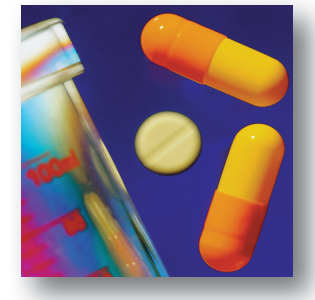

Eluxadoline (Viberzi)

A Mu-Opioid Receptor Agonist for the Treatment Of Irritable Bowel Syndrome With Diarrhea

Fraidy Maltz, PharmD, BCACP; and Brooke Fidler, PharmD

INTRODUCTION

According to the World Gastroenterology Organization Global Guidelines, "irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation and/or a change in bowel habit."[1] General features or characteristics of IBS may include bloating, distention, abdominal pain, diarrhea, and/or constipation. IBS is generally diagnosed using the Rome Diagnostic Criteria for Functional Gastrointestinal Disorders, which assesses recurrent abdominal pain associated with defecation and changes in stool frequency and appearance over a specified period of time.[2] The criteria for IBS were updated in May 2016 in the fourth edition of the Rome Diagnostic Criteria (known colloquially as Rome IV) (Table 1).[2,3]

IBS is classified into three main subtypes according to bowel habits: IBS diarrhea predominant (IBS-D), IBS constipation predominant (IBS-C), or IBS mixed diarrhea and constipation (IBS-M). Patients with IBS who do not fit into the three subtypes may be classified as IBS unclassified (IBS-U).[2] It is estimated that 25 million to 45 million people in the United States suffer from IBS. Although it can affect people of any age, IBS is usually observed in those 50 years of age or younger.[4] The estimated prevalence of IBS worldwide is 10% to 15%; IBS-D is the most common subtype, affecting approximately 40% of patients.[5]

Drs. Maltz and Fidler are Assistant Professors of Pharmacy Practice at the Arnold and Marie Schwartz College of Pharmacy and Health Sciences at LIU Pharmacy in Brooklyn, New York. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi and Associates in New York, New York.

Disclosures: The authors report no financial or commercial relationships in regard to this article.

While nearly 20% to 40% of all visits to gastroenterologists are due to IBS symptoms, it can take years for diagnosis after symptoms begin.[4] The exact underlying causes of IBS remain unknown and are not fully understood. Genetic factors, altered gut bacteria, disturbances in gut motility, and psychosocial issues, such as stress, are all thought to play a role in the etiology of IBS.[4,5,6] Evaluation of IBS may vary depending on the patient-specific characteristics and their clinical presentation. Confirmation of IBS diagnosis is typically based on exclusion of other diseases, clinical history, psychological assessment, and physical exam.[1] Nonpharmacological management of IBS includes making dietary changes, addressing psychosocial issues, increasing physical activity, and avoiding factors that lead to symptoms.[2,6] Pharmacological management for IBS, specifically IBS-D, has focused on fiber supplements, antidiarrheal medications (i.e., loperamide), probiotics, antispasmodics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and the 5-hydroxytryptamine-3 receptor antagonist alosetron.[2,6] Alosetron was withdrawn from the market in 2000 due to life-threatening gastrointestinal side effects; however, it was reintroduced in 2002 with a restricted indication for use only in women with severe IBS-D.[7]

In 2015, two new agents were approved by the Food and Drug Administration (FDA) for the management of IBS-D in adults, including rifaximin (Xifaxan, Salix Pharmaceuticals),[8] which already had an indication for travelers' diarrhea caused by *Escherichia coli*, and eluxadoline (Viberzi, Allergan).[9] This *Drug Forecast* will focus on the use of eluxadoline and its role in the management of IBS-D in adults.

PHARMACOLOGY

Eluxadoline, a Schedule IV controlled substance, is a mixed mu-opioid receptor agonist with delta-opioid receptor antagonist activity and kappa-opioid agonist activity. The role of the kappa-opioid receptor and its binding affinity has not been fully determined.[9] The opioid receptors in the gut play a part in regulating gastrointestinal motility, secretions, and visceral sensations.[10] An estimated 95% of patients with IBS experience enhanced visceral and sensory responses, which contribute to the symptoms of pain, gas, and intestinal contractions.[5] In patients with IBS-D, there is increased colonic transit and enhanced peristaltic contractions, most notably after meals.[11] Pain medications that solely target the mu-opioid receptor are known to cause significant constipation and potential for tolerance or dependence. A mixed-opioid medication, such as eluxadoline, provides relief of IBS-D–related symptoms with lower rates of side effects, specifically constipation.[6,12,13] Eluxadoline targets local opioid receptors in the gut, which reduces the chance of additional central nervous system side effects.[6]

