubin (Safety analysis set); pooled analysis of Phase II and III studies (All studies)

Highest Post-Baseline Value	Eluxadoline 75mg BID (N=807) n (%)	Eluxadoline 100mg BID (N=1032) n (%)	Placebo BID (N=975) n (%)
>ULN	26 (3.2%)	27 (2.6%)	26 (2.7%)
>1.5xULN	15 (1.9%)	13 (1.3%)	12 (1.2%)

Percentages are calculated using the safety analysis set as denominator. Subjects were eligible for study entry with total bilirubin up to 3 mg/dL.

Table 16: Post-randomisation increase in ALT by prior cholecystectomy status (Safety analysis set); pooled analysis of Phase III studies (N = (%) of patients)

Highest Post-Randomization Value	Eluxadoline 75 mg BID	Eluxadoline 100 mg BID	Placebo BID
Prior cholecystectomy: Yes	**N=165**	**N=183**	**N=158**
Normal at Baseline: Highest prescreen and baseline ALT ≤ ULN			
> 1 × ULN – 3 × ULN	27 (16.4)	23 (12.6)	18 (11.4)
> 3 × ULN – 5 × ULN	1 (0.6)	2 (1.1)	2 (1.3)
> 5 × ULN – 10 × ULN	4 (2.4)	3 (1.6)	0
> 10 × ULN – 20 × ULN	1 (0.6)	1 (0.5)	0
> 20 × ULN	1 (0.6)	0	0
Abnormal at Baseline: Highest prescreen or baseline ALT > ULN			
> 1 × ULN – 3 × ULN	15 (9.1)	19 (10.4)	18 (11.4)
> 3 × ULN – 5 × ULN	5 (3.0)	5 (2.7)	4 (2.5)
> 5 × ULN – 10 × ULN	2 (1.2)	1 (0.5)	3 (1.9)
>10 × ULN – 20 × ULN	0	0	0
> 20 × ULN	0	0	0
Prior cholecystectomy: No	**N=642**	**N=676**	**N=650**
Normal at Baseline: Highest prescreen and baseline ALT ≤ ULN			
>1 × ULN – 3 × ULN	87 (13.6)	100 (14.8)	106 (16.3)
>3 × ULN – 5 × ULN	4 (0.6)	1 (0.1)	2 (0.3)
>5 × ULN – 10 × ULN	0	2 (0.3)	1 (0.2)
>10 × ULN – 20×ULN	0	0	0
> 20 × ULN	0	0	0
Abnormal at Baseline: Highest prescreen or baseline ALT > ULN			
>1 × ULN – 3 × ULN	67 (10.4)	85 (12.6)	71 (10.9)
>3 × ULN – 5 × ULN	4 (0.6)	3 (0.4)	7 (1.1)
>5 × ULN – 10 × ULN	4 (0.6)	1 (0.1)	1 (0.2)
>10 × ULN – 20×ULN	0	2 (0.3)[a]	0
> 20 × ULN	0	0	0

Patient base: Safety analysis set (all patients who received at least 1 dose of study drug; based on the treatment actually received at the time the measurement was taken, regardless of assigned treatment according to the planned randomisation); a) Includes Patient [information redacted] with congenital agenesis of the gallbladder and Patient [information redacted] with laboratory values that were suspicious for specimen errors. Percentages were calculated using the number of patients with or without a prior cholecystectomy (Safety analysis set) as the denominator. Patients were eligible for study entry with ALT up to 3 x ULN. Incidence rates of ALT elevations were presented separately for those patients with baseline values below ULN and those with baseline values above ULN. Prior cholecystectomy status was only collected in Phase III studies

Constipation

The overall incidence of constipation AEs was 7.4% in patients who received 75 mg eluxadoline, 8.1% for 100 mg, and 2.5% with placebo patients.

Of the patients in the 75 mg and 100 mg groups who ever reported AEs of constipation, approximately 82.9% reported constipation AEs within the first 13 weeks of treatment.

Constipation was seen in higher proportions of female than male patients treated with 75 mg (8.0% and 6.3%, respectively) and 100 mg (9.0% and 6.4%, respectively) eluxadoline and in placebo patients (2.6% and 2.1%, respectively).

Fall, syncope

AEs of fall were reported in 1.6%, 0.9%, and 0.4% of patients across the 75 mg, 100 mg, and placebo groups, respectively; no patient in the 5 mg, 25 mg, or 200 mg groups experienced a fall event. No major injuries occurred as a result of a fall event, none of the events of fall was considered serious, and none led to discontinuation of study.

Road traffic accident

A road traffic accident occurred with 8 eluxadoline patients (5 and 3 patients who received 75 mg and 100 mg, respectively) and 2 placebo patients. 2 patients on eluxadoline were passengers.

Electrocardiograph findings and cardiovascular safety

Angina pectoris was reported in 0.5% (4/807), 0.4% (4/1032), and 0.1% (1/975) of patients who received 75 mg eluxadoline, 100 mg eluxadoline, and placebo, respectively. Palpitations were reported in 0.1% (1/807), 0.4% (4/1032), and 0.2% (2/975) of patients in the 75 mg, 100 mg, and placebo groups, respectively. All other cardiac disorders AEs were reported in ≤ 3 patients in any treatment group. Cardiac disorders as serious adverse events (SAE) were reported across the 75 mg, 100 mg, and placebo groups (0.4%, 0.4%, and 0.2%, respectively).

Non-cardiac chest pain was reported in 0, 0.6% (6/1032), and 0.3% (3/975) patients in the 75 mg, 100 mg, and placebo groups, respectively; chest pain was reported for 0.5% (4/807), 0.5% (5/1032), and 0.2% (2/975) patients, respectively; and chest discomfort was reported for 0.1% (1/807), 0.3% (3/1032), and 0.2% (2/975) patients, respectively. 4 patients had chest pain that resulted in hospitalisation.

AEs that led to discontinuation included sinus tachycardia, coronary artery disease, angina pectoris (2 events), myocardial infarction and chest discomfort. There was one death.

For Study CPS-1008 the primary endpoint (placebo-adjusted change of QTcI[20] from Baseline), maximally 4.10 ms at 1 h after dosing for the 100 mg eluxadoline treatment with a one-sided 95% upper confidence bound of 5.81 msec, did not reach the threshold for significance for QT interval prolongation. The largest mean time-matched difference in change from Baseline from placebo for the eluxadoline 100 mg dose was 1.20 ms at 0.5 h after dosing, with a one-sided 95% upper confidence bound of 2.91 msec.

AEs of prolonged QT interval occurred in 1 patient each in the 25 mg and 75 mg groups, 3 patients in the 100 mg group, and 3 patients in the placebo group. ECG signs of myocardial ischemia occurred for 3 patients in the placebo group. Abnormal ST segment, abnormal T wave, and T wave inversion occurred for 1 patient each in the 100 mg group and the placebo group. All other ECG-related AEs occurred for only 1 patient overall and included abnormal ECG (75 mg), QRS complex abnormal (placebo), ST segment elevation (75 mg), ST-T change (25 mg), and increased T wave amplitude (100 mg)

[20] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate, that is, the faster the heart rate, the shorter the R–R interval and QT interval and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia giving a corrected QT (QTc).

Serious skin reactions

Of the 75 mg, 100 mg eluxadoline and placebo patients, rash was reported for 1.2%, 0.9%, and 0.6% of patients; and pruritus was reported for 0.6%, 0.4%, and 0.6% of patients, respectively.

2 (0.2%) patients who received 75 mg and 100 mg eluxadoline and 1 (0.1%) placebo patient were discontinued due to skin and subcutaneous tissue disorders AEs, including pruritus, urticaria, alopecia and rash.

Renal function and renal toxicity

Patients with renal dysfunction were not excluded in the Phase III program albeit haematology requirements could have (and did) exclude patients with end stage renal disease.

Across the 75 mg, 100 mg, and placebo groups, 96, 119 and 132 patients, respectively, had mild renal dysfunction at baseline and 6, 6 and 12 patients, respectively, had moderate renal dysfunction at Baseline.

Patients with mild renal dysfunction most often reported AEs of nausea, which were seen in 10.4%, 10.1% and 6.1% of patients in the 75 mg, 100 mg, and placebo groups, respectively. The number of patients with moderate renal dysfunction is too small to interpret this stratum. No increase in the incidence of AEs based on renal dysfunction status (mild or moderate) was observed.

Haematology and haematological toxicity

No treatment-related trends were observed in mean haematology results over time and the mean values observed at End of Treatment (EOT)/Early Withdrawal were similar to those observed at Baseline for each treatment group.

Vital signs and clinical examination findings

In the first in human dose escalation study (Study EDI-1001) and the initial food effect study (Study EDI-1002), there was an increased incidence of orthostatic hypotension in subjects administered doses ≥ 500 mg of eluxadoline compared with placebo.

For the Phase II Study IBS-2001, the incidence of a priori defined asymptomatic orthostatic hypotension was comparable across treatment groups at every assessment time point. Mean ambulatory blood pressure results were similar between treatment groups (eluxadoline 5, 25, 100 and 200 mg bd; placebo), and the mean values observed at Week 2 were similar to those observed at Baseline.

Postmarketing data

No data submitted.

