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Post-marketing reports of pancreatitis in eluxadoline-treated patients pre and post US label change

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Abstract

Background: Eluxadoline, a United States Food and Drug Administration (FDA)-approved treatment for irritable bowel syndrome with diarrhea (IBS-D), underwent a change to its US prescribing information on 21 April 2017, contraindicating it in patients without a gallbladder due to increased risk of pancreatitis. This study aimed to elucidate the potential role of eluxadoline's label change on the number of reported spontaneous adverse events (AEs) of pancreatitis.

Methods: A pharmacovigilance database (Oracle Argus) was searched for eluxadoline use and spontaneously reported pancreatitis cases from 1 January 2016 to 30 June 2018. Pancreatitis cases were reported as a proportion of the total number of reported AE cases in the safety database. The FDA's adverse event reporting system (AERS) was also interrogated for cases of pancreatitis concomitantly reported with eluxadoline use.

Results: In patients who received eluxadoline, 273 reported cases of pancreatitis were recorded (total AEs $n = 2191$; 12.5%). When known, 28.2% of patients reporting pancreatitis had intact gallbladders (49/174). Eluxadoline was withdrawn in 97.5% of cases, with 87.1% of patients improving or recovered at time of reporting. Importantly, the reporting proportion of pancreatitis cases decreased from 14.4% to 8.9% post label change. Findings were supported by the AERS results, which demonstrated a decrease in reporting proportion from 21.2% to 12.8%.

Conclusions: While cautious interpretation is warranted, post-marketing data indicate that the contraindication of eluxadoline in patients without a gallbladder led to reduced reported cases of pancreatitis, with no additional reports of moderately severe or severe cases. Eluxadoline is a safe and well-tolerated treatment option for IBS-D when used according to the label.

Keywords: functional gastrointestinal diseases, gallbladder, irritable bowel syndrome, pancreatitis

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Background

Eluxadoline is a mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist approved in the United States (US) in 2015 for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.[1] Activation of the μ-opioid receptor in the intestine can decrease gastrointestinal transit and is thought to account, in part, for eluxadoline's efficacy in alleviating IBS-D symptoms;[2,3] μ-opioid receptor activation has also been shown to increase sphincter tone within the gastrointestinal tract.[2] Studies indicate that opioid agonism is involved in increased flow of pancreatic and biliary secretions through the sphincter of Oddi (SO), a smooth muscle valve that regulates the flow of pancreatic and biliary secretions into the duodenum, and increased pressure in the SO in the absence of a gallbladder has also been reported. Agents that simultaneously increase flow and SO tone (e.g. contractility or spasm)

could potentially be associated with pancreaticobiliary events.

In phase III clinical trials, eluxadoline demonstrated efficacy in treating IBS-D symptoms using a composite endpoint of simultaneous improvement in worst abdominal pain and stool consistency on ⩾50% of treatment days.[4] Eluxadoline was well tolerated in clinical trials, with the most common adverse events (AEs) being constipation and nausea.[4–6] However, in phase II and III clinical trials of eluxadoline, 10 sphincter of Oddi spasm (SOS) events occurred in patients treated with either 75 mg or 100 mg of eluxadoline twice daily (10/1839 patients; 0.5%). The events were evaluated using the revised Atlanta criteria for the diagnosis of acute pancreatitis. Acute pancreatitis was clinically defined as having at least two of the following three criteria: abdominal pain suggestive of pancreatitis (epigastric pain often radiating to the back), with the start of such pain considered to be the onset of acute pancreatitis; serum amylase or lipase levels three or more times normal; and characteristic findings on computerized tomography, magnetic resonance imaging, or transabdominal ultrasonography.[7] Eight of the 10 SOS events presented with elevated aminotransferases (alanine aminotransferase/aspartate aminotransferase) associated with abdominal pain, and one was adjudicated as mild pancreatitis (defined by the revised Atlanta criteria for pancreatitis as the absence of both organ failure and local or systemic complications).[7] The remaining event presented as a mild lipase elevation (1.6 times the upper limit of normal) with abdominal pain, which was adjudicated as not meeting the revised Atlanta criteria for pancreatitis. Importantly, all SOS-related events observed in these trials occurred in patients without a gallbladder. Eight cases occurred with the higher dose of eluxadoline (100 mg twice daily) within 1 week of treatment initiation, and all resolved with eluxadoline discontinuation. The one case of SOS-associated mild pancreatitis resolved within 24 h of discontinuation.