PHARMACOKINETICS

Eluxadoline undergoes significant first-pass hepatic extraction. Therefore, it has poor oral absorption with a systemic bioavailability of approximately 1%.[6,9] Following an oral dose of 300 mg, 82% of the dose was recovered in the feces after 336 hours, and 0.12% was recovered in the urine after 192 hours. The half-life of eluxadoline ranges from 3.7 to 6.0 hours. Although the exact metabolism of eluxadoline is still unknown, a slow formation of a glucuronide metabolite was found in the urine after the administration of a 1,000-mg oral dose.[13]

DRUG–DRUG INTERACTIONS

In vitro studies suggest that drug–drug interactions between eluxadoline and drugs metabolized by cytochrome P450 (CYP) are unlikely. However, due to the unclear metabolic pathways of eluxadoline, precautions are still recommended with strong CYP inhibitors (i.e., cipro-

Table 1 Rome Diagnostic Criteria for Functional Gastrointestinal Disorders* Update[3]

Rome III (Previous Criteria)	Rome IV (Current Criteria)	IBS-D	IBS-C	IBS-M
Recurrent abdominal pain or discomfort† for more than three days per month in the last three months associated with two or more of the following criteria: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool	Recurrent abdominal pain, on average, at least one day per week in the last three months associated with two or more of the following criteria: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool	Loose stools > 25% Hard stools < 25%	Loose stools < 25% Hard stools > 25%	Loose stools > 25% Hard stools > 25%

IBS-C = constipation-predominant irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome; IBS-M = mixed diarrhea and constipation irritable bowel syndrome

* Criteria fulfilled for at least three months with symptom onset at least six months before diagnosis.
† Discomfort defined as uncomfortable sensation not described as pain.

floxacin, fluconazole, gemfibrozil) and drugs that are substrates of CYP3A with narrow therapeutic indices (i.e., cyclosporine, fentanyl, tacrolimus). Appropriate patient monitoring for adverse effects and drug concentrations should be considered with coadministration. Studies suggest that eluxadoline could be a substrate for organic anion transporter (OAT) 3, OATP1B1, and multidrug resistance-associated protein 2 and an inhibitor of OATP1B1 depending on drug concentrations.[6,9,13] When eluxadoline is coadministered with an OATP1B1 inhibitor, such as cyclosporine, gemfibrozil, antiretrovirals, or rifampin, a 75-mg dose of eluxadoline should be administered twice daily to prevent increased risk of eluxadoline-related side effects.[9] Rosuvastatin, which is an OAT1B1 and breast cancer resistance protein substrate, should also be coadministered with caution as it could increase exposure to rosuvastatin; the lowest effective dose of rosuvastatin is recommended.[9]

DOSING AND ADMINISTRATION

The recommended dose of eluxadoline is 100 mg twice a day with food. If a dose is missed, patients should take the next dose as scheduled; two doses should not be taken at the same time.[9]

SPECIAL POPULATIONS

The safety and efficacy of eluxadoline have not been established in the pediatric population. In clinical trials that included geriatric patients, no differences in efficacy were noted between younger and older patients. However, while the types of adverse reactions experienced by younger and older patients were the same, a higher percentage of adverse effects were experienced by the elderly study group.[9]

Eluxadoline is contraindicated in patients with severe hepatic impairment (Child–Pugh C). Patients with mild (Child–Pugh A) or moderate (Child–Pugh B) hepatic impairment should take a reduced dose of 75 mg twice a day and be closely monitored for adverse reactions.[9]

Other patients who require a dosage reduction to 75 mg twice daily include those: without a gallbladder; who cannot tolerate the twice-daily 100-mg dose; receiving concomitant OATP1B1 inhibitors; with known or suspected biliary duct obstruction; with sphincter of Oddi disease or dysfunction; with a history of alcoholism, alcohol abuse, or alcohol addiction; with a history of pancreatitis; and/or with a history of chronic or severe constipation.[9]

Eluxadoline should be discontinued in patients who develop severe constipation for more than four days due to complications of bowel obstruction. Risk versus benefit should be evaluated for use during pregnancy or lactation.[9]