Evaluator's conclusions on safety

For the 75 mg and 100 mg treatment groups, AEs were similar in incidence but higher than placebo (8.4%, 8.0% and 4.3% respectively); discontinuations were within 5% of each other (37.4%, 34.5% and 32.7%). For SAEs related to treatment there were 5 incidences on 75 mg and 7 incidences on 100 mg.

However, the incidence and a summary of treatment related AEs (adverse reactions) were not submitted. Instead, selected AEs were reviewed including liver and pancreatitis events

and their relationship to cholecystectomy and sphincter of Oddi spasm, constipation, syncope, urticaria and rash.

The major risks of serious adverse effects from use appear to be increased potential for pancreatitis, spasm in the sphincter of Oddi and hepatobiliary abnormalities. The adverse events that were more frequently reported by patients taking eluxadoline compared with placebo are listed in Table 17 (see below) and include for the 100 mg bd eluxadoline dose regimen versus placebo comparison in the pooled Phase II and III studies: constipation (8% versus 2%); nausea (7% versus 5%); abdominal pain (7% versus 4%); and vomiting 4% versus 1%).

The major risks of serious adverse effects from use appear to be increased potential for pancreatitis, spasm in the sphincter of Oddi and hepatobiliary abnormalities.

The AEs that were more frequently reported by patients taking eluxadoline compared with placebo are listed below in Table 18 (AEs reported by ≥ 2% of patients in any eluxadoline treatment group and at a greater incidence than placebo (Safety set); pooled Phase II and III studies) and include for the 100 mg bd eluxadoline dose regimen versus placebo comparison in the pooled Phase II and III studies: constipation (8% versus 2%); nausea (7% versus 5%); abdominal pain (7% versus 4%); and vomiting 4% versus 1%).

The potential for abuse appears low.

Table 17: Overall incidence of AEs and gastrointestinal AEs by interval (Safety set); pooled Phase II and III studies

	Number (%) of Patients					
	Eluxadoline 5 mg BID (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807)	Eluxadoline 100 mg BID (N=1032)	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975)
Overall[a]						
Number of patients with ≥ 1 AE	48 (44.0)	86 (49.7)	486 (60.2)	575 (55.7)	91 (53.2)	533 (54.7)
Number of patients with ≥ 1 GI AE	20 (18.3)	38 (22.0)	242 (30.0)	273 (26.5)	48 (28.1)	185 (19.0)
Within First Week of Treatment						
Number of patients with ≥ 1 AE	20 (18.3)	34 (19.7)	147 (18.2)	201 (19.5)	50 (29.2)	116 (11.9)
Number of patients with ≥ 1 GI AE	9 (8.3)	18 (10.4)	96 (11.9)	127 (12.3)	34 (19.9)	57 (5.8)
Within First 2 Weeks of Treatment						
Number of patients with ≥ 1 AE	26 (23.9)	45 (26.0)	208 (25.8)	258 (25.0)	55 (32.2)	190 (19.5)
Number of patients with ≥ 1 GI AE	10 (9.2)	23 (13.3)	130 (16.1)	153 (14.8)	36 (21.1)	76 (7.8)
Within First 12 Weeks of Treatment						
Number of patients with ≥ 1 AE	47 (43.1)	81 (46.8)	398 (49.3)	457 (44.3)	86 (50.3)	413 (42.4)
Number of patients with ≥ 1 GI AE	20 (18.3)	37 (21.4)	200 (24.8)	223 (21.6)	46 (26.9)	145 (14.9)
Within First 26 Weeks of Treatment						
Number of patients with ≥ 1 AE	48 (44.0)	86 (49.7)	453 (56.1)	525 (50.9)	91 (53.2)	483 (49.5)
Number of patients with ≥ 1 GI AE	20 (18.3)	38 (22.0)	228 (28.3)	261 (25.3)	48 (28.1)	168 (17.2)

Patient base: Safety analysis set (all patients who received at least 1 dose of study drug; based on the treatment actually received at the time the measurement was taken, regardless of assigned treatment according to the planned randomisation); Multiple occurrences of AEs in the GI System Organ Class within a patient are counted once only. The Phase II study evaluated doses of 5 mg, 2 mg, 100 mg, and 200 mg eluxadoline and placebo for up to 12 weeks.a) All AEs with a start date between treatment start date and date of last study visit inclusive (or last contact date if last study visit was missing) are included.

Table 18: AEs reported by ≥ 2% of patients in any eluxadoline treatment group and at a greater incidence than placebo (Safety set); pooled Phase II and III studies

	Number (%) of Patients					
System Organ Class Preferred Term	Eluxadoline 5 mg BID (N=109)	Eluxadoline 25 mg BID (N=173)	Eluxadoline 75 mg BID (N=807)	Eluxadoline 100 mg BID (N=1032)	Eluxadoline 200 mg BID (N=171)	Placebo BID (N=975)
Total number of AEs	100	224	1556	1804	238	1573
Number of patients with ≥1 AE	48 (44.0)	86 (49.7)	486 (60.2)	575 (55.7)	91 (53.2)	533 (54.7)
Gastrointestinal disorders	**20 (18.3)**	**38 (22.0)**	**242 (30.0)**	**273 (26.5)**	**48 (28.1)**	**185 (19.0)**
Nausea	6 (5.5)	10 (5.8)	65 (8.1)	73 (7.1)	18 (10.5)	49 (5.0)
Constipation	2 (1.8)	5 (2.9)	60 (7.4)	84 (8.1)	6 (3.5)	24 (2.5)
Abdominal pain	3 (2.8)	6 (3.5)	33 (4.1)	47 (4.6)	13 (7.6)	25 (2.6)
Vomiting	1 (0.9)	7 (4.0)	32 (4.0)	43 (4.2)	12 (7.0)	12 (1.2)
Flatulence	1 (0.9)	3 (1.7)	21 (2.6)	33 (3.2)	4 (2.3)	17 (1.7)
Abdominal distension	0	0	21 (2.6)	28 (2.7)	1 (0.6)	15 (1.5)
Dry mouth	1 (0.9)	4 (2.3)	15 (1.9)	13 (1.3)	5 (2.9)	15 (1.5)
Diarrhea	0	8 (4.6)	14 (1.7)	13 (1.3)	2 (1.2)	10 (1.0)
Gastroesophageal reflux disease	2 (1.8)	5 (2.9)	11 (1.4)	13 (1.3)	1 (0.6)	10 (1.0)
Infections and infestations	**18 (16.5)**	**30 (17.3)**	**199 (24.7)**	**222 (21.5)**	**25 (14.6)**	**230 (23.6)**
Upper respiratory tract infection	3 (2.8)	5 (2.9)	27 (3.3)	53 (5.1)	1 (0.6)	38 (3.9)
Nasopharyngitis	5 (4.6)	8 (4.6)	33 (4.1)	31 (3.0)	6 (3.5)	33 (3.4)
Sinusitis	5 (4.6)	6 (3.5)	27 (3.3)	27 (2.6)	1 (0.6)	35 (3.6)
Bronchitis	4 (3.7)	4 (2.3)	26 (3.2)	30 (2.9)	1 (0.6)	21 (2.2)
Gastroenteritis viral	1 (0.9)	3 (1.7)	22 (2.7)	14 (1.4)	4 (2.3)	18 (1.8)
Urinary tract infection	0	2 (1.2)	17 (2.1)	18 (1.7)	4 (2.3)	17 (1.7)
Nervous system disorders	**8 (7.3)**	**17 (9.8)**	**81 (10.0)**	**112 (10.9)**	**24 (14.0)**	**99 (10.2)**
Headache	3 (2.8)	12 (6.9)	32 (4.0)	44 (4.3)	7 (4.1)	44 (4.5)
Dizziness	4 (3.7)	4 (2.3)	21 (2.6)	33 (3.2)	11 (6.4)	21 (2.2)
Somnolence	1 (0.9)	1 (0.6)	1 (0.1)	11 (1.1)	4 (2.3)	3 (0.3)
Investigations	**5 (4.6)**	**8 (4.6)**	**77 (9.5)**	**70 (6.8)**	**4 (2.3)**	**78 (8.0)**
Alanine aminotransferase increased	2 (1.8)	0	17 (2.1)	26 (2.5)	1 (0.6)	14 (1.4)
General disorders and administration site conditions	**5 (4.6)**	**9 (5.2)**	**47 (5.8)**	**64 (6.2)**	**15 (8.8)**	**65 (6.7)**
Fatigue	2 (1.8)	3 (1.7)	21 (2.6)	20 (1.9)	4 (2.3)	23 (2.4)
Respiratory, thoracic, and mediastinal disorders	**4 (3.7)**	**10 (5.8)**	**58 (7.2)**	**55 (5.3)**	**7 (4.1)**	**66 (6.8)**
Cough	0	5 (2.9)	13 (1.6)	9 (0.9)	1 (0.6)	19 (1.9)
Vascular disorders	**0**	**4 (2.3)**	**25 (3.1)**	**25 (2.4)**	**7 (4.1)**	**25 (2.6)**
Hypertension	0	3 (1.7)	20 (2.5)	14 (1.4)	5 (2.9)	16 (1.6)

Patient base: Safety analysis set (all patients who received at least 1 dose of study drug; based on the treatment actually received at the time the measurement was taken, regardless of assigned treatment according to the planned randomisation). For the System Organ Class and Preferred Term level summaries, multiple occurrences of an SOC or preferred term within a patient are counted once only. All occurrences of a preferred term are included in the total number of AEs. All AEs with a start date between treatment start date and date of last study visit inclusive (or last contact date if last study visit was missing) are included.