In addition, five cases of pancreatitis not associated with SOS were reported in patients receiving 75 mg and 100 mg eluxadoline twice daily in the phase II and III clinical trials. Of these five cases, three were associated with excessive alcohol intake, one was associated with biliary sludge, and the fifth case occurred in a patient who had discontinued eluxadoline treatment 2 weeks prior to the onset of pancreatitis symptoms. All independently adjudicated cases of pancreatitis were mild, as classified per the revised Atlanta criteria. In addition, all cases resolved clinically and biochemically within 1–2 days, with the exception of one patient with severe alcoholism who demonstrated clinical improvement within 1–2 days but whose pancreatic enzymes took several weeks to normalize.[6] As SOS and pancreatitis cases were found more often in patients receiving the 100 mg eluxadoline dose, the original US Food and Drug Administration (FDA)-approved label for eluxadoline recommended that patients without a gallbladder receive the lower approved 75 mg dose. Eluxadoline was also contraindicated in patients with a history of pancreatitis, known or suspected SO dysfunction, or excessive alcohol use.[6]

Upon commercial availability of eluxadoline, standard post-marketing surveillance found additional cases of pancreatitis, and subsequent analysis showed that most of these cases occurred in patients without gallbladders.[8] As a result of these additional post-marketing data, the FDA updated eluxadoline's US label in April 2017 to be consistent with the European and Canadian labels, contraindicating its use in patients without a gallbladder.[1,6,9]

Analysis of post-marketing data is a key component of pharmacovigilance. This process updates the safety of a drug throughout its lifecycle and helps effectively communicate important new safety information to healthcare providers, as well as the public.[10,11] Reports of drug-related AEs can help inform safety labeling changes as well as identify any potential negative impacts on patients.[12] Given the high prevalence of IBS-D and its impact on the healthcare system,[13,14] it is important to analyze emerging data on the real-world safety of eluxadoline vigorously. Herein, we describe a post-marketing database evaluation of the number of spontaneous AEs of pancreatitis reported before and after the change in eluxadoline's US label, to elucidate the potential role of contraindicating the use of eluxadoline in patients without a gallbladder.

Methods

Search of pharmacovigilance database

Allergan's global safety database, the pharmacovigilance database Oracle Argus, was searched for eluxadoline use and spontaneously reported

Table 1. Characteristics and demographics of patients with cases of pancreatitis.

n (%)	All cases (*N* = 273)	Cases in patients with a gallbladder (*n* = 49)	Cases in patients without a gallbladder (*n* = 125)	Unknown gallbladder status (*n* = 99)
Sex				
Female	200 (73.3)	25 (51.0)	104 (83.2)	71 (71.7)
Male	46 (16.8)	12 (24.5)	16 (12.8)	18 (18.2)
Unknown	27 (9.9)	12 (24.5)	5 (4.0)	10 (10.1)
Age				
Adult (18–<65 years)	111 (40.7)	20 (40.8)	58 (46.4)	33 (33.3)
Elderly (⩾65 years)	41 (15.0)	5 (10.2)	25 (20.0)	11 (11.1)
Unknown	121 (44.3)	24 (49.0)	42 (33.6)	55 (55.6)
Severity of pancreatitis				
Moderately severe/severe	6 (2.2)[a]	0	6 (4.8)	0
Alcohol use[b]	24 (8.8)	4 (8.2)	13 (10.4)	7 (7.1)
Smoker	8 (2.9)	2 (4.1)	5 (4.0)	1 (1.0)