CLINICAL TRIALS

FDA Recommendations For IBS Clinical Trials

In May 2012, the FDA issued specific recommendations for conducting clinical trials to evaluate the efficacy of drug therapy for the treatment of IBS.[14] These recommendations included primary endpoints, entry criteria, and responder definitions for both constipation and IBS-D. In clinical trials that evaluate efficacy of drug treatment of IBS-D, primary endpoints should include assessment of stool consistency and abdominal pain. Stool consistency should be measured using the Bristol Stool Form (BSF) scale, which provides both illustrative and written descriptions of stool types.[14] Abdominal pain intensity should be assessed on an 11-point scale (0–10), rating the patient's worst abdominal pain over the past 24 hours. Other study outcomes, such as global symptom scores and relief of IBS symptoms, may be used as secondary outcomes.[14] The European Medicines Agency (EMA) has similar recommendations for clinical trials assessing drug therapy for the treatment of IBS.[15]

Phase 2 Clinical Trial[16]

Dove et al. conducted a phase 2 clinical trial to evaluate the safety and efficacy of eluxadoline in patients with IBS-D. The investigators tested 5 mg, 25 mg, 100 mg, and 200 mg of eluxadoline twice daily compared with placebo for 12 weeks. Both the 100-mg and 200-mg doses demonstrated efficacy in treating patents with IBS-D; however, due to the adverse events associated with the administration of the 200-mg twice-daily dose, the 100-mg twice-daily dose was preferred.

Phase 3 Clinical Trials[10]

Lembo et al. conducted two phase 3 trials (IBS-3001 and IBS-3002) to assess the efficacy and safety of eluxadoline in patients with IBS-D. The two trials were randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational studies conducted in the U.S., United Kingdom, and Canada from May 2012 through July 2014. Patients

18 to 80 years of age were included in the trials if they were diagnosed with IBS-D according to Rome III criteria. Specifically, patients were required to have an average worst abdominal pain (WAP) score greater than 3 on a scale of 0–10, with 0 signifying no pain and 10 signifying the worst imaginable pain. In addition, patients were required to have an average stool consistency score of 5 or greater based on the BSF scale for at least five days with an IBS-D global symptom score of 2 or greater. IBS-D global symptom scores range from 0 to 4, with 0 signifying no symptoms of IBS-D and 4 signifying very severe symptoms of IBS-D. Patients were excluded from the trials if they had a history of inflammatory bowel disease, celiac disease, thyroid dysfunction, a history of binge drinking or alcohol abuse, pancreatitis, sphincter of Oddi dysfunction, post-cholecystectomy biliary pain, or cholecystitis within the past six months. Additional exclusion criteria were known allergy to opioids, pregnancy, breastfeeding, or concomitant antidiarrheal, antispasmodic, or narcotic drugs.

Both studies started with a pre-treatment period, which included a one-week prescreening period followed by a three-week screening period. Following the pre-treatment phase, patients were randomized to receive oral eluxadoline tablets (either 75 mg or 100 mg) or placebo twice daily. Both studies included 26 weeks of double-blind, placebo-controlled treatment to assess efficacy. In IBS-3001, patients received an additional 26 weeks of double-blind treatment for long-term safety assessment only, which was followed by a two-week post-treatment follow-up. In IBS-3002, patients were continued on a four-week, single-blinded placebo withdrawal to assess for rebound worsening of symptoms. In both trials, during the 26-week treatment phase, patients were assessed for WAP scores, extent of discomfort and bloating, stool consistency score, number of bowel movements, and the IBS-D global symptom score. Patients were also monitored for adequate relief of IBS symptoms and IBS quality of life (IBS-QOL) using a 34-item questionnaire. Although patients were not permitted to receive rescue medication during the screening/pre-treatment periods, patients were allowed loperamide rescue as needed for acute, uncontrolled diarrhea during the double-blind treatment period. No other antidiarrheals or agents for IBS-D were allowed in the study. Patients were permitted to take aspirin and other nonsteroidal anti-inflammatory drugs; however, patients were not permitted to take any narcotic- or opioid-containing products.

The primary efficacy endpoint in both studies was overall composite response. This was noted as improvement in both the daily WAP score of 30% or greater compared with baseline and a reduction in BSF scale score to less than 5 on 50% of the days within the first 12 weeks of the study (FDA endpoint) and at 26 weeks (EMA endpoint). Patients were required to record a minimum of 60 diary entries from weeks 1–12 to demonstrate a response. Patients were also considered to have a response day if they saw improvement in daily WAP by at least 30% without experiencing a bowel movement.