First Round Benefit-Risk Assessment

First round assessment of benefits

Table 19 (see below) summarises the first round assessment of benefits.

Table 19: First round assessment of benefits

Indication: *'Eluxadoline (Viberzi) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d)'.*	
Benefits	**Strengths and Uncertainties**
In Study 3001, while both the 75 mg and 100 mg groups showed statistically superiority to placebo in the percentage of composite responders at 12 weeks, only the 100 mg dose did so at 26 weeks.	The response rates in Study 2001 both for eluxadoline and placebo were less than used in calculating the study population. The clinical significance of the modest improvement in some outcomes compared with placebo was not discussed, however for those whose problems are not going to spontaneously resolve, it may be considered an efficacy option. The sponsor has undertaken subgroup analyses in an effort to identify an appropriate population but without successful result.
In Study 3002, the primary endpoint, the proportion of composite responders for the 75 mg and 100 mg treatment groups, was statistically superior to placebo for Weeks 1 to 12 ($P < 0.001$) and Weeks 1 to 26 ($P \leq 0.001$).	
In Study 2001, at Week 4, primary response rates were statistically superior to that of placebo only for the 25 mg and 200 mg treatment groups. While at Week 12 only the 100 mg treatment group was statistically superior to placebo.	
In the meta-analysis both 75 mg and 100 mg showed statistical superiority at Weeks 12 and 26.	
The primary results for other secondary outcomes are generally supportive.	The IMMPACT statement;[19] in relation to chronic pain recommends (as well as assessment of pain scores) the assessment of: • usage of rescue analgesics; • physical functioning; • emotional functioning; and • participant ratings of global improvement and satisfaction with treatment. The sponsor has successfully reviewed many of these components.

First round assessment of risks

Table 20, shown below, summarises the first round assessment of risks.

Table 20: First round assessment of risks

Risks	Strengths and Uncertainties
The incidence and a summary of treatment related AEs (adverse reactions) were not submitted.	The sponsor proposes that since the class related effects were well known rather than reviewing all treatment related AEs the sponsor considered selected AES that were considered class related. The class definition has varied from the specific MOR agonist/DOR antagonist to opioid. No comparative list of class related AEs was submitted. While the specific systemic effects likely to cause problems with a μ opioid receptor agonist and of δ opioid receptor antagonist although not submitted may be known, the adverse reactions of a MOR agonist/DOR receptor antagonist with poor oral availability cannot be known since the sponsor is proposing its uniqueness as a treatment. It is interesting to note that, while in the Clinical Overview and Clinical Summaries no mention is made of any KOR activity, it is mentioned in the PI and in the Nonclinical Overview that there is weak KOR agonist activity. There is a list of AEs with an incidence ≥ 2% and higher than in placebo group. However, it is not particularly sensitive as for example it misses all pancreas and liver events except raised ALT.
Constipation and pain are intrinsic to IBS	The sponsor has made no comparative studies with alternative treatments for IBS-d predominant though claiming advantage over loperamide and alosetron (not on ARTG). The sponsor in this submission has made a comparison in those whose historical data showed inadequate symptom control with lamotrigine between those on placebo and those on eluxadoline, this evaluator however gives it little weight as it is not a direct comparison of efficacy with lamotrigine.
Abuse potential	Based on submitted trial data the potential for abuse appears low.
Spasm of sphincter of Oddi	The sponsor has shown that this is particularly a problem in those whose gallbladder is absent.

First round assessment of benefit-risk balance

The overall benefit-risk balance is considered unfavourable:

- With the modest improvement compared with placebo the limited benefit needs to be balanced by a comparable risk.
- The lack of a clear presentation of the risk of all treatment related AEs makes the comparison unfavourable.

First Round Recommendation Regarding Authorisation

It is not recommended that the proposed authorisation be approved.

The lack of a clear presentation of the risk of all treatment related AEs makes the comparison unfavourable with the modest improvement seen compared with placebo.

Second Round Evaluation of clinical data submitted in response to questions

First round evaluation errata

None notified by sponsor.

For details of the sponsor's responses to questions raised by the evaluator and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

While the sponsor has further elucidated the extent and consistency of the extent of benefit from treatment with eluxadoline, the overall benefit in the treatment of IBS-d remains modest. The clinical trial data suggest that clinically significant improvement in symptoms can be expected in from 8 to 13% of patients. The major effect is in improving stool consistency.

Second round assessment of risks

Eluxadoline appears to have a similar risk profile to other opioid agonists with less risk of CNS effects. The major concerns are an increased risk of pancreatitis and pain due to sphincter of Oddi spasm. These risks can be minimised by adherence to the proposed contraindications to use and precautionary statements in the PI and Consumer Medicine Information (CMI) and by reducing the dose to 75 mg bd for patients without a gallbladder.

The risk of AEs due to higher exposure in some patient groups can also be addressed by reducing the dose of eluxadoline in these groups (patients with mild or moderate hepatic impairment, and patients taking concomitant OATP1B1 inhibitors).

Second round assessment of benefit-risk balance

On review of the additional information supplied by the sponsor, the evaluator considers the benefit-risk balance is favourable for eluxadoline in the following indication:

> *Viberzi (eluxadoline) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d).*

Second round recommendation regarding authorisation

The evaluator recommends that eluxadoline (Viberzi) be approved for the following indication:

> *Viberzi (eluxadoline) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d).*

VI. Pharmacovigilance findings

Risk management plan

- The sponsor submitted a Risk Management Plan (RMP): EU-RMP version 1.5 (date not specified; data lock point (DLP) 15 December 2014) and an undated Australian Specific Annex ((ASA); no version control identified) in support of this application. In the sponsor's response of 4 May 2017, the sponsor clarified the authorisation date of EU-RMP version 1.5 as 20 July 2016, and provided ASA version 1.1 (dated 2 May 2017, DLP 15 December 2014).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 21.

Table 21: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Decreased GI motility shown as constipation	✓	–	✓	–
	Sphincter of Oddi (SO) spasm: • Pancreatitis • Hepatic enzyme elevations associated with biliary-type pain	✓*	–	✓	–
Important potential risks	Potential complications of decreased GI motility (for example, serious faecal impaction, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, or toxic megacolon)	✓*	–	✓	–
	Pancreatitis independent of sphincter of Oddi spasm	✓*	–	✓	–
	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 the paediatric population	✓	–	✓	–
	Use in pregnancy and lactation	✓	–	✓	–
	Use in patients with renal impairment	✓	✓	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in patients of ethnic origin other than White	✓	–	✓	–
	Use in patients with impaired intestinal barriers (IBD and coeliac Disease)	✓	–	✓	–
	Drug-drug interactions with drugs metabolised by CYP1A2 or 3A4/5	✓	✓	✓	–

*includes targeted follow-up questionnaires

- There is no Australian involvement in any of the additional pharmacovigilance studies. The renal pharmacokinetics study, the midazolam interaction study, the CYP3A4/5 and CYP1A2 study (in vivo and in vitro studies) and the Drug Utilisation Study are considered by the sponsor to be relevant to the Australian population.
- The sponsor has proposed routine risk minimisation for all safety concerns and missing information.

New and outstanding recommendations following the second round evaluation

There are no outstanding or new RMP recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement EU-RMP (version 1.5, date 20 July 2016, data lock point 15 December 2014) with Australian Specific Annex (version 1.1, date 2 May 2017) and any future updates as a condition of registration.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration from a quality or biopharmaceutics perspective.

Nonclinical

- The nonclinical data had no major deficiencies.
- Primary pharmacology in vitro studies showed that eluxadoline was a potent MOR agonist and DOR antagonist, an inhibitor of propulsive upper GI motility and did not

prevent gastric emptying. Overall, the in vitro and in vivo nonclinical studies submitted support the drug's use for the proposed indication.

- Secondary pharmacodynamics and safety pharmacology studies indicate that eluxadoline does not inhibit or stimulate receptors associated with abuse potential. Overall, based on the nonclinical studies submitted, there are no clinically relevant hazards identified.
- Repeat-dose toxicity studies by the oral route showed no major toxicities with minimal and reversible treatment-related observations. Based on the nonclinical studies submitted, there are no clinically relevant effects which may be expected in patients.
- Eluxadoline is not considered to pose a genotoxic or carcinogenic hazard.
- The proposed Pregnancy Category is B1, which is appropriate based on the animal findings.[13]
- There are no nonclinical objections to registration.
- Amendments to the draft Product Information document were also recommended to the Delegate.

Clinical

See Attachment 1 for details of the TGA's clinical evaluation of the sponsor's clinical submission.

