

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 5, 2015

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

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Subject: Review evaluates if a REMS is needed for eluxadoline

Drug Name(s): eluxadoline

Therapeutic Class: locally-acting mu opioid receptor agonist and delta opioid receptor antagonist

Dosage form: oral tablet

Application Type/Number: NDA 206-940

Applicant/sponsor: Furiex Pharmaceuticals, Inc.

OSE RCM #: 2014-1795

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) eluxadoline. On June 26, 2014 the Agency received an original NDA from Furiex Pharmaceuticals, Inc. (Furiex) for eluxadoline to treat irritable bowel syndrome with diarrhea (IBS-d).

Furiex did not submit a proposed REMS for eluxadoline, however the Applicant voluntarily submitted a risk minimization strategy which included a Medication Guide (MG), communication plan and sales force training. The goal was to inform prescribers about the risk of pancreatitis and hepatobiliary sphincter of Oddi (SO) spasm events, and educate them on appropriate patient selection in order to minimize the occurrence of these events.

1.1 PRODUCT BACKGROUND

Eluxadoline is a locally active, mixed mu opioid receptor (μ OR) agonist and delta opioid receptor (δ OR) antagonist that primarily exerts its pharmacologic activity in the gastrointestinal tract, to treat IBS-d with low systemic bioavailability. As a mixed agonist at mu-opioid receptors and antagonist at delta-opioid receptors, eluxadoline's pharmacologic profile is unique.

The proposed indication is for the treatment of IBS-d:

- 100 mg oral tablet twice daily with food
- 75 mg oral tablet twice daily with food in patients with prior cholecystectomy or who cannot tolerate the 100 mg dose

Eluxadoline should not be used by patients with a history of alcoholism, alcohol abuse or addiction, or who consume > 3 alcoholic beverages/day due to an increased risk for pancreatitis in these patients. In addition, patients with a history of pancreatitis or structural diseases of the pancreas, severe hepatic impairment, chronic or severe constipation, or known/suspected mechanical gastrointestinal obstruction should not take eluxadoline.

1.2 DISEASE BACKGROUND

IBS is a functional bowel disorder that often presents with symptoms including abdominal pain or discomfort, gas, bloating, and changes in bowel function in the absence of a detectable structural abnormality. The severity of symptoms is widely variable among patients and can significantly impact quality of life. IBS affects 10-20% of adults in the U.S., and has been cited as the most common condition diagnosed by gastroenterologists.¹ While the pathogenesis of IBS is complex and both highly variable and poorly understood, central neural dysfunction, mucosal inflammation, abnormal gut motor and sensory activity, stress and psychological disturbances have been proposed as contributing factors.

¹ Owyang C. Chapter 296. Irritable Bowel Syndrome, in *Harrison's Principles of Internal Medicine*, 18th ed.

Diagnosing IBS can be challenging given the highly variable symptom presentation and poorly understood pathogenesis, however the Rome III criteria (described in Table 1) is considered to have high specificity in making an IBS diagnosis.²

Table 1: Diagnostic Criteria^a for IBS

<p>Recurrent abdominal pain or discomfort^b at least 3 days per month in the last 3 months, associated with <u>2 or more</u> of the following:</p> <ul style="list-style-type: none"> ▪ Improvement with defecation ▪ Onset associated with a change in frequency of stool ▪ Onset associated with a change in form (appearance) of stool
<p>^a Criteria fulfilled for the last 3 months with symptoms onset at least 6 months prior to diagnosis.</p>
<p>^b Discomfort means an uncomfortable sensation not described as pain.</p>
<p>Note: one important exception to the Rome III diagnostic criteria is patients who feel abdominal pain continuously. In this case, the diagnosis is likely “functional abdominal pain” which is an unusual and severe condition in which patients tend to respond poorly to treatment and often have an underlying psychological condition.</p>

It is important to note however, that many symptoms common to IBS including abnormal stool form (hard, loose, or both) and frequency (<3 times/week or >3 times/week), bloating, urgency, straining at defecation and the passage of mucus by rectum and not part of the Rome III criteria. Many patients experience intermittent flares (lasting 2-4 days) followed by periods of remission; women with IBS can experience a worsening of symptoms at the time of menstruation.