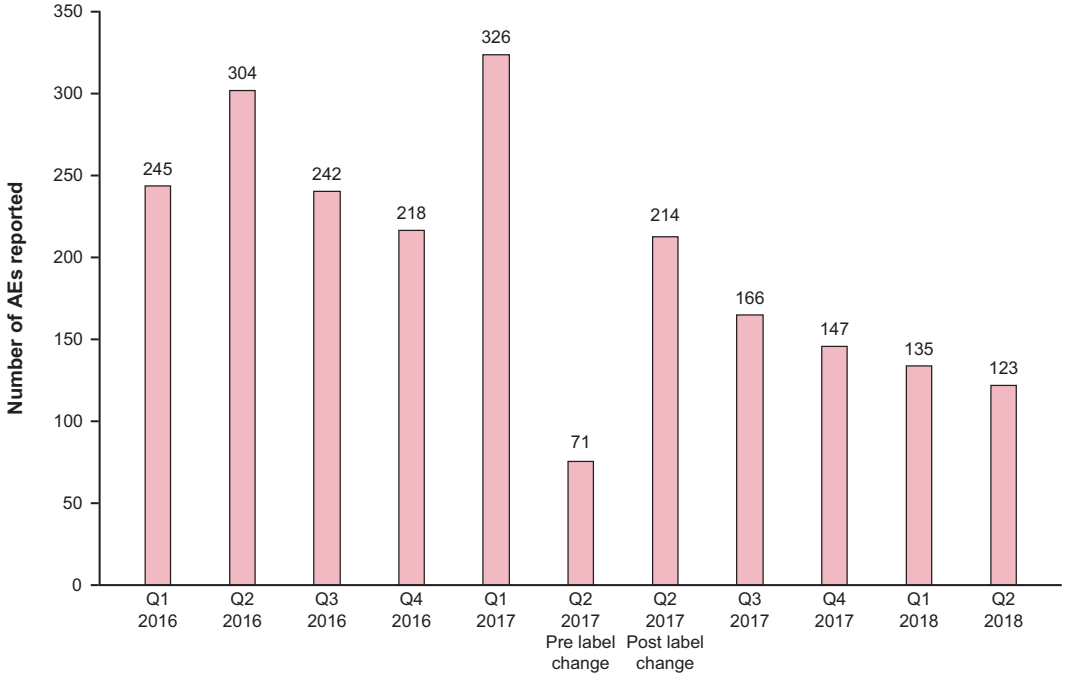
Percentages may not equal 100 due to rounding.
[a]Two of these cases could not be assessed for severity due to a lack of necessary information; they are included in the count because the patients died, although causality to pancreatitis was either considered not related or not assessable.
[b]Quantitative data for the extent of alcohol consumption are not available.

pancreatitis cases, using the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) for acute pancreatitis (broad) version 21.0, from 1 January 2016 to 30 June 2018. As recommended in the 'Introductory Guide for Standardised MedDRA Queries' post-retrieval, an algorithmic search consisting of a combination of broad search terms among various categories was employed to refine further the identification of cases of interest, yielding greater sensitivity compared to the narrow search and greater specificity compared to the broad search. For the acute pancreatitis SMQ, the broad search terms are grouped into two categories: category B is a list of laboratory values and category C is a list of signs and symptoms. The algorithm for the acute pancreatitis SMQ defines a case of interest as a record coded with either at least one term in category A [narrow scope (e.g. event terms with the word 'pancreatitis', other than those indicative of chronic conditions)] or with a combination of at least one term in category B AND one term in category C [i.e. A or (B and C)] (Supplemental Table 1). It is important to note that the reported cases of pancreatitis retrieved through this search strategy were not required to be confirmed by diagnostic imaging, laboratory testing, or a healthcare professional to appear in the dataset.

Additionally, the FDA's adverse event reporting system (AERS) was interrogated cumulatively up to a data lock point of 31 December 2019, to search for pancreatitis cases concomitantly reported with eluxadoline use. Pancreatitis cases were defined as any event term with the word 'pancreatitis' (e.g. 'pancreatitis', 'pancreatitis acute', and 'pancreatitis necrotizing').

Data collection and analysis

Reports of AE cases were assessed for demographic information, date of AE occurrence and reporting, eluxadoline dose, latency (time from medication initiation) to the report of pancreatitis, gallbladder status, any treatment adjustment, and patient outcome information. The eluxadoline dose received was determined based on the dose the patient was prescribed, regardless of frequency. Gallbladder



	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Q1 2017	Q2 2017 Pre	Q2 2017 Post	Q3 2017	Q4 2017	Q1 2018	Q2 2018
Total number of patients on eluxadoline	11,835	22,344	31,161	34,894	35,773	33,511		32,610	32,367	29,686	30,048

Figure 1. Number of reported AEs before and after eluxadoline US label change.
AEs, adverse events.