- The sponsor argues that eluxadoline is in a different class from loperamide by being both a MOR agonist/DOR antagonist, however in relation to treatment related AEs the sponsor only considers *'selected AEs based on known class effects of MOR agonists and opioids'.*
- The clinical evaluator stated in the first evaluation report that it is not recommended that the proposed authorisation be approved.
- The lack of a clear presentation of the risk of all treatment related AEs makes the comparison unfavourable with the modest improvement seen compared with placebo.
- However, in the second round, the clinical evaluator stated that: 'The clinical evaluator recommends that eluxadoline (Viberzi) be approved for the following indication: *'Viberzi (eluxadoline) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d).'*

Risk management plan

The evaluator stated that ACM advice on the RMP was not sought for this submission.

There are no outstanding or new RMP recommendations. The RMP evaluator recommended wording for the Conditions of Registration (see above).

Risk-benefit analysis

Delegate's considerations

As mentioned in the 'Product background' section (see above), IBS is a functional GI disorder that is characterised by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics.[1] IBS with predominant chronic or recurrent diarrhoea (IBS-d) is a subset of IBS and requires proper diagnosis, given that IBS appears

to be a diagnosis of exclusion. Pharmacological agents with specificity for IBS-d type symptoms are rare.

The beneficial effects of eluxadoline in treating IBS-d arise via local action within the GI tract, where the extensive expression of opioid receptors plays a key role in regulating GI motility, secretion, and visceral sensation.[6]

The low bioavailability of eluxadoline may reduce systemic side effects as well as the potential for abuse and dependence. While the evaluated data support the efficacy of eluxadoline in IBS-d, the latter is considered moderate. That aside, all the TGA evaluators have subsequently raised no objection to the approvability of eluxadoline although, there are now postmarketing reports of severe pancreatitis (sometimes fatal) warranting contraindication in both the FDA and Australian PIs. The latter is in addition to the postmarketing reports of increased constipation warranting precautionary statement in the Australian PI.

The TGA evaluators have suggested modifications to the draft PI. Regarding the RMP, the sponsor is requested to harmonise the proposed Australian 'Contraindications' with those of the EU.

Summary of Issues

The TGA evaluators have raised no objection to the approvability of eluxadoline. However, in addition to some hints from the gamut of clinical data provided, there are recent postmarketing reports (see italicised text below) of severe pancreatitis (sometimes fatal) in patients without a gallbladder, qualifying for contraindication in both the FDA and Australian PIs in that population subgroup. The latter is in addition to the overall postmarketing reports of increased constipation warranting precautionary statement, in the Australian PI.

> *In clinical trials, some of these events of SO spasm and pancreatitis led to brief hospitalizations, but all had favourable outcomes with no sequelae. In the post-marketing setting, severe cases of acute pancreatitis, sometimes fatal, were observed following the use of eluxadoline in patients without a gallbladder. As a result, both the FDA and the Sponsor have determined that the benefit-risk balance in this patient population is no longer favourable. Therefore, the Sponsor is updating the United States Prescribing Information (USPI) and the proposed Australian labelling to include a contraindication for eluxadoline use in patients who do not have a gallbladder. As all cases of SO spasm in clinical trials and approximately 85% of SO/pancreatitis cases in the post marketing setting have been reported in patients without a gallbladder (100% of cases that would be classified as severe), the inclusion of this contraindication in the Australian PI, would serve to significantly reduce the most significant risk associated with eluxadoline, thereby reinforcing the positive benefit-risk balance of eluxadoline*

Proposed action

Based on the available evidence from the evaluated submitted data, the Delegate was inclined at this stage to favour the approval of the application subject to resolving issues arising from the ACM deliberations and finalising matters pertaining to the suggested draft PI modifications as per the nonclinical, clinical and RMP evaluators to the satisfaction of the TGA.

Request for ACM advice

Approvability of the submission based on moderate efficacy finding for eluxadoline for the proposed indication, given the recent postmarket emergent reports of:

1. Increased of severe cases of acute pancreatitis, sometimes fatal, that were observed following the use of eluxadoline in patients without a gallbladder; (Note: Now a contraindication in both the US and Australian PIs).
2. SAEs of constipation requiring hospitalisation or medical intervention prior to 4 days of symptom onset; (Note: The Australian PI now has a precautionary statement on the issue).

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Sponsor's comments on evaluations

The sponsor agrees with the recommendation of the Delegate to approve the application for eluxadoline and to amend the Australian PI as suggested by the Delegate. As indicated in the sponsor's comments on the PI document, the Delegate's recommendations have been addressed and adopted in the latest draft PI version provided to the TGA.

The sponsor comments on the issues for which the advice of the ACM is sought, as outlined in the Delegate's Overview, are presented below.

ACM advice sought by the Delegate

> *'Approvability of the submission based on moderate efficacy finding for eluxadoline for the proposed indication, given the recent post marketing emergent reports of:*
>
> *1. Increased of severe cases of acute pancreatitis, sometimes fatal, that were observed following the use of eluxadoline in patients without a gallbladder (Note: Now a contraindication in both the US and Australian PIs)'.*

4 cases of moderately severe to severe pancreatitis have been reported from the time of the International Birth Date of eluxadoline on 27 May 2015 to 31 August 2017. The receipt of these 4 cases prompted the sponsor to conduct a signal assessment to examine cumulative cases of pancreatitis, including those associated with local/systemic complications, organ failure, and/or death, the results of which may be found in the Eluxadoline Periodic Safety Update Report (PSUR) 1.0. Apart from the above 4 cases, the cases of pancreatitis from the cumulative postmarketing experience appear consistent with those seen in the eluxadoline clinical trials (for example, all cases were considered mild and, where known, nearly all were recovered or improving at the time of reporting). The majority of the postmarketing pancreatitis cases describe known safety concerns associated with eluxadoline. Amongst cases where gallbladder status was known, approximately 80% of cases occurred in patients without a gallbladder. Importantly, all 4 moderately severe to severe cases of pancreatitis occurred in patients without a gallbladder. Aside from the 4 moderately severe to severe cases under review, the postmarketing pancreatitis cases did not indicate any local or systemic complications, organ failure, or fatal outcomes and would be considered mild according to the revised Atlanta Classification criteria, based on the available information in the reports.

Upon completion of the signal assessment, the sponsor subsequently updated their Company Core Data Sheet (CCDS) and the US Prescribing Information (USPI) in April 2017 to include a contraindication for eluxadoline use in patients who do not have a gallbladder, thus aligning the US PI with all approved markets globally. Since the US PI update, there have been no new cases of moderately severe to severe pancreatitis reported. Additionally, since product launch in the EU in April 2017 and in Canada in April 2017, regions where a contraindication of use in patients without a gallbladder has been in place since approval, there have been no reported cases of pancreatitis in either of these regions. As all cases of sphincter of Oddi spasm in clinical trials and over 80% of sphincter

of Oddi/pancreatitis cases in the postmarketing setting have been reported in patients without a gallbladder (100% of cases that could be classified as moderately severe to severe), the inclusion of this contraindication globally has dramatically reduced the most significant risk associated with eluxadoline, thereby reinforcing the positive benefit-risk balance of eluxadoline.

> *'Approvability of the submission based on moderate efficacy finding for eluxadoline for the proposed indication, given the recent post marketing emergent reports of:*
>
> 2. *Serious adverse events of constipation requiring hospitalization or medical intervention prior to 4 days of symptom onset; (Note: The Australian PI now has a precautionary statement on the issue'.*

The original approved language in the USPI (as well as the originally proposed language for the Australian PI) stated that patients should discontinue Viberzi if they develop severe constipation for more than 4 days:

> '*Discontinue Viberzi in patients who develop severe constipation for more than 4 days*.'

The sponsor's intent was that if a patient developed constipation which lasted for more than 4 days then that would be considered 'severe' and the patient should discontinue treatment with Viberzi. On 15 March 2017, the sponsor received a request from the FDA stating that the recommendation to discontinue Viberzi secondary to severe constipation should be amended to remove the requirement for 4 days' duration given that, at the time, three postmarketing serious adverse event cases reported hospitalisation and required medical intervention prior to 4 days of symptom onset.

Following the sponsor's review of cases of constipation, the sponsor agreed with the FDA's recommendation given that the postmarketing cases indicated that constipation requiring hospitalisation and/or medical intervention can occur earlier in some patients. Therefore, as requested by the FDA, the sponsor agreed to remove language from the USPI (as well as the CCDS) specifying the number of days of constipation by which patients should be instructed to stop treatment and seek medical attention. The removal of this clause places the emphasis on the patient's qualitative symptomatology, rather than on a quantitative duration of symptoms.

The USPI, CCDS, and proposed Australian PI, have all been updated to reflect this change. In the proposed Australian PI, it now states the following:

> *'If patients develop severe constipation they should be instructed to stop Viberzi and seek medical attention.'*

As of 31 August 2017, there have been a total of 8 serious spontaneous adverse events of constipation reported since the International Birth Date of eluxadoline on 27 May 2015. Of these 8 serious cases of constipation, four were reported describing either hospitalisation or the requirement for urgent medical attention/intervention prior to 4 days of symptom onset. While constipation is an identified risk with the use of eluxadoline, at this time, there is no confirmed signal for severe constipation or complications of decreased gastrointestinal motility.

The proposed language for the Australian PI (which mirrors that found in the USPI and CCDS) serves as a precautionary measure and deemphasises the quantitative duration of symptoms in favour of qualitative symptomatology.