IBS has the following four different IBS subtypes: 1) constipation predominant, 2) diarrhea predominant, 3) mixed, and 4) untyped as described below in Table 2.

Table 2: IBS Subtyping by Predominant Stool Pattern

IBS Subtype	Description
IBS with Diarrhea (IBS-d)	Loose (mushy) or water stools >25% and hard or lumpy stools <25% of bowel movements
IBS with Constipation (IBS-c)	Hard or lumpy stools >25% and loose (mushy) or watery stools <25% of bowel movements
Mixed IBS (IBS-m)	Hard or lumpy stools >25% and loose (mushy) or watery stools >25% of bowel movements
Untyped IBS	Insufficient abnormality of stool consistency to meet criteria for IBS-d, IBS-c, or IBS-m

² Friedman S. Chapter 24. Irritable Bowel Syndrome, in *Current Diagnosis & Treatment: Gastroenterology, Hepatology, & Endoscopy*, 2nd ed.

The treatment approach for IBS can vary based on the severity of the disorder. Patients with mild to moderate symptoms (correlating with altered GI physiology) often experience these symptoms intermittently; treatment includes pharmacologic agents that act at the gut including fiber supplements, antidiarrheals, antispasmodics and gut serotonin modulators. Patients with more severe IBS-related symptoms typically experience psychosocial difficulties and chronic pain. These patients are often managed with antidepressants and psychosocial interventions. Drug therapies commonly used to treat IBS are described below in Table 3.

Table 3: Drug Therapies Commonly Used to Treat IBS-Related Symptoms

Diarrhea	Constipation	Abdominal Pain
<ul style="list-style-type: none"> • Loperamide • Cholestyramine resin • Alosetron 	<ul style="list-style-type: none"> • Psyllium husk • Methylcellulose • Calcium polycarbophil • Lactulose syrup • 70% sorbitol • Polyethylene glycol 3350 • Lubiprostone • Magnesium hydroxide • Tegaserod maleate 	<ul style="list-style-type: none"> • Antispasmodics (e.g., dicyclomine hydrochloride) • Tricyclic antidepressants • Selective Serotonin Reuptake Inhibitors (SSRIs)

Alosetron is the only FDA approved therapy to treat IBS-d and is marketed under a restricted REMS program to mitigate the risk of ischemic colitis (IC) and serious complications of constipation (CoC).

1.3 REGULATORY HISTORY

The following is an overview of the regulatory history for NDA 206-940, received on June 26, 2014 and amended on September 22, 2014 and October 24, 2014.

- April 22, 2014: Type B, Pre-NDA Meeting for eluxadoline convened in which the Agency informed the Applicant that is REMS is not likely to be necessary for eluxadoline based on the information currently available.
- June 26, 2014: Furiex submitted NDA 206-940 for eluxadoline to treat diarrhea and abdominal pain symptoms in men and women with IBS-d.
- September 9, 2014: Filing Communication sent to the Applicant. The Agency informed the Applicant that their proposed risk management plan suggests there were risks associated with eluxadoline that may require mitigation strategies beyond labeling and routine pharmacovigilance. The Applicant was asked to provide further rationale as to why risk mitigation beyond labeling [e.g., Dear

Healthcare Professional (DHCP) and Dear Professional Society (DPS) letters, product fact sheet, and sales force training on risk messages] was necessary to assure safe use of eluxadoline.