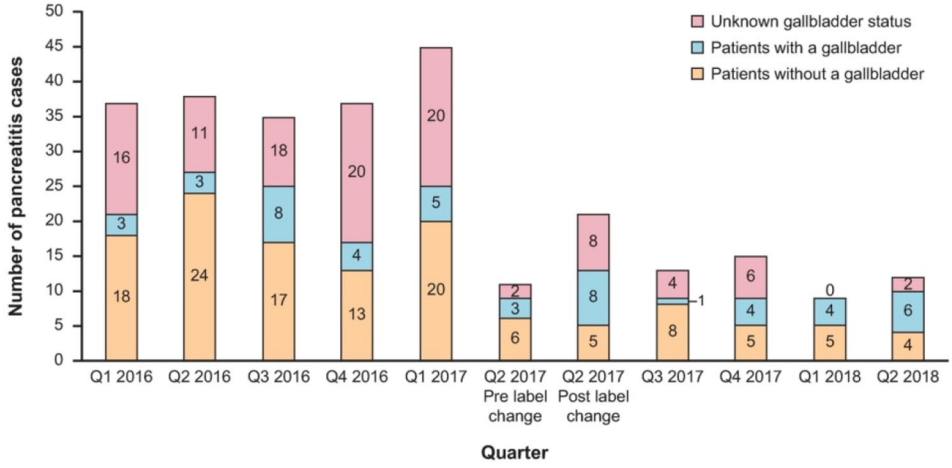
status was defined as follows: patient is reported to have a gallbladder, patient does not have a gallbladder, or unknown. The number of pancreatitis cases and total number of AE cases per quarter were assessed. All data were analyzed descriptively, with missing entries categorized as 'unknown'. Pancreatitis cases were reported as a proportion of all AE cases reported in the database (i.e. reporting proportion), in order to control for fluctuations in overall AE reporting, as it corrects for the expected higher overall rate of AE reporting observed with newly introduced products (i.e. the Weber effect). Cases retrieved *via* the FDA's AERS were also reported as a reporting proportion.

The number of patients taking eluxadoline was calculated using the IQVIA Total Patient Tracker®, a national-level estimate of the total number of unique patients in the retail outpatient setting, based on patient-level data projected to the national level using a factor consistent with total prescription number (TRx) projections. This estimate and subsequent projection also account for patients taking multiple medications and removes double counting, along with the application of other stability measures. The number of patients is calculated as: projected total patient tracker patients = [projected TRx (national audits)/unprojected TRx (from IQVIA Data Warehouse)] × patients (from IQVIA Data Warehouse).

Results

Reporting proportion of pancreatitis cases

Overall, 2191 AE cases were reported in patients receiving eluxadoline between 1 January 2016 and 30 June 2018. The number of AE cases reported ranged from 123 in Q2 2018 to 326 in Q1 2017, in an estimated 30,048 and 35,773 patients receiving eluxadoline, respectively (Figure 1). Among AE cases in which gender and age were reported, 78% were reported in females and 45% were reported in adults aged ⩾65 years. Of the total AE cases, 273 cases of pancreatitis were reported during this period: a reporting proportion of 12.5% (Figure 2). Prior to the eluxadoline label change (the period from



	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Q1 2017	Q2 2017 Pre	Q2 2017 Post	Q3 2017	Q4 2017	Q1 2018	Q2 2018
Total number of pancreatitis cases/ Total number of AE cases (Reporting proportion of total AEs)	37/245 (15.1%)	38/304 (12.5%)	35/242 (14.5%)	37/218 (17.0%)	45/326 (13.8%)	11/71 (15.5%)	21/214 (9.8%)	13/166 (7.8%)	15/147 (10.2%)	9/135 (6.7%)	12/123 (9.8%)
Total number of patients on eluxadoline	11,835	22,344	31,161	34,894	35,773	33,511		32,610	32,367	29,686	30,048

Figure 2. Number of reported pancreatitis cases, reporting proportion and number of patients receiving eluxadoline before and after eluxadoline US label change.
AEs, adverse events.

1 January 2016 to 20 April 2017), the reporting proportion of pancreatitis cases among all reported AE cases was 14.4% (203/1406 AE cases). Following the label change (the period from 21 April 2017 to 30 June 2018), the reporting proportion of pancreatitis cases decreased by 38.2% [from 14.4% to 8.9% (70/785 AE cases)]. Of the 174 pancreatitis cases in which gallbladder status was known, 125 (71.8%) occurred in patients without a gallbladder. Prior to the label change, of the 124 reported pancreatitis cases in which gallbladder status was known, 98 (79.0%) occurred in patients without gallbladders, whereas after the label change, 27 of the 50 (54.0%) reported pancreatitis cases were in patients without gallbladders.