Benefit-risk analysis

The sponsor believes that the weight of evidence clearly supports the effectiveness of eluxadoline to treat the multiple abdominal and bowel symptoms of IBS-d and that its availability provides a much needed treatment option for patients with IBS-d.

In addition to demonstrating statistical superiority to placebo for the primary endpoint of composite response of simultaneous improvement in abdominal pain and stool consistency, the endpoint recommended by the EMA Guidelines on IBS, eluxadoline was also demonstrated to positively impact multiple bothersome symptoms of IBS-d and to improve patients' quality of life. Eluxadoline is therefore differentiated from other available treatment options for IBS-d, which typically aim at treating individual symptoms and which have not been subjected to current regulatory standards involving large, prospective, double-blind, randomised and controlled trials.

Eluxadoline has a favourable tolerability profile. In clinical trials, eluxadoline demonstrated low rates of treatment emergent AEs that were generally reported at similar rates to placebo. Postmarketing data confirms the safety profile demonstrated during clinical development with the use of eluxadoline. From the approval of the product in May 2015 to August 2017, the sponsor has not identified any newly confirmed safety signals in the post- marketing setting with the exception of severe pancreatitis in patients without a gallbladder. On identification of this risk, the USPI and CCDS were expeditiously updated. There have been no new serious unexpected adverse events considered causally-related to eluxadoline which warrant inclusion in the CCDS (or proposed Australian PI). A '*cumulative and interval summary tabulation of serious and non-serious adverse reactions from postmarketing sources'* may be found in the Eluxadoline PSUR 1.0.

With regards to the important identified risks of sphincter of Oddi spasm and pancreatitis, in clinical trials some of these events led to brief hospitalisations but all had favourable outcomes with no sequelae. In the postmarketing setting, while nearly all cases behaved in the manner described above during clinical development, four moderately severe to severe cases of acute pancreatitis, 2 of which were fatal, were observed following the use of eluxadoline in patients without a gallbladder. These four cases that constituted this signal (the only 4 cases that were not classified as 'mild' per Atlanta criteria based on available data) all occurred in patients without a gallbladder and were reported in the US where the use of the 75 mg bd dose was recommended for this patient population.

The sponsor subsequently updated their CCDS and the USPI to include a contraindication for eluxadoline use in patients who do not have a gallbladder, thus aligning the USPI with all approved markets globally. Since that time, there have been no new cases of moderately severe to severe pancreatitis reported. Additionally, since product launch in the EU in April 2017 and in Canada in April 2017, there have been no reported cases of pancreatitis in either of these regions. As all cases of sphincter of Oddi spasm in clinical trials and over 80% of sphincter of Oddi/pancreatitis cases in the postmarketing setting have been reported in patients without a gallbladder (100% of cases that could be classified as moderately severe to severe), the inclusion of this contraindication globally has dramatically reduced the most significant risk associated with eluxadoline, thereby reinforcing the positive benefit-risk balance of eluxadoline. With regards to constipation, as previously mentioned, while an identified risk, at this time, there is no confirmed signal for severe constipation or complications of decreased gastrointestinal motility.

Eluxadoline provides an important treatment option for patients with IBS-d. Given the consistent findings for the effectiveness of the product, the overall favourable tolerability profile, and the risk mitigation efforts in place for patients without a gallbladder, the sponsor believes that the benefit-risk of eluxadoline remains positive and agrees with the recommendation of the Delegate to approve the application for eluxadoline.

Advisory committee considerations

The ACM taking into account the submitted evidence of efficacy, safety and quality, and noting the delegate's concerns, considered Viberzi tablet containing 75 mg and 100 mg of eluxadoline to have an overall negative benefit-risk profile for the proposed indication:

Eluxadoline (Viberzi) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d).

In making this recommendation the ACM:

- noted contraindication concerns in both the US and Australian Product Information regarding postmarketing reports relating to severe pancreatitis (including fatal cases), primarily, but not exclusively in patients without a gall bladder;
- noted concern of overall postmarketing reports of increased constipation warranting a precautionary statement in the Australian PI; and
- noted that there was no comparative study submitted against non-pharmacological treatment modalities.

The ACM noted that the clinical benefits of eluxadoline in the management of a non-fatal condition, diarrhoea-predominant irritable bowel syndrome, were modest.

The ACM's main concern was the postmarketing data reporting an increased rate of pancreatitis in patients commencing eluxadoline. These episodes had a close temporal association with the initiation of eluxadoline, 2 of which were fatal. The sponsor noted that these episodes mostly occurred in those who had had prior cholecystectomy, and recommended that patients without gallbladders be listed as a contraindication to its use.

The ACM noted that the mechanisms by which eluxadoline caused pancreatitis had not been elucidated and that pancreatitis had been documented in patients without prior cholecystectomy.

The ACM concluded that there was an overall negative risk-benefit profile given the modest benefit of the medication in a condition not associated with any mortality, and the low, but definite risk of pancreatitis, a potentially fatal condition. The ACM did not feel that the contra-indication in patients without gallbladders adequately mitigated against the development of pancreatitis since cases occurred in patients without prior cholecystectomy, and because its pathogenesis was not understood.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

Approvability of the submission based on the moderate efficacy finding for eluxadoline for the proposed indication, given the recent postmarketing emergent reports of:

1. *An increase of severe cases of acute pancreatitis, sometimes fatal, that were observed following the use of eluxadoline in patients without a gallbladder; (Note: Now a contraindication in both the US and Australian PIs).*

The ACM's opinion was negative regarding approvability of the submission while noting the proposed contraindication of eluxadoline in the PI in patients without a gallbladder.

2. *SAEs of constipation requiring hospitalisation or medical intervention prior to 4 days of symptom onset; (Note: Australian PI now has a precautionary statement on the issue).*

The ACM noted the proposed precautionary statement for severe constipation longer than 4 days in the PI and, suggested that patients should cease eluxadoline in that case while seeking medical advice.

Resolution

That eluxadoline not be registered for the treatment of irritable bowel syndrome with predominant diarrhoea, in adults.

Sponsor's response to the Delegate regarding ACM resolution

The sponsor would like to clarify some important inaccuracies contained within the ACM's Resolution and, at the same time, provide some additional information on more up-to-date postmarketing cases of pancreatitis. The sponsor believes this information is critical in demonstrating the effectiveness of the product labelling to reduce the risk of pancreatitis and reinforces the positive benefit-risk balance of eluxadoline in patients with a gallbladder. The sponsor does not concur with the ACM Resolution that '*eluxadoline not be registered for the treatment of irritable bowel syndrome with predominant diarrhoea, in adults'*. In contrast, the sponsor noted that pharmaceutical quality, nonclinical and clinical evaluators had no objections and recommended Viberzi be approved for registration in the proposed indication. In addition, the sponsor has requested clinical opinion from two Key Opinion Leaders (KOL) based in Australia. The KOLs have addressed the risk management concerns raised in recent post- marketing surveillance as well as the real unmet clinical need for patients suffering this condition. The KOL communications were provided to the TGA.

The Delegate sought the ACM's advice about 'the approvability of the submission based on the moderate efficacy finding for eluxadoline for the proposed indication, given the recent post marketing emergent reports of:

1. *'An increase of severe cases of acute pancreatitis, sometimes fatal, that were observed following the use of eluxadoline in patients without a gallbladder; (Note: Now a contraindication in both the US and Australian PIs).*
2. *SAEs of constipation requiring hospitalization or medical intervention prior to 4 days of symptom onset; (Note: Australian PI now has a precautionary statement on the issue).'*

These 2 issues raised by the Delegate to the ACM, as well as the ACM's response to these issues, will be addressed separately below.

Pancreatitis

The Delegate sought the ACM's advice about the approvability of eluxadoline due to:

> *'An increase of severe cases of acute pancreatitis, sometimes fatal, that were observed following the use of eluxadoline in patients without a gallbladder; (Note: Now a contraindication in both the US and Australian PIs).'*

The ACM's response to the overall approvability of eluxadoline in the Resolution was the following:

> *'The ACM taking into account the submitted evidence of efficacy, safety and quality, and noting the delegate's concerns, considered Viberzi tablet containing 75 mg and 100 mg of eluxadoline to have an overall negative benefit-risk profile for the proposed indication: 'Eluxadoline (Viberzi) is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-d)''.*

The ACM states that, in making this recommendation, they noted the following regarding pancreatitis:

> *'noted contraindication concerns in both the US and Australian PI regarding postmarketing reports relating to severe pancreatitis (including fatal cases), primarily, but not exclusively in patients without a gallbladder.'*

The sponsor wishes to point out an inaccuracy in the preceding statement. The ACM states that cases of severe pancreatitis (including fatal cases) occurred 'primarily, but not exclusively', in patients without a gallbladder. This statement is factually incorrect. To date, there have been 4 cases of moderately severe to severe pancreatitis (including 2 fatal cases) observed with the use of eluxadoline, *all* of which occurred in the postmarketing

period in patients without a gallbladder. It was these 4 cases in patients without a gallbladder that confirmed a safety signal for severe pancreatitis in patients without a gallbladder and ultimately led to the added contraindication in the USPI and the sponsor's CCDS. All cases of pancreatitis which have occurred in patients with a gallbladder have been mild as per Atlanta Classification criteria based upon available information and followed a course generally consistent with those cases observed in pre-marketing clinical trials (that is, they were not associated with organ failure or death, and, where known, nearly all had recovered or were recovering following discontinuation of treatment). This is a crucial distinction that needs to be clarified with regard to the positive benefit-risk balance in patients with a gallbladder and if misinterpreted, may have contributed to the ACM's negative opinion on the approvability of eluxadoline.