- September 22, 2014: Furiex submitted an amendment to provide updated dissolution data, and informed the Agency that the proposed additional risk management measures were not considered necessary to ensure that the benefits of eluxadoline outweigh the risks, rather they are to be considered as voluntary risk measures beyond labeling and routine pharmacovigilance, to further inform key safety messages to prescribers.
- October 24, 2014: Furiex submitted an amendment to provide a 120 Day Safety Update.
- November 21, 2014: The Agency informed the Applicant that the October 24, 2013 submission constituted a major amendment to the application; the goal date was extended by three months.
- December 10, 2014: The Mid-Cycle Communication occurred with the Applicant in which the Agency informed the applicant that there is currently no anticipated need for a REMS. The following were identified as clinical issues warranting further discussion:
 - Apparent imbalance of adverse events of abdominal pain in the eluxadoline treatment arms compared to placebo in the context of both efficacy and safety.
 - Feasibility of marketing the 75 mg dose as an alternative to the 100 mg dose in patients who cannot tolerate the 100 mg dose.

Furiex informed the Agency that they would “explore the potential for marketing both the 75 mg and 100 mg” however they did not have PK data at the 75 mg dose.

- February 25, 2015: Type C Meeting was convened with the Controlled Substance Staff (CSS) and Applicant to discuss the abuse potential of eluxadoline. The Applicant agreed with the Agency that the available data suggests that eluxadoline has abuse potential and should be scheduled. That Applicant agreed to re-submit a revised proposal for scheduling and an Eight Factor Analysis proposing Schedule IV.
- March 11, 2015: Late Cycle Meeting convened with the Applicant where the abuse potential of eluxadoline was further discussed in which CSS (b) (4) [REDACTED]
[REDACTED] The Applicant agreed to reassess their proposal for scheduling and submit a new proposal.
- March 11, 2015: Furiex submitted a modified Eight Factor Analysis proposing Schedule IV and revised Section 9 (DRUG ABUSE AND DEPENDENCE) of the label to denote the proposed scheduling.

2 MATERIALS REVIEWED

2.1 APPLICANT SUBMISSIONS

The following submissions from the Applicant were reviewed for this review:

- Furiex. Original New Drug Application (NDA 206-940) submission for eluxadoline, received June 26, 2014 (S-001/Seq 0000)
 - Section 2.5, Clinical Overview
 - Section 2.7.3, Summary of Clinical Efficacy [Indication]
 - Section 2.7.4, Summary of Clinical Safety
- Furiex. Draft Prescribing Information for eluxadoline, received June 26, 2014 (S-001/Seq 000)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- FDA. Mid-Cycle Communication Meeting Minutes for eluxadoline, dated December 10, 2014.
- FDA. Type C Meeting Minutes- Guidance: Controlled Substance Staff (CSS) for eluxadoline, dated February 25, 2015.
- Muldowney, L. DGIEP Clinical Review for eluxadoline, dated February 27, 2015.
- Yeh-Fong, C. Division of Biometrics (DBIII) Statistical Review and Evaluation for eluxadoline, dated March 9, 2015.

3 REVIEW FINDINGS FOR ELUXADOLINE

3.1 OVERVIEW OF CLINICAL PROGRAM FOR ELUXADOLINE

Eluxadoline's safety and effectiveness in the treatment of IBS-d was established based on two pivotal Phase 3 clinical studies (IBS-3001 and IBS-3002), and one supportive Phase 2 clinical study (IBS-2001). The Phase 3 studies were designed to assess the efficacy, safety and tolerability of eluxadoline for proposed indication, while the Phase 2 study was designed to identify the optimal drug regimen.

The primary efficacy endpoint was composite response [simultaneous improvement in abdominal pain (improved by $\geq 30\%$ compared to baseline) and Bristol Stool Score (BSS)³ for more than 50% of the days with daily electronic diary entries)] through week 12.

3.1.1 Phase 3 Pivotal Studies (IBS-3001 and IBS-3002)

Studies IBS-3001 and IBS-3002 were Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies of adult patients with a IBS-d diagnosis (based

³ The Bristol Stool Score was derived from the Bristol Stool Form Scale, a clinical tool used to define the stool spectrum from constipation to diarrhea. The scale ranges from 1 [separate hard lumps like nuts (difficult to pass)] to 7 (watery, no solid pieces, entirely liquid). A patient was considered a "responder" if the BSS < 5 or absence of a bowel movement if accompanied by $\geq 30\%$ improvement in worst abdominal pain compared to baseline.

on the Rome III criteria) who met baseline criteria for pain⁴, stool consistency⁵, IBS-d global symptom score⁶ and compliance with diary entry⁷ during the week prior to randomization. Subjects were randomized to eluxadoline or placebo.