Demographics and characteristics of patients with reported pancreatitis

Among cases in which sex and age were reported, the majority of pancreatitis cases were reported in female patients (200/246; 81.3%) and a large proportion were in patients aged 18 to <65 years (111/152; 73.0%), although 44.3% (121/273) of cases were in patients of unknown age (Table 1). Patient characteristics and demographics were generally similar between patients with and without a gallbladder, although a higher proportion of patients without a gallbladder were females [104/120 (86.7%), as compared to 25/37 (67.6%) of patients with a gallbladder].

Severity of reported pancreatitis cases

Four reported cases of pancreatitis were classified as moderately severe or severe (based on the revised Atlanta classification), including two cases of co-reported end organ failure (one of which was fatal), one case of necrotizing pancreatitis, and one case which required jejunal tube feeding. Two additional fatal cases involved female patients in whom the relationship with eluxadoline was unknown; these cases could not be classified according to the revised Atlanta criteria due to a lack of information necessary to attribute death to pancreatitis. One case involved a 50-year-old female patient who died of unknown etiology, but her death was not thought to be related to eluxadoline treatment. The second fatal case involved a 68-year-old female patient who died due to anoxic injury and the relation to

Table 2. Eluxadoline dose, onset latency, and treatment adjustment in pancreatitis cases.

n (%)	Total (*N* = 273)	Patients with a gallbladder (*n* = 49)	Patients without a gallbladder (*n* = 125)	Unknown gallbladder status (*n* = 99)
Latency				
⩽1 day	80 (29.3)	11 (22.4)	46 (36.8)	23 (23.2)
>1 day to ⩽1 week	50 (18.3)	9 (18.4)	31 (24.8)	10 (10.1)
>1 week	33 (12.1)	7 (14.3)	12 (9.6)	14 (14.1)
Unknown	110 (40.3)	22 (44.9)	36 (28.8)	52 (52.5)
Outcomes				
Recovered	112 (41.0)	18 (36.7)	58 (46.4)	36 (36.4)
Improved	9 (3.3)	1 (2.0)	5 (4.0)	3 (3.0)
Ongoing	15 (5.5)	2 (4.1)	9 (7.2)	4 (4.0)
Unknown	134 (49.1)	28 (57.1)	50 (40.0)	56 (56.6)
Dose[a]				
75 mg	123 (45.1)	9 (18.4)	87 (69.6)	27 (27.3)
100 mg	56 (20.5)	22 (44.9)	13 (10.4)	21 (21.2)
Unknown	94 (34.4)	18 (36.7)	25 (20.0)	51 (51.5)
Treatment adjustment				
None	1 (0.4)	0	0	1 (1.0)
Decreased dose	2 (0.7)	2 (4.1)	0	0
Temporarily suspended	2 (0.7)	1 (2.0)	0	1 (1.0)
Withdrawn	195 (71.4)	32 (65.3)	99 (79.2)	64 (64.6)
Unknown	73 (26.7)	14 (28.6)	26 (20.8)	33 (33.3)
Deaths	3 (1.1)	0	3 (2.4)[b]	0

Percentages may not equal 100 due to rounding.
[a]Not always specified whether 75 mg and 100 mg doses were taken once or twice daily.
[b]Two of these three patients are included because pancreatitis was co-reported in a patient who died of unknown causes.

eluxadoline was unknown. All six cases occurred in patients without a gallbladder and occurred prior to the label change in April 2017 (Tables 1 and 2).

Latency of reported pancreatitis cases

When latency status was known, a large proportion of pancreatitis cases occurred within 1 week of starting eluxadoline treatment (130/163; 79.8%) (Table 2), and 80 of the 163 cases were reported within 1 day (49.1%). Eluxadoline treatment was withdrawn following reported pancreatitis in 97.5% of cases in which the treatment adjustment was known (195/200). Among cases in which outcomes were known, 89.0% of patients had fully recovered or improved at the time of AE reporting (121/136) (Table 2).