The ACM Resolution goes on to state:

- That the main concern of the ACM was the postmarketing data reporting an increased rate of pancreatitis in patients commencing eluxadoline.
- The ACM also noted that the mechanisms by which eluxadoline caused pancreatitis had not been elucidated and that pancreatitis had been documented in patients without prior cholecystectomy.
- The ACM did not feel that the contraindication in patients without gallbladders adequately mitigated against the development of pancreatitis since cases occurred in patients without prior cholecystectomy, and because its pathogenesis was not understood.
- Rate of pancreatitis.

The sponsor believes that the ACM's statement regarding an increased rate of pancreatitis is unsubstantiated. During the clinical development program of eluxadoline, there were a total of 6 cases of pancreatitis reported at the 100 mg bd dose and 2 cases reported at the 75mg bd dose for an incidence rate of approximately 0.4% (4/1032) and 0.2% (2/807), respectively.

Cumulatively, since the International Birth Date, 27 May 2015, through 31 July 2017, the US eluxadoline exposure from marketing experience provided by Quintiles IMS National Prescription Audit is estimated to be 305,687 total prescriptions, of which 102,380 are new to brand prescriptions. The new to brand measure shows the volume of National Prescription Audit prescriptions that are associated with first time use of a product. It reports prescriptions for patients who are starting therapy with a product for the first time within the previous 12 months. Considering the total number of pancreatitis cases reported from international birth date to 31 July was 230, there does not appear to be an increased rate of pancreatitis reporting in the postmarketing period. There *was*, however, an increased severity of pancreatitis, as all of the cases which occurred during clinical development were adjudicated as 'mild' by Atlanta Classification criteria and 4 cases of moderately severe to severe pancreatitis were seen in the postmarketing setting, all of which occurred in patients without a gallbladder.

In the ACM's ratified minutes from the meeting on 5 to 6 October 2017, the ACM also makes reference to an analysis published online on 9 September 2017, conducted by Gawron A, et al.,[21] of the US Federal Adverse Events Reporting System (FAERS) as further evidence outlining the risk of pancreatitis. This study concluded that there was an increased risk of developing pancreatitis compared to other opioid agonists and to other agents recently introduced for the treatment of IBS-d. In lieu of discussing a point by point critique of the analysis, the sponsor wishes to point out inherent flaws and limitations in

[21] Gawron A et al.. Risk of pancreatitis following treatment of IBS with eluxadoline, Clinical Gastroenterology and Hepatology, 2017; http://dx.doi.org/10.1016/j.cgh.2017.08.006

the methodology used in Gawron's analysis. FAERS is a database that contains AE reports, medication error reports and product quality complaints resulting in AEs that were submitted to FDA. Reports are submitted voluntarily by healthcare professionals, consumers, and manufacturers. While FAERS is a useful tool for the FDA for activities such as looking for new safety concerns that might be related to a marketed product, it is not appropriate for use in a comparative assessment between products, whether of a similar class or indication.

Notable limitations include:

- There is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event.
- FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the length of time a product has been marketed and publicity about an event.
  - Considering the fact that eluxadoline is a newly approved drug and that there has been recently published information about pancreatitis related to eluxadoline, results are likely to be skewed due to recognition and reporting bias.
  - Newly introduced treatments lack a sense of familiarity and may be subjected to more scrutiny than treatments that have been used for a number of years.

There are also duplicate reports where the same report was submitted by a consumer and by the sponsor, which are not always recognisable due to limited case information.

- Information contained within FAERS reports are limited, often missing important information useful in determining potential causality with the use of the suspected medication
- Rates of occurrence cannot be established with reported events.
  - The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. Due to the items mentioned above (that is, reports not received for every AE that occurs, reporting bias) as well as an inability to accurately determine the number of patients taking the medication (especially a drug that is provided over the counter as such loperamide), information in these reports cannot be used to estimate the incidence of the reactions reported.
  - In that same vein, the FDA considers it improper to do between-drug comparisons with this data, which is the precise methodology used by Gawron et al., in their analysis.

The FDA, in their own analysis of the FAERS data, did not make claims as to the overall safety of eluxadoline compared to other opioid agonists or IBS treatments, but rather analysed the data for eluxadoline independently leading to their decision that eluxadoline should be contraindicated in patients without a gallbladder, an analysis which the sponsor independently conducted and agreed with. The FDA, as well as the regulators in all other markets in which this drug is currently approved, considers the benefit-risk balance in patients with a gallbladder to be favourable.

- Mechanism of cause of pancreatitis/pancreatitis in patients with a gallbladder

The ACM states that the mechanisms by which eluxadoline causes pancreatitis had not been elucidated and that pancreatitis had been documented in patients without a cholecystectomy. The sponsor would like to point out that this is not entirely accurate. The effect of MOR agonism on the sphincter of Oddi has been well documented in scientific literature. Cholecystectomy is known to be a risk factor for sphincter of Oddi dysfunction

and for opioid-induced SO spasm. Ingestion of a fatty meal is followed by release of cholecystokinin (CCK) which causes the gallbladder to contract and the sphincter of Oddi to relax. Coordination of gallbladder and sphincter of Oddi function may also be influenced by nerve bundles which connect the gallbladder and sphincter of Oddi via the cystic duct.

Cholecystectomy may influence normal sphincter of Oddi function by disrupting this nerve pathway and altering its response to CCK, leading to dysfunction of the sphincter of Oddi. Additionally, the gallbladder serves as a reservoir or safety valve that can accommodate increases in sphincter of Oddi/biliary/pancreatic duct pressure due to opiate induced spasm. If the gallbladder is absent, patients are more susceptible to transient cholestasis (transaminase abnormalities) or transient pancreatitis. It should be noted that the presence of a gallbladder does not preclude the possibility of development of pancreatitis secondary to sphincter of Oddi spasm, or certainly secondary to other causes (for example, alcohol), however, all of the cases of pancreatitis demonstrated in clinical development and in the postmarketing setting, in patients with a gallbladder, have been mild in nature and rapidly reversed without sequelae upon discontinuation of treatment.

A search of the sponsor's Safety Database for post marketing eluxadoline cases from 27 May 2015 (the International Birth Date of eluxadoline) through 31 July 2017 was performed using the Medical Dictionary for Regulatory Affairs (MedDRA) Standardized MedDRA Query for 'Acute pancreatitis' (broad) and yielded a result of 230 cases. These 230 cases consisted of 219 cases with a reported diagnosis of pancreatitis (189 reported cases of 'pancreatitis', 21 cases of 'pancreatitis acute', 1 case of 'pancreatitis necrotising') and 11 cases reporting both a symptom and a laboratory value indicative of pancreatitis. Case narratives were reviewed for information on gallbladder status.

Of the 230 cases:

- 140 cases had a known gallbladder status:
  - 106/140 cases (76%) reported a history of cholecystectomy or no gallbladder present.
  - 34/140 cases (24%) reported that either the patient's gallbladder was intact or that there was no history of a prior cholecystectomy.
- 90 cases did not report a gallbladder status.

Although the sponsor is considering the reporting of no prior history of cholecystectomy as indication of an intact gallbladder, this does not exclude the possibility of gallbladder agenesis (estimated incidence of 10 to 65 per 100,000 population).

In general, the 34 cases which occurred in patients with either an intact gallbladder or no history of cholecystectomy reported minimal information precluding the ability to determine the potential mechanism of pancreatitis in these patients, a diagnosis which, incidentally, lacked either laboratory or diagnostic imaging confirmation in approximately 68% of cases. Analysis of alternative aetiologies of pancreatitis was hindered by the scarcity of any reported medical history and concomitant medications (absent in approximately 74 to 76% of cases), as well as social history of alcohol use or smoking. Importantly, all of the reported cases were mild, as they did not describe local/systemic complications, organ failure, and/or death, and, where reported, 93% of patients had recovered/improved, at the time of the report. Overall, these cases are consistent with the sponsor's expectations and contributed to the interpretation that the benefit-risk balance has not changed in patients with an intact gallbladder.