Exclusion criteria included subjects who used any loperamide rescue medication within the 14 days prior to randomization. Loperamide was prohibited during the 3-week screening phase, however its use was permitted during the double-blind treatment and blinded withdrawal phases as rescue therapy for acute, uncontrolled diarrhea.

The following medications were prohibited for use prior to/or as concomitant therapy:

- 5HT3 antagonists (prohibited within 14 days of pre-screening)
- Aspirin (or aspirin-containing medications) or NSAIDS (taken specifically for IBS) within 14 days of randomization
- Narcotics, opioid-containing agents, or tramadol (prohibited within 14 days of randomization)
- Enemas, docusate, or GI preparations (e.g., antacids, anti-diarrheals, anti-nausea agents, etc.) were prohibited within 14 days of randomization
- Rifaximin (prohibited within 28 days of randomization)

Antidepressants or medications to treat allergies, chronic medical conditions, or migraine headaches were allowed for prior or concomitant use unless as indicated above.

Study IBS-3001

Subjects (n=1282) were randomized in a 1:1:1 ratio to the following groups:

- Group 1: eluxadoline 75 mg oral tablets twice daily
- Group 2: eluxadoline 100 mg oral tablets twice daily
- Group 3: matching placebo oral tablets twice daily

IBS-3001 consisted of a pre-treatment phase (up to 1-week prescreening period and up to 1-week screening period), 52-week double-blind treatment phase, and 2-week post-treatment follow-up phase. Efficacy and safety data was collected when all patients had completed 26 weeks of treatment; treatment was continued through week 52 to assess long-term safety with a placebo control. In IBS-3001, the proportion of composite responders over Weeks 1-12 was significantly higher in both the eluxadoline 100 mg and 75 mg groups compared to placebo [25.1% vs. 17.1%, (p=0.004)] and [23.9% vs. 17.1%, (p=0.014)] respectively.

⁴ Average of worst abdominal pain scores in the past 24 hours must be >3.0 (on a 0-10 scale) over the week prior to randomization.

⁵ Average stool consistency score (BSS) must be ≥ 5.5 and at least 5 days with a BSS ≥ 5 (on a 1-7 scale) over the week prior to randomization.

⁶ Average daily IBS-d global symptom score must be ≥ 2.0 (on a 0-4 scale) over the week prior to randomization.

⁷ Subjects must have completed electronic diary entries on at least 6 of the 7 days during the week prior to randomization and at least 11 of the 14 days during the 2 weeks prior to randomization.

Study IBS-3002

Subjects (n=1146) were randomized in a 1:1:1 ratio to the following groups:

- Group 1: eluxadoline 75 mg oral tablets twice daily
- Group 2: eluxadoline 100 mg oral tablets twice daily
- Group 3: matching placebo oral tablets twice daily

IBS-3002 consisted of a pre-treatment phase identical to IBS-3001, 26-week double-blind treatment phase, and 4-week blinded withdrawal phase. The total study duration did not exceed 34 weeks for each patient. Daily diary data was collected through Week 30, however primary and key secondary efficacy data was collected through Week 26. The 4-week blinded withdrawal phase allowed for the evaluation of rebound effects on study drug discontinuation. In IBS-3002, the proportion of composite responders over Weeks 1-12 was significantly higher in both the eluxadoline 100 mg and 75 mg groups compared to placebo [29.6% vs. 16.2%, ($p<0.001$)] and [28.9% vs. 16.2%, ($p<0.001$)] respectively.

3.1.2 Phase 2 Supportive Study (IBS-2001)

Study IBS-2001 was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of adult patients with an IBS-d diagnosis (based on the Rome III criteria) who met baseline criteria for pain, stool consistency, and compliance with diary entry during screening. Subjects were randomized to eluxadoline or placebo.