Secondary endpoints were improvements in each composite endpoint individually, improvement in global symptom score, adequate relief of IBS symptoms, and change from baseline in IBS-QOL. In addition, the composite response was recorded as a secondary endpoint at each four-week visit. The investigators also performed a worst-case analysis that required 50% positive-response days during the study period to count as a patient response to treatment. The worst-case analysis accounted for days with missing diary entries as days with nonresponse to treatment.

Efficacy data were analyzed using the intent-to-treat population. Efficacy data in both studies were analyzed as pooled data and were prospectively determined in the study designs. Safety data were collected in both the IBS-3001 and IBS-3002 trials during the 26-week treatment period. In IBS-3001, safety data were collected for an additional 26 weeks for a total of 52 weeks.

Phase 3 Results[10]

A total of 2,428 patients were enrolled in the trials (IBS-3001, N = 1,282; IBS-3002, N = 1,146). One patient dropped out before randomization in IBS-3001, and one patient was randomized twice in both trials. Therefore, the intent-to-treat population included a total of 2,425 patients (IBS-3001, N = 1,280; IBS-3002, N= 1,145). Baseline characteristics were similar within study groups and in both studies. Patients were on average 45 years of age, 66% women, and 86% white. Mean WAP and mean BSF scale scores were 6.1 and 6.2, respectively.

Patients achieved the primary efficacy endpoint if they had a significant composite response after 12 weeks (FDA) and after 26 weeks (EMA) of treatment compared with placebo. After 12 weeks of treatment, significantly more patients who received eluxadoline 75 mg or 100 mg twice daily achieved the FDA endpoint response compared with patients who received placebo in both studies. In patients in the IBS-3002 study who received eluxadoline 75 mg or 100 mg twice daily for 26 weeks, the EMA endpoint response was greater than in the patients receiving placebo. In the IBS-3002 study, more patients taking 75 mg and 100 mg of eluxadoline twice daily achieved a significant composite response after 26 weeks compared with the patients on placebo. Primary efficacy results for both trials are summarized in Table 2.

Secondary efficacy endpoints from weeks 1–12 included worst-case analysis, improvements in abdominal pain, stool consistency (BSF scale), IBS-D global symptoms, and adequate relief of IBS symptoms. According to the worst-case analysis, composite scores improved significantly ($P < 0.01$) in the 75-mg and 100-mg treatment groups compared with placebo in both trials; however, there were no significant improvements noted in mean WAP scores in the 75-mg and 100-mg groups. Significant improvements in stool consistency and adequate relief of IBS-D symptoms were noted in both the 75-mg and 100-mg treatment groups compared with placebo ($P < 0.05$). Although IBS-D global symptom scores showed significant improvement in both dosage groups compared with placebo in the IBS-3002 trial ($P < 0.001$), they did not show statistically significant improvement in the IBS-3001 trial.

ADVERSE EVENTS

Safety data were reported for more than 1,700 patients in one phase 2[16] and two phase 3 clinical trials[10] at three months (n = 1,391), six months (n = 1,001), and one year (n = 488). Adverse events occurring in more than 2% of eluxadoline-treated patients in the trials at an incidence greater than placebo appear in Table 3. The three most common adverse events indicated by the pooled data were

Table 2 Primary Efficacy Results of Phase 3 Studies of Eluxadoline in Patients With IBS-D: Composite Response[10]

	IBS-3001 Trial			IBS-3002 Trial			Pooled Data		
	Eluxadoline 75 mg (n = 426)	Eluxadoline 100 mg (n = 427)	Placebo (n = 427)	Eluxadoline 75 mg (n = 382)	Eluxadoline 100 mg (n = 382)	Placebo (n = 381)	Eluxadoline 75 mg n = 806	Eluxadoline 100 mg n = 809	Placebo (n = 808)
Composite response at 12 weeks (%)	23.9*	25.1%*	17.1	28.9**	29.6**	16.2	26.2**	27.0**	16.7
Composite response at 26 weeks (%)	23.4	29.3**	19.0	30.4*	32.7**	20.2	26.7**	31.0**	19.5

IBS-D = diarrhea-predominant irritable bowel syndrome.

* $P < 0.05$ versus placebo; ** $P < 0.001$ versus placebo.