Table 22: Case details; Patients with a gallbladder (N = 34)

Description	(N =) (Total N = 34)
Latency reported	N = 17
1 day	8
> 1 day to 1 week	5
> 1 week	4 ('within 2 weeks', 34 days, '4 to 6 weeks', and 90 days)
Action taken Reported	N = 27
Discontinued treatment	24
Decreased dose	2
Temporarily discontinued treatment	1
Outcome Reported	N = 15
Ongoing	1
Recovered/Improved	14
Severity per Revised Atlanta Classification criteria	N = 34
Mild	34
Presence of supporting labs or imaging/diagnostic tests	N = 11
Alcohol Use Reported	N = 12
No prior history of alcohol use/alcoholism and/or no concomitant alcohol use	10
Use of alcohol	2
Smoking history reported	N = 3
No history of smoking	1
Smoking history reported	2
Body Mass Index (BMI) reported	N = 3
Normal BMI	2
Obese	1 (BMI 45.6)
Concomitant medications reported	N = 8
Medical history and/or concomitant disease reported relevant info:	N = 9
Medical of high cholesterol	1
Hyperlipidaemia and BMI 45.6 (obese)	1
Co-reported sphincter of Oddi dysfunction	2
Concomitant stone in the common bile duct	1
Medical history of chronic abdominal pain and family history of gallbladder disease	1

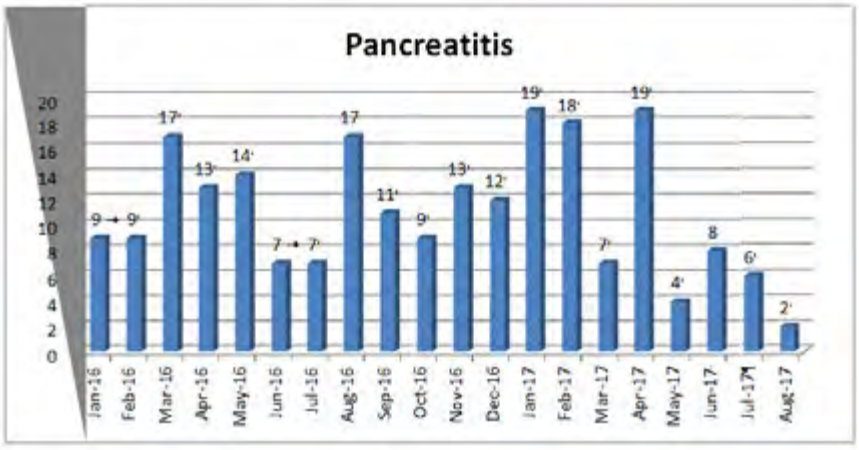
- Contraindication in patients without a gallbladder

The ACM did not feel that the contraindication in patients without gallbladders adequately mitigate against the development of pancreatitis since cases occurred in patients without prior cholecystectomy, and because its pathogenesis was not understood. In addition to the previous arguments presented above, the sponsor feels strongly that the contraindication in patients without a gallbladder does in fact adequately mitigate against the development of pancreatitis.

A critical appraisal on whether there was a change in reporting of cases of pancreatitis before and after the contraindication in the US was introduced was conducted by the sponsor. The impact of the contraindication of use in patients without a gallbladder to the USPI, while still recent, has already demonstrated observable effects on the number of pancreatitis cases reported (defined as a reported diagnosis of pancreatitis). This is especially likely considering the lack of confirmed onset dates for many of the events, some of which may have occurred prior to the date of the USPI update.

As shown in Figure 2, since the addition of the contraindication of use in patients without a gallbladder to the USPI on 21 April 2017, the number of pancreatitis cases has significantly decreased, reporting the lowest monthly numbers of pancreatitis cases since the drug was approved.

Figure 1: Eluxadoline postmarketing cases reporting Preferred Terms of pancreatitis/pancreatitis



Since the USPI update on 21 April 2017 through to 31 August 2017 there have been 28 cases of pancreatitis received which reported the following PTs: pancreatitis (26) and pancreatitis acute (2). All 28 cases were from the US, to date, the only country which has reported any cases of pancreatitis and the only country to not have a contraindication for use in patients without a gallbladder from the outset (that is, since product launch in the EU in April 2017 and in Canada in April 2017, there have been *no* reported cases of pancreatitis in either of these regions). Of these 28 cases, 10 were reported in patients without a gallbladder, which may reflect either occurrence prior to the implementation of the contraindication or inappropriate prescribing. Another 10 occurred in patients with an unknown gallbladder status. The remaining 8 cases were reported in patients with a gallbladder and were similar to all other postmarketing cases of pancreatitis in patients with a gallbladder in that the majority of cases failed to have a confirmatory diagnosis supported by either laboratory or imaging. Importantly, based on all available information, all 28 of these cases were considered mild as they did not describe local/systemic complications, organ failure and/or death.

At this time, the risk minimisation measure approved in the US, Canada and the EU is the contraindication in the product labelling (for example, the USPI in the US; the Product Monograph in Canada; and the Summary of Product Characteristics and Patient Information Leaflet in the EU), wherein the use of eluxadoline is contraindicated in

conditions which may predispose a patient to sphincter of Oddi spasm or pancreatitis. The contraindication for use in patients without a gallbladder has been in place in both Canada and the EU since initial approval of the product in those regions and, as stated above, there have been no cases of pancreatitis reported in these regions. The contraindication was added to the USPI on April 2017.

The proposed Australian PI currently contraindicates risk factors for pancreatitis and sphincter of Oddi spasm which are well established by the known epidemiology data on pancreatitis and the clinical trial experience with eluxadoline. These are:

- Alcoholism, alcohol abuse, alcohol addiction or chronic or acute excessive alcohol use.
- Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction.
- 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.
- Patients without a gallbladder (for example, due to cholecystectomy or agenesis).

The sponsor believes that the proposed contraindications in the Australian PI are effective risk minimisation measures and are sufficient to mitigate the risk of pancreatitis.

Constipation

The Delegate sought the ACM's advice about the approvability of eluxadoline due to

> *'SAEs of constipation requiring hospitalization or medical intervention prior to 4 days of symptom onset; (Note: Australian PI now has a precautionary statement on the issue).'*

The ACM stated that in making their recommendation on the overall approvability of eluxadoline they noted the following regarding constipation:

> *'noted concern of overall postmarketing reports of increased constipation warranting a precautionary statement in the Australian PI.'*

The sponsor wishes to point out the inaccuracy of this statement. During the clinical development program of eluxadoline, constipation was reported at an incidence rate of 7.4% (60/807) and 8.1% (84/1032) in patients taking 75 mg and 100 mg, respectively, compared with 2.5% (24/975) of placebo patients. As of 31 August 2017, there have been a total of 174 spontaneous cases of constipation, 8 of which were serious, reported since the International Birth Date of eluxadoline on 27 May 2015 during which time there have been approximately 102,380 new to brand prescriptions of eluxadoline. Considering the total number of constipation cases reported since approval, there does not appear to be an increased rate of constipation reporting in the postmarketing period.

Of the 8 serious cases of constipation reported as of August 31, 2017, 4 were reported describing either hospitalisation or the requirement for urgent medical attention/intervention prior to 4 days of symptom onset. While constipation is an identified risk with the use of eluxadoline, at this time, there is no confirmed signal for severe constipation or complications of decreased gastrointestinal motility.

Therefore, the ACM have incorrectly concluded that the statement for severe constipation in the Australian PI was included due to an increase in constipation, as this was not the case. Nor was the precaution included due to a signal of serious adverse events of constipation requiring hospitalization or medical intervention, but rather as a precautionary measure to proactively prevent complications of constipation from developing. The original approved language in the USPI (as well as the originally proposed language for the Australian PI) stated that patients should discontinue Viberzi if they develop severe constipation for more than 4 days:

'Discontinue Viberzi in patients who develop severe constipation for more than 4 days.'

The sponsor's intent was that if a patient developed constipation which lasted for more than 4 days then that would be considered 'severe' and the patient should discontinue treatment with Viberzi. On 15 March 2017, the sponsor received a request from the FDA stating that the recommendation to discontinue Viberzi secondary to severe constipation should be amended to remove the requirement for 4 days' duration given that, at the time, three postmarketing serious adverse event cases reported hospitalisation and required medical intervention prior to 4 days of symptom onset.

Following the sponsor's review of cases of constipation, the sponsor agreed with the FDA's recommendation given that the postmarketing cases indicated that constipation requiring hospitalisation and/or medical intervention can occur earlier in some patients. Therefore, as requested by the FDA, the sponsor agreed to remove language from the USPI (as well as the CCDS) specifying the number of days of constipation by which patients should be instructed to stop treatment and seek medical attention. The removal of this clause places the emphasis on the patient's qualitative symptomatology, rather than on a quantitative duration of symptoms.

The USPI, CCDS, and proposed Australian PI have all been updated to reflect this change. In the proposed Australian Product Information, it now states the following:

'If patients develop severe constipation they should be instructed to stop Viberzi and seek medical attention'.

The proposed language for the Australian PI (which mirrors that found in the USPI and CCDS) serves as a precautionary measure and deemphasizes the quantitative duration of symptoms in favour of qualitative symptomatology.

Benefit-Risk balance

The sponsor believes that the benefit-risk balance of eluxadoline remains positive and unchanged for the proposed indication since initial marketing authorisation (in the US) for the treatment of patients with IBS-d with a gallbladder. The sponsor believes that the weight of evidence clearly supports the effectiveness of eluxadoline in IBS-d and that the proposed contraindications in the Australian PI are sufficient to minimise the most important risks of the product. Further, the availability of eluxadoline fulfils an otherwise unmet need for products able to treat the multiple bothersome symptoms of IBS-d.

IBS is the most common functional gastrointestinal disorder with a global prevalence estimated at 11.2%. The IBS-d subtype comprises one half to a third of all cases, and its global prevalence is estimated at between 3 and 4%.[22] While not life threatening, IBS is a chronic, relapsing condition marked by bothersome and often unpredictable symptoms which can dramatically impact patients' quality of life. Prior to the approval of eluxadoline, there were no pharmacologic treatments approved specifically for IBS-d. As such, treatment options for IBS-d are limited, with pharmacological therapies generally aimed at treating individual symptoms with the rationale of modulating intestinal motility, decreasing visceral sensitivity, or treating associated disorders, such as anxiety and/or depression.