Subjects (n=807) were randomized in a 1:1:1 ratio to the following groups:

- Group 1: eluxadoline 5 mg oral tablets twice daily
- Group 2: eluxadoline 25 mg oral tablets twice daily
- Group 3: eluxadoline 100 mg oral tablets twice daily
- Group 4: eluxadoline 200 mg oral tablets twice daily
- Group 5: matching placebo oral tablets twice daily

Subjects in IBS-2001 treated with eluxadoline the 100 mg or 200 mg doses were twice as likely as placebo subjects to achieve a study response [overall response rate of 28.0% ($p=0.002$) and 28.5% ($p=0.002$) respectively] based on post-hoc analysis and using the “responder” criteria from Phase 3 studies. The 100 mg twice daily dose was selected for Phase 3 studies given the lack of improvement in post-hoc response rate, and slight increase in GI adverse events (AEs) with the 200 mg dose. Although the efficacy of a 75 mg dose was not explored in Phase 2, this dose was included in Phase 3 studies based on efficacy trends and a favorable safety profile with eluxadoline doses up to 100 mg twice daily, as observed in Phase 2 studies.

3.2 SAFETY CONCERNS⁸

The safety analysis population was defined as all subjects enrolled in the eluxadoline clinical development program who received a least one dose of the study drug (n=2562). The most common non-serious AEs adverse were GI-related and included nausea, constipation, abdominal pain and flatulence. A slightly higher incidence of abdominal pain was observed in subjects treated with the 100 mg eluxadoline dose compared to 75 mg, and this was particularly evident in subjects with a prior cholecystectomy. The Applicant has proposed marketing the 75 mg eluxadoline dose for patients with a prior cholecystectomy who are unable to tolerate the 100 mg dose. There was also an increased risk of SO dysfunction observed in eluxadoline-treated subjects; these events included pancreatitis and hepatobiliary events, both of which completely resolved upon discontinuation of eluxadoline therapy.

Discontinuation from Phase 2 or 3 studies occurred in 340 (34.5%) 100 mg eluxadoline-treated subjects compared to 320 (32.7%) placebo subjects. The most common reason for discontinuation in eluxadoline-treated subjects was GI-related AEs.

Division of Gastroenterology and Inborn Errors Products (DGIEP) Clinical Safety Reviewer Comment: *The higher discontinuation rate in eluxadoline treatment arms for AEs of abdominal pain is somewhat concerning to this reviewer, given the treatment is intended to improve abdominal pain. This is not entirely inconsistent with the efficacy results, however, which seem to show that improvements in stool consistency are driving the results.*

3.2.1 Serious Adverse Events (SAEs)

There were no deaths reported in subjects during the time of participation in the eluxadoline clinical development program. One death, determined not to be related to the study drug, was reported in a patient who died (b) (6) days after receiving the last eluxadoline dose.

More non-fatal SAEs were reported in eluxadoline-treated patients compared to placebo [4.2% (75 mg), 4.0% (100 mg), and 2.6% (placebo)]. Pancreatitis was the most common SAE with 11 reported cases. Other SAEs included small bowel obstruction (2 cases; 1 with 100 mg and 1 in placebo) and ischemic colitis (1 case with 100 mg dose). Additionally, 2 cases of pancreatitis were reported in 200 mg-treated subjects in IBS-2001.

DGIEP Clinical Safety Reviewer Comment: *The overall rates of SAEs are low and the proportions were similar across treatment arms. Pancreatitis was the most commonly reported SAE in eluxadoline treated patients, and it is included in Warnings and Precautions of the Prescribing Information. Small bowel obstruction occurred equally in patients in the eluxadoline and placebo arms.*

The single case of ischemic colitis in an older patient with multiple comorbidities-while ischemic colitis has been associated with alosetron, the MOA of the two drugs is

⁸ Please see Dr. Laurie Muldowney's full review of safety (DGIEP Clinical Review for eluxadoline, dated February 27, 2015).

different, and the patient in IBS-3002 did not appear to experience any constipation. By history, the most plausible explanation was that a GI bleeding event (history of diverticulitis) led to hypotension and ischemic colitis.