Table 3 Adverse Events Related to Eluxadoline in Clinical Trials[9]

Adverse Events*	Eluxadoline		Placebo (n = 975) %
	100 mg twice daily (n = 1,032) %	75 mg twice daily (n = 807) %	
Constipation	8	7	2
Nausea	7	8	5
Abdominal pain	7	6	4
Upper respiratory infection	5	3	4
Vomiting	4	4	1
Nasopharyngitis	3	4	3
Abdominal distention	3	3	2
Bronchitis	3	3	2
Dizziness	3	3	2
Flatulence	3	3	2
Rash	3	3	2
Increased alanine transaminase level	3	2	1
Fatigue	2	3	2
Viral gastroenteritis	1	3	2

*Reported in more than 2% of patients treated with eluxadoline at either dose at an incidence greater than patients treated with placebo.

constipation, nausea, and abdominal pain.[9] Approximately half of all constipation events occurred within the first two weeks of therapy, and the majority of patients reported this event within the first three months of therapy. Approximately 8% of patients treated with either 75 mg or 100 mg of eluxadoline and 4% of patients treated with placebo discontinued therapy early due to adverse events. Constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg) were the most common adverse events leading to discontinuation of eluxadoline. In contrast, less than 1% of patients treated with placebo discontinued therapy because of constipation and abdominal pain. Serious adverse events included sphincter of Oddi spasm and pancreatitis. Approximately 0.2% of patients treated with 75 mg and 0.8% of patients treated with 100 mg of eluxadoline twice daily developed a sphincter of Oddi spasm. About 80% of sphincter of Oddi spasm cases were reported within the first week of treatment, and no cases were reported after one month of treatment. One patient receiving eluxadoline 100 mg developed sphincter of Oddi spasm-induced pancreatitis, which occurred several minutes after receiving the first dose of eluxadoline. All cases of sphincter of Oddi spasm resolved after discontinuation of treatment. Pancreatitis unrelated to sphincter of Oddi spasm was noted in 0.2% (two of 807) and 0.3% (three of 1,032) of patients treated with 75 mg and 100 mg of eluxadoline, respectively.[9]

COST AND FORMULARY CONSIDERATIONS

Three prescription medications are approved by the FDA for IBS-D: eluxadoline, rifaximin, and alosetron. Eluxadoline and rifaximin are approved for both men and women,[8,9] but alosetron is indicated for women only.[7] These medications can benefit patients who have had no relief of their symptoms using nonpharmacological management or loperamide.

Clinical studies comparing the efficacy of the currently approved IBS-D treatments are lacking. As a result, clinicians need to base their treatment choice on patient response rates for individual therapies, patient safety, drug interactions, and cost.

Prescribers should be aware of the specific warnings that are associated with each medication to determine which would be most appropriate for their patient. The available treatment options offer different mechanisms of action, and because eluxadoline is an opioid receptor agonist, it is designated as a Schedule IV controlled substance by the

Drug Enforcement Administration. As an antibiotic, rifaximin may pose a potential concern for drug resistance and overgrowth of *Clostridium difficile* leading to *C. difficile*-associated diarrhea.[8] Alosetron has a boxed warning for serious gastrointestinal effects, such as ischemic colitis and other serious complications from constipation.[7] As previously mentioned, eluxadoline should not be used by active alcoholics or by those with a history of pancreatitis, severe hepatic impairment, or severe constipation.[9]

Eluxadoline also has poor systemic bioavailability, which limits its potential for drug interactions and side effects. Compared to alosetron, rifaximin and eluxadoline have less potential for drug interactions. Alosetron, which is primarily metabolized by CYP1A2 and to a lesser extent by CYP3A4 and CYP2C9, is contraindicated with fluvoxamine.[7] Although rifaximin has the potential to induce CYP3A4 in patients with normal hepatic function at the recommended dosing, it is not expected to induce the enzyme.[8] The side effects profiles are similar between rifaximin and eluxadoline (i.e., nausea, dizziness, abdominal pain), while the side effects of alosetron are primarily gastrointestinal in nature.[7–9]

Dosing is different among these medications. Unlike eluxadoline and alosetron, which are chronic long-term regimens,[7,9] rifaximin is a two-week treatment that can be repeated twice if IBS-D symptoms recur.[8]