In contrast to other treatment options, eluxadoline has been clearly demonstrated to treat multiple abdominal and bowel symptoms of IBS-d in large, replicated Phase III trials. In addition to demonstrating statistical superiority to placebo for the primary endpoint of composite response of simultaneous improvement in abdominal pain and stool consistency, eluxadoline also positively impacted bowel movement urgency and frequency and abdominal discomfort and bloating, as well as patients' quality of life. Eluxadoline is

[22] Lovell R, Ford A (2012). Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):712-721.e4.

therefore differentiated from other available treatment options for IBS-d, which typically aim at treating individual symptoms and which have not been subjected to current regulatory standards involving large, prospective, double-blind, randomised and placebo-controlled trials.

Eluxadoline has a favourable tolerability profile in IBS-d patients with a gallbladder. In clinical trials, eluxadoline demonstrated overall low rates of primarily GI related AEs that were generally reported at similar rates to placebo. In patients with a gallbladder, rates of AEs, SAEs and AEs leading to discontinuation were all markedly reduced compared to those whose gallbladder had been removed, demonstrating a greater tolerability in this subset of patients. In the postmarketing setting, the cumulative experience with eluxadoline, inclusive of more than 26,363 patient-year exposures, confirms the safety profile demonstrated during clinical development. Other than the signal for severe pancreatitis in US patients without a gallbladder, the sponsor has not identified any other confirmed safety signals in the postmarketing setting since the product was launched in November 2015. Thus, the sponsor believes that the risks of eluxadoline remain unchanged for IBS-d patients with a gallbladder, the indicated population per the Australian PI.

In summary, eluxadoline provides an important treatment option for patients with IBS-d. Given the consistent findings for the effectiveness of the product and the appropriateness of the product labelling, the sponsor strongly believes that the benefit-risk of eluxadoline remains positive.

ACM reply to the post-ACM response

The main concerns expressed by ACM were:

1. the association between the use of eluxadoline and the development of pancreatitis;
2. the mechanisms by which eluxadoline induces pancreatitis are unknown; hence
3. the proposed restrictions on its usage may not adequately mitigate against the development of pancreatitis.

Issue 1

> *'The association between the use of eluxadoline and the development of pancreatitis is not disputed by the sponsor'.*

The sponsor acknowledges that there is a rate of pancreatitis that develops shortly after exposure to eluxadoline which ranges from 0.2 and 0.4%. The argument that this rate is the same and has not increased from the clinical development program to the postmarketing reports does not address the main concern: patients commencing eluxadoline have an increased risk of developing pancreatitis.

The strongest evidence supporting causation is the close temporal association between exposure and the onset of the disease. This is recorded in [a table accompanying] the sponsor's response, which shows that pancreatitis developed within a week in 13 of the 17 cases of patients with a gallbladder in whom the latency was reported. The external review of the cases of severe pancreatitis provided by the applicant in its submissions also noted this close temporal association.

The applicant points out that all cases of severe pancreatitis occurred in patients who had had prior cholecystectomy and highlights the evidence that all episodes of pancreatitis in those with gallbladders were 'mild'. Whilst this may appear reassuring, it is important to note that 'mild' pancreatitis is not a mild disease. In a retrospective analysis of patients

presenting with acute pancreatitis to 4 tertiary hospitals in Sydney over a 4 year period, Nesvaderani et al.,[23] found that the median length of hospitalisation for patients was 4 days (range 1 to 106 days). Length of stays for gallstone, other cause, alcohol, and idiopathic pancreatitis were 8 days, 7.3 days, 5.8 days and 5.4 days, respectively. Furthermore, there was no statistically significant relationship between severe pancreatitis and death (odds ratio 1.61, 95% CI 0.19 to 13.94), with 1.2% of patients with severe pancreatitis dying compared to 0.7% with mild pancreatitis.

The ACM Minutes refer to further evidence outlining the risk of pancreatitis that was provided by an analysis of the US FAERS.[24] The limitations of FAERS are acknowledged but the main point stands: this analysis provides independent confirmation that there is an increased risk of pancreatitis in patients exposed to eluxadoline.

Issue 2

'The mechanisms by which eluxadoline induce pancreatitis are unknown'.

The sponsor suggests that the likely mechanism by which eluxadoline causes pancreatitis is by MOR agonism on the sphincter of Oddi: '*Cholecystectomy is known to be a risk factor for sphincter of Oddi dysfunction and for opioid-induced sphincter of Oddi dysfunction*.' The sponsor adds that the presence of a gallbladder does not preclude the possibility of development of pancreatitis secondary to sphincter of Oddi dysfunction [without references and in a very controversial field of clinical research] or other causes, and points out that all reported cases of pancreatitis in patients with a gallbladder exposed to eluxadoline were 'mild' in nature (please see above) and rapidly reversed without sequelae upon its discontinuation.

If the proposed mechanism (MOR agonism on the sphincter of Oddi) were the cause of pancreatitis in patients exposed to eluxadoline, pancreatitis would be an expected adverse event reported in a proportion of patients exposed to other μ opioid receptor agonists. A PubMed search on 13 November 2017 using the terms 'pancreatitis' and 'loperamide', an alternative MOR agonist, resulted in 2 relevant reports which described a total of 6 cases in the world literature to November 2015.[25,26] This analysis of the risks of loperamide is, of course, subject to several of the limitations outlined in the applicant's comments regarding the FAERS data.

The sponsor suggests that there may have been alternative explanations for the development of pancreatitis in the patients with an intact gallbladder, but an analysis of alternative aetiologies 'was hindered by the scarcity of any reported medical history and concomitant medications (absent in approximately 74 to 76% of cases), as well as social history of alcohol use or smoking' in the sponsor's Safety Database for postmarketing eluxadoline cases from 27 May 2015 to 31 July 2017.

Pancreatitis may occur by mechanisms other than sphincter of Oddi dysfunction or alcohol ingestion. Azathioprine induced pancreatitis is an example discussed by the key opinion leaders, and there are other well-documented drug causes of pancreatitis. There is also increasing recognition of various genetic factors that predispose to the development of acute, acute relapsing and chronic pancreatitis, and the aetiology is unknown ('idiopathic') in a significant proportion of cases. Without establishing a definitive mechanism, the proposed contraindications aimed at preventing the development of pancreatitis may not be effective.

[23] Nesvaderani M et al., Epidemiology, aetiology and outcomes of acute pancreatitis: A retrospective cohort study. Int J Surg. 2015 Nov; 23(Pt A):68-74.
[24] Gawron A, Bielefeldt K. Risk of pancreatitis following treatment of IBS with eluxadoline, Clinical Gastroenterology and Hepatology, 2017.
[25] Hwee Min L et al., Can Loperamide Cause Acute Pancreatitis? Pancreas. 40(5):780-781, Jul 2011.
[26] Labgaa I et al., Loperamide-induced recurrent acute pancreatitis. Clin Res Hepatol Gastroenterol. 2016 Feb;40(1):e13-4.

Issue 3

> *'The proposed restrictions on its usage may not adequately mitigate against the development of pancreatitis.'*

The sponsor uses the same sponsor's Safety Database from 27 May 2015 to 31 August 2017 to show, without statistical analysis, that the number of cases of pancreatitis has 'significantly decreased' since the changes to the USPI on 21 April 2017. They reported 28 cases of pancreatitis from 21 April to 31 August 2017, 18 of whom had an intact gallbladder (8), or in whom the gallbladder status was unknown (10 cases). Again, the argument was made that these cases were considered 'mild'. The sponsor reports that there have been no cases of pancreatitis reported in Canada or the EU since the product launch in April 2017 but does not provide information about the extent of its use in those jurisdictions.

The evidence provided in the sponsor's post-ACM response shows that patients, with and without gallbladders, exposed to eluxadoline, are still developing pancreatitis even after the introduction of the new USPI. Whether or not the risks are reduced by the recommended contraindications remains to be seen.

Responses of key opinion leaders

The key opinion leaders argue for the need for effective therapies for the treatment of IBS. Neither of the 2 disputes the observation that there is an increased risk of pancreatitis. Both argue that the risk will be minimised by appropriate usage. The argument that other agents induce pancreatitis is not pertinent to the registration of eluxadoline. The argument that azathioprine would not be accepted now as a new agent highlights the difficulties in deregistering an agent once approved. The mechanism of drug-induced pancreatitis caused by azathioprine is unknown, highlighting the fact that there are other mechanisms by which drugs can induce pancreatitis other than by sphincter of Oddi dysfunction or alcohol ingestion.

The key issue is:

> *'What is an acceptable risk of pancreatitis in a condition that is not associated with end-organ damage or mortality?'*

The advice of the ACM was that any increased risk of pancreatitis was unacceptable given the modest benefits of eluxadoline for the treatment of diarrhoea-predominant IBS.

Outcome

The sponsor withdrew their application on the 24 November 2017, prior to a decision being made by the TGA.

Attachment 1. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au