3.2.2 Adverse Events of Special Interest

The AEs of special interest with eluxadoline include SO spasm (including pancreatitis and hepatobiliary events), serious complications of constipation and ischemic colitis, and abuse potential.

3.2.2.1 Sphincter of Oddi (SO) Spasm (including pancreatitis and acute hepatobiliary events)

Nine subjects were adjudicated as having pancreatitis, and 9 subjects as having acute biliary events; all received study drug. Three cases were consistent with SO spasm and all pancreatitis cases completely resolved after study drug discontinuation and brief hospitalization.

All 9 subjects with acute hepatobiliary events were adjudicated as SO spasm; events were described as transient and “resolved rapidly” upon treatment (including 1 hospitalization) and study drug discontinuation.

Clinical Safety Reviewer Comment: *SOD [sphincter of Oddi Dysfunction] is a known class effect with opiate use, and it often occurs early in the treatment course. The incidence of SOD in patients receiving mu agonist, however, is not well described in the literature.*

The Sponsor currently proposes eluxadoline be contraindicated in patients with a history of pancreatitis, alcoholism, alcohol abuse, or alcohol addiction, or structural disease of the pancreas, known or suspected biliary or pancreatic tract obstruction, or SO disease or dysfunction.

The rate of SOD with eluxadoline appears consistent with that of other opiates, and this reviewer believes that placement of issues related to SOD is appropriate for W&P but not an absolute contraindication.

3.2.2.2 Serious Complications of Constipation and Ischemic Colitis

Eluxadoline is mixed μ OR agonist and δ OR antagonist, a mechanism of action which differs from that of alosetron (5-HT_{2A} antagonist). Alosetron is the only currently approved treatment for IBS-d and is marketed with a restricted REMS program due to the serious GI-related events reported with its use.

There were no reports of serious complications of constipation reported in the eluxadoline clinical development program. Two SAEs related to small bowel obstruction (1 with study drug/1 placebo) and one event related to ischemic colitis were reported in eluxadoline studies. The event of ischemic colitis was deemed unlikely related to the study drug given the patient’s high risk of GI bleeding due to multiple comorbidities, some which may have contributed to the event.

DGIEP Clinical Safety Reviewer Comment: *Constipation occurred more frequently in the eluxadoline treatment groups. This is expected given the drug’s mechanism of action.*

Importantly none of these AEs of constipation were SAEs, and they were generally mild in severity. Given there was also a single case in the placebo arm, this reviewer does not believe there is any indication that eluxadoline contributes to small bowel obstruction.

There was a single case of ischemic colitis reported during the eluxadoline clinical development program. This event was likely unrelated to drug. Finally, while there is believed to be an increased risk for ischemic colitis with alosetron, the only approved therapy for IBS-D, eluxadoline is a different mechanism of action, and there is no known association between other opiates and ischemic colitis. This reviewer agrees that this SAE was unlikely related to study drug.

At this time, it appears that eluxadoline increases the risk of constipation, however, there is no evidence to indicate that eluxadoline increases the risk of serious complications of constipation or ischemic colitis.

3.2.2.3 Abuse Potential

Eluxadoline exerts its pharmacologic activity in the gastrointestinal tract with low systemic bioavailability. The Applicant conducted abuse potential studies using oral and intranasal eluxadoline, and a self-injection study in Rhesus monkeys.

The incidence of AEs potentially related to abuse was 7.9% (75 mg), 9.6% (100 mg) and 8.1% (placebo); dizziness and fatigue were the events most commonly reported. Additionally, euphoric mood was reported in 2 eluxadoline (100 mg)-treated subjects.