Cost is another aspect to consider when choosing among the current treatment options. Eluxadoline is available in 75-mg and 100-mg tablets and is supplied 60 tablets per bottle. The average wholesale price (AWP) for a one-month supply of either strength is $1,256.[17] Rifaximin is available as 550-mg tablets for the treatment of IBS-D. For the two-week treatment period, patients take one 550-mg tablet three times a day.[8] Rifaximin has an AWP of $1,630 for a 14-day supply (42 tablets).[17] Alosetron is supplied as either a 0.5-mg or 1.0-mg tablet. The recommended starting dose is 0.5 mg twice daily, and the maximum recommended dose is 1.0 mg twice daily.[7] Several generic versions of alosetron are available. At the time of writing, the lowest AWPs for a 30-count bottle of 0.5-mg or 1.0-mg tablets were $781 and $1,414, respectively.[17]

DISCUSSION

In two phase 3 trials, eluxadoline 100 mg and 75 mg twice daily provided long-term relief from the diarrhea and abdominal pain associated with IBS-D compared with placebo.[10] In addition, eluxadoline improved secondary outcome measures, including a decrease in stool frequency and urgency. Common adverse events with eluxadoline use included constipation, severe abdominal pain, and nausea. Eluxadoline has been associated with serious adverse effects such as sphincter of Oddi spasm and pancreatitis.[9] Sphincter of Oddi spasm occurred in patients without a gallbladder, and pancreatitis was associated with excessive alcohol use and biliary disorders. Therefore, it is important to consider the risk–benefit of using eluxadoline in patients without a gallbladder or who consume excessive alcohol.

Eluxadoline offers an additional option for the treatment of IBS-D in both men and women. Although it is a newer therapy and was not included in recent IBS guidelines,[1,18] it may be offered as a treatment option if patients do not see the resolution of IBS-D symptoms with other therapies.

REFERENCES

1. World Gastroenterology Organisation. Irritable bowel syndrome: a global perspective. September 2015. Available at: www.worldgastroenterology.org/guidelines/global-guidelines/irritable-bowel-syndrome-ibs/irritable-bowel-syndrome-ibs-english. Accessed February 1, 2017.
2. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology* 2016;150(6):1393–1407.
3. Health Union, LLC. New Rome IV diagnostic criteria for IBS. December 13, 2016. Available at: https://irritablebowelsyndrome.net/clinical/new-rome-iv-diagnostic-criteria. Accessed February 1, 2017.
4. International Foundation for Functional Gastrointestinal Disorders. About IBS. Available at: www.aboutibs.org. Accessed February 1, 2017.
5. Lacy BE, Moreau JC. Diarrhea-predominant irritable bowel syndrome: diagnosis, etiology, and new treatment considerations. *J Am Assoc Nurse Pract* 2016;28(7):393–404.
6. Rivkin A, Rybalov S. Update on the management of diarrhea-predominant irritable bowel syndrome: focus on rifaximin and eluxadoline. *Pharmacotherapy* 2016;36(3):300–316.
7. Lotronex (alosetron hydrochloride) prescribing information. San Diego, California: Prometheus Laboratories, Inc.; 2014.
8. Xifaxan (rifaximin) prescribing information. Raleigh, North Carolina: Salix Pharmaceuticals, Inc.; 2015.
9. Viberzi (eluxadoline) prescribing information. Cincinnati, Ohio: Forest Pharmaceuticals, Inc.; 2015.
10. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med* 2016;374(3):242–253.
11. Coleman N, Spiller R. New pharmaceutical approaches to the treatment of IBS: Future development and research. *Ann Gasteroenterol* 2002;15(3):278–289.
12. Fujita W, Gomes I, Dove LS, et al. Molecular characterization of eluxadoline as a potential ligand targeting mu-delta opioid receptor heteromers. *Biochem Pharmacol* 2014;92(3):448–456.
13. Davenport JM, Covington P, Bonifacio L, et al. Effect of uptake transporters OAT3 and OATP1B1 and efflux transporter MRP2 on the pharmacokinetics of eluxadoline. *J Clin Pharmacol* 2015;55(5):534–542.
14. Center for Drug Evaluation and Research. Guidance for industry: irritable bowel syndrome—clinical evaluation of drugs for treatment. May 2012. Available at: www.fda.gov/downloads/drugs/guidances/ucm205269.pdf. Accessed February 2, 2017.
15. European Medicines Agency. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. September 25, 2014. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173457.pdf. Accessed February 2, 2017.
16. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology* 2013;145(2):329–338.
17. Red Book Online. Ann Arbor, Michigan; Truven Health Analytics. Accessed May 25, 2017.
18. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014;147(5):1146–1148. ■