Among cases in which the relevant information was available, the majority of patients without a gallbladder were receiving 75 mg eluxadoline (87/100; 87.0%) and experienced onset of pancreatitis within 1 week of starting treatment (77/89; 86.5%), and all were withdrawn from treatment (99/99; 100.0%). When information was available, the majority of patients without a gallbladder recovered fully or improved (63/72; 87.5%).

Reporting proportion of pancreatitis cases from the FDA's AERS

Cumulatively, 1947 total AE cases concomitant with eluxadoline use were reported in the FDA's AERS database to 31 December 2019. Among AE cases in which gender and age were reported, 78% were reported in females and 40% were reported in adults aged ⩾65 years. Of these 1947 cases, 1042 were reported on or before 21 April 2017 (the date of the US label change) and 905 were reported after the label change. Of the total AE cases, 337 pancreatitis cases were reported (event terms included 'pancreatitis', 'pancreatitis acute', 'pancreatitis chronic', 'pancreatitis relapsing' and 'pancreatitis necrotizing'), with 221 cases occurring prior to the eluxadoline label change (reporting proportion of 21.2%) and 116 cases occurring after the label change (reporting proportion of 12.8%). These data demonstrate a 39.6% decrease in the reporting proportion of pancreatitis cases following the eluxadoline label change, consistent with the 38.2% decrease observed in the data from the Oracle Argus pharmacovigilance database.

Discussion

A post-marketing analysis was completed in 2017 using the FDA's AERS, identifying 119 cases of pancreatitis associated with eluxadoline from 27 May 2015 to 15 February 2017.[8] In this analysis, it was found that patients without a gallbladder were over-represented among patients who developed pancreatitis and had more severe outcomes. On 21 April 2017, a change to the US label for eluxadoline was made, contraindicating its use in patients without a gallbladder.[1] The analysis presented here includes reports of pancreatitis in patients receiving eluxadoline both before and after the FDA label change.

Using a pharmacovigilance database, 273 cases of pancreatitis associated with the use of eluxadoline were identified from 1 January 2016 to 30 June 2018. After the US label change in April 2017 through to 30 June 2018, a 38.2% decrease in the reporting proportion of pancreatitis cases was observed (relative to all AE cases), from an average reporting proportion of 14.4% to an average of 8.9%, while the total number of patients receiving eluxadoline did not notably decrease. This observed decrease in the reporting proportion of pancreatitis cases following the label change is notable, particularly by the first 6 months of 2018. The overall decrease in reported AE cases resulting from fewer reports of SOS and associated signs and symptoms (e.g. abdominal pain with or without hepatic enzyme elevation) and pancreatitis should also be noted. It is important to mention that cases included in the post-label change category were classified according to when they were reported. At least four of the cases in the post-label change category are known to have occurred before the label change but were reported on or after 21 April 2017, based on the available information. Importantly, it should also be stated that no cases of moderately severe or severe pancreatitis were reported to have occurred post label change.

Consistent with previous analyses, among patients with known gallbladder status, nearly three-quarters of patients prescribed eluxadoline who reportedly experienced pancreatitis did not have a gallbladder (71.8%). Of the patients without gallbladders, nearly 90% received the lower approved 75 mg dose, when the dose was known. However, it should be noted that roughly half (50.9%) of pancreatitis cases that occurred post label change occurred in patients without a gallbladder, indicating that patients are continuing to receive eluxadoline against updated recommendations. This could be due to a variety of reasons, including a lack of awareness of the label change or possibly the healthcare providers' unwillingness to discontinue the drug if it was deemed effective for IBS-D symptoms. In addition, as previously mentioned, four cases of pancreatitis were reported after the label change, even though the event occurred prior to the label change. A total of three deaths occurring in patients with co-reported pancreatitis have been reported in the post-marketing setting; however, in all but one case, the cause of death was unknown, including one case that was considered by the reporting physician to be unrelated to the use of eluxadoline.