Clinical Reviewer Comment: *no data to suggest an imbalance in AEs potentially related to abuse.*

3.2.3 Postmarketing Requirements (PMRs) and Commitments (PMCs)

At the time of this review, the Agency has recommended the following PMCs for eluxadoline:

- Renal impairment study
- In-vivo drug-drug interaction (DDI) study with CYP3A4 substrates to evaluate eluxadoline's potential to inhibit CYP3A4
- In-vitro study to evaluate eluxadoline's potential to induce CYP2B6
- In-vitro study to evaluate eluxadoline's potential to induce CYP2C8

The Applicant has agreed to the following PMRs under the Pediatric Research Equity Act (PREA):

- Randomized, double-blind, dose-ranging study to evaluate the safety and effectiveness of eluxadoline in pediatric subjects (aged 6-17 years) with IBS-d
- Randomized, double-blind study to confirm the safety and effectiveness of eluxadoline in pediatric subjects (aged 6-17 years) with IBS-d
- Open-label safety study of eluxadoline in pediatric subjects (aged 6-17 years) with IBS-d

4 DISCUSSION

Patients with IBS-d often experience a constellation of symptoms GI-related symptoms that can significantly impact quality of life. In this population of patients, when dietary changes, over-the-counter anti-diarrheals and other approaches become insufficient to address the pain and diarrhea associated with IBS-d, the use of eluxadoline may present a viable option.

Eluxadoline is a peripherally acting mixed mu opioid receptor agonist and delta opioid receptor) antagonist that acts in the GI tract to treat IBS-d. The benefits of eluxadoline were demonstrated in both pivotal Phase 3 studies and include a statistically significant improvement in both abdominal pain and stool consistency. Alosetron is the only drug currently FDA approved to treat IBS-d, however it is only indicated for use in women with severe disease, and is marketed under a restricted REMS program given safety concerns related to ischemic colitis and serious complications of constipation. Therefore, eluxadoline would serve as a needed additional treatment option, particularly for men with IBS-d given the lack of approved therapies for this patient population.

The most common AEs observed in Phase 3 studies included nausea, constipation, abdominal pain and flatulence.

Pancreatitis and hepatobiliary events related to SO spasm were reported in eluxadoline-treated patients, both which completely resolved upon discontinuation of drug therapy. The proposed labeling for eluxadoline includes information on the risk of pancreatitis, (b) (4) and SO spasm in the Warnings and Precautions section. A Medication Guide will be distributed to further facilitate communication of the SO spasm-related risks with eluxadoline. Additionally, the Applicant voluntarily plans to inform prescribers about the SO spasm-related risks via DHCP and DCP letters and sales force training.

While constipation occurred more frequently in eluxadoline-treated patients, there were no reports of serious complications of constipation. Additionally, the single case of ischemic colitis observed was deemed unlikely related to study drug.

Eluxadoline's abuse potential appears to be low when administered orally. However, the Agency expressed concern with findings from a primate self-injection study suggesting an abuse potential comparable to oxycodone when eluxadoline is given by injection. A key concern from the Agency is opioid abusers gaining access to injectable eluxadoline given that the active pharmaceutical ingredient (API) is "easily extractable from the formulation for administration by alternate routes."

A meeting was convened with the Applicant and CSS on February 25, 2015 to further discuss eluxadoline's abuse potential. The applicant agreed that the available data suggests abuse potential with eluxadoline and that the drug should be scheduled; a proposal for scheduling eluxadoline as a Schedule IV drug was submitted to the Agency on March 11, 2015.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for eluxadoline, NDA 206-940. Eluxadoline has proven efficacy in the treatment of IBS-

d. There were no serious or severe safety issues which warrant a boxed warning for eluxadoline. Thus, the benefit-risk profile for eluxadoline is acceptable and the risks can be mitigated through professional labeling and a MG.

Should DGIEP have any concerns or questions, feel that a REMS may be warranted for this product, or new safety information becomes available; please send a consult to DRISK.

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/s/

NYEDRA W BOOKER
04/06/2015

REEMA J MEHTA
04/06/2015
I concur.