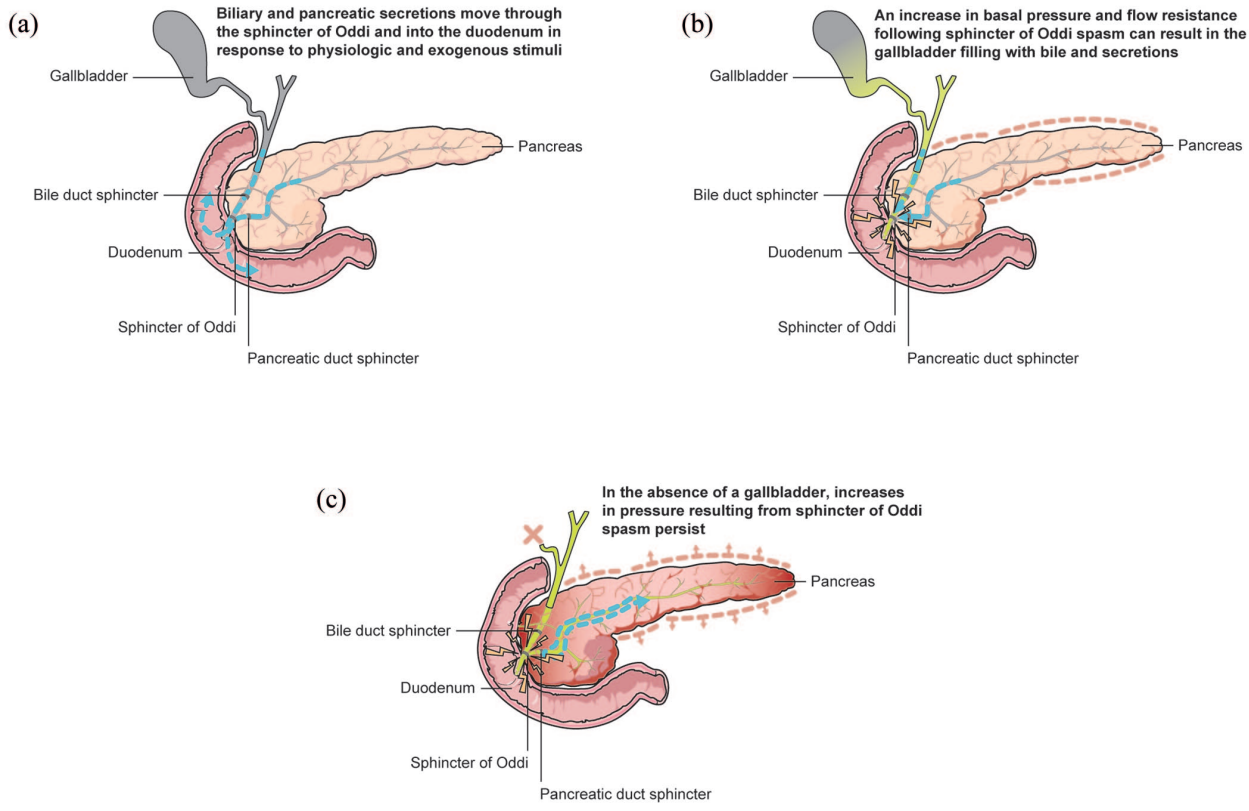


Figure 3. (a) Sphincter of Oddi function; (b) sphincter of Oddi spasm; and (c) sphincter of Oddi spasm post-cholecystectomy.

Acute pancreatitis is relatively rare, occurring in 13–45 people per 100,000 (0.013–0.045%);[15] however, many opioids used for the treatment of pain have been linked to SO dysfunction and pancreatitis.[8] Activation of the μ-opioid receptor can decrease gastrointestinal transit[2] and increase the contractility of the SO, and it is hypothesized that eluxadoline treatment could increase SO tone. Typically, bile is diverted into the gallbladder on SO closure. It has been hypothesized that the absence of this reservoir (e.g. post-cholecystectomy) could lead to increased pressure in the pancreaticobiliary ductal system which could potentiate clinical signs and symptoms of SOS or pancreatitis[16] (Figure 3). However, the exact mechanisms behind pancreaticobiliary symptoms in patients with previous cholecystectomy are not entirely understood. As the current analysis included pancreatitis cases identified by broad terms, including elevated aminotransferase and/or pancreatic enzyme levels and abdominal pain, the incidence of SOS was not investigated separately. Future studies could also investigate SOS in patients receiving eluxadoline due to its potential association with pancreatitis if appropriate diagnostic tools were available. However, while manometry of the SO is considered a gold-standard test for diagnosis,[16] it is not widely available outside of specialized centers, is costly, and is associated with significant risks, including acute pancreatitis, so it would not be appropriate for use in patients receiving eluxadoline.

Post-marketing data can provide valuable safety information about a drug throughout its lifecycle.[12,16] Perhaps equally important, but generally lacking, is an assessment of the effects of label changes on clinical outcomes of interest, which remains to be explored. There are limitations to these types of analyses that should be noted. These reports are submitted voluntarily and there is a significant degree of heterogeneity in the quality and clinical detail. In addition, the magnitude of over- and underreporting is unknown. Fluctuations in AE reporting occur for a variety of reasons, including time on the market, a drug's publicity (e.g. news coverage of safety aspects), overall consumer and physician awareness regarding the drug and any potential safety concerns, the seriousness of the AE, and any regulatory actions.[10]

Due to the many factors that contribute to over- and underreporting, as well as an inability to know the exact number of patients taking the product, we have presented pancreatitis cases as a proportion of total reported AE cases, rather than incidence rates. Furthermore, the data are of variable quality due to a number of different factors, including unknown or missing information pertaining to patient characteristics such as comorbidities or body mass index, inclusion of reports from both healthcare practitioners and consumers, and the qualitative nature of variables such as alcohol consumption, all of which can make data interpretation difficult. An additional variable to consider is that while not mandatory for reporting, the majority of cases of pancreatitis, while reported by healthcare practitioners, were often reported without confirmatory laboratory or imaging results, precluding the ability to verify the diagnosis of pancreatitis independently. Nevertheless, these cases were regarded as confirmed pancreatitis unless proved otherwise during follow-up investigations. Finally, there is no definitive proof of the causal relationship between exposure to the product and the reported event.[10] Given the nature of these limitations, post-marketing surveillance data must be interpreted with caution and in context with carefully controlled clinical trials.

Overall, this analysis of post-marketing AE reports is consistent with safety signals identified in the phase II and III clinical trials, as well as other post-marketing analyses of patients receiving eluxadoline, and indicates a risk of the development of pancreatitis, primarily among patients without a gallbladder. Following the change in eluxadoline's US label in April 2017, wherein the use of eluxadoline was contraindicated in patients without a gallbladder, the reporting proportion of pancreatitis cases in patients receiving eluxadoline decreased by 38.2%, with no further cases of moderately severe or severe pancreatitis reported. This decrease was supported by a similar reduction in the FDA's AERS database, wherein there was a 39.6% reduction in the proportion of pancreatitis cases concomitantly reported with eluxadoline use. Furthermore, results from the real-world RELIEF study (a phase IV multicenter, multinational, prospective, randomized, placebo-controlled, double-blinded parallel-group study to assess the efficacy of eluxadoline in the treatment of IBS-D in patients who report inadequate control of IBS-D symptoms with prior loperamide use), which excluded patients without gallbladders in line with the label change, further support these findings, as no events of pancreatitis or SOS were reported in the 171 patients receiving eluxadoline in that study.[17]

While post-marketing data should be interpreted with caution, the data indicate that the label change for eluxadoline, contraindicating its use in patients without a gallbladder, was associated with a reduction in the reported cases of pancreatitis, with no additional reports of moderately severe or severe cases after the label change. This study reaffirms the importance of adherence to label indications as well as the importance of effective communication of the label information to patients and healthcare providers alike. Eluxadoline is a safe and well-tolerated treatment option for IBS-D when used in accordance with the label.

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Author contributions

BDC, BEL, CW, PSS, and DW: data analysis and interpretation. All authors were also involved in the development and review of the manuscript, and approved the final draft and the final authorship list prior to submission.

Conflict of interest statement

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Brooks D. Cash has served as a consultant and speaker and is on advisory committees or review panels for Allergan plc (prior to acquisition by AbbVie Inc.), Ironwood, Inc., Salix Pharmaceuticals, Shire, and Takeda Pharmaceuticals. Brian E. Lacy has served as a consultant for Ironwood, Inc. and Salix Pharmaceuticals. Cheryl Watton is a former employee of Allergan plc and may own stock/stock options. Philip S. Schoenfeld has served as a consultant for Ironwood, Inc., Allergan plc (prior to acquisition by AbbVie Inc.), Salix Pharmaceuticals, Synergy Pharmaceuticals, Commonwealth Diagnostics International, and Shionogi; as a speaker for Ironwood, Inc., Allergan plc (prior to acquisition by AbbVie Inc.), Salix Pharmaceuticals, and Shionogi;

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Supplemental material

Supplemental material for this article is available online.

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