

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206940Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	May 27, 2015
From	Julie Beitz, MD
Subject	Office Director Decisional Memo
NDA #	206940
Applicant Name	Furiex Pharmaceuticals Inc.
Date of Submission	June 27, 2014
PDUFA Goal Date	May 27, 2015
Proprietary Name / Established (USAN) Name	Viberzi (eluxadoline)
Dosage Forms / Strengths	Tablets / 75 mg and 100 mg
Proposed Indication	Treatment of diarrhea and abdominal pain symptoms in men and women with diarrhea predominant irritable bowel syndrome (IBS-D)
Action:	Approval
Approved Indication	Treatment of adults with irritable bowel syndrome with diarrhea (IBS-D)

Materials Reviewed/Consulted	Discipline Reviewers
OND Action Package, including reviews from:	
Medical Officer	Laurie Muldowney, MD
CDTL	Ruyi He, MD
Division Director, DGIEP	Donna Griebel, MD
Statistics	Yeh-Fong Chen, PhD
Pharmacology /Toxicology	Tamal Chakraborti, PhD
Product Quality	Yichun Sun, PhD
DPMH	Carol H. Kasten, MD / Ethan Hausman, MD
Clinical Pharmacology	Dilara Jappara, PhD / Sue Chih Lee, PhD
OPDP	Adewale Adeleye, PharmD, MBA
OSI	Susan Leibenhaut, MD / LCDR LaKisha Williams-Patterson, USPHS
OSE/DMEPA	Sherly Abraham, RPh
OSE/DRISK	Nyedra W. Booker, PharmD, MPH
CSS	Katherine Bonson, PhD / Silvia Calderon, PhD

CDTL = Cross-Discipline Team Leader

CSS = Controlled Substance Staff

DGIEP = Division of Gastroenterology and Inborn Errors Products

DMEPA = Division of Medication Error Prevention and Analysis

DPMH = Division of Pediatrics and Maternal Health

DRISK = Division of Risk Management

OND = Office of New Drugs

OPDP = Office of Prescription Drug Promotion

OSE = Office of Surveillance and Epidemiology

OSI = Office of Scientific Investigations

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Viberzi (eluxadoline) is a mu opioid receptor agonist and a new molecular entity. It is also a delta opioid receptor antagonist, and a kappa opioid receptor agonist. I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Viberzi (eluxadoline) tablets for the treatment of adults with irritable bowel syndrome with diarrhea (IBS-D). IBS-D is a common condition; although not life-threatening, recurrent signs and symptoms can be debilitating and negatively impact quality of life. Current treatment options include lifestyle and dietary modifications, anti-diarrheal agents, and Lotronex (alosetron), approved only for women with severe IBS-D and marketed with a REMS to mitigate the risks of serious complications of constipation and ischemic colitis. Additional treatment options for patients with IBS-D are needed, particularly for men with the condition given the lack of approved therapies for men.

Two Viberzi (eluxadoline) treatment regimens, 75 mg and 100 mg BID, were studied and found to be efficacious for the treatment of adults with IBS-D in two randomized, double-blind, placebo-controlled trials. Composite responses assessed simultaneous changes in abdominal pain and stool consistency. In both trials, composite responses in both eluxadoline treatment groups exceeded that of placebo in men and women, and in patients 65 years and older as well as patients aged 18-64 years. The efficacy of eluxadoline has not been established in pediatric patients with IBS-D; this will be further assessed in a post-approval clinical study.

The Applicant has adequately characterized the safety profile of Viberzi (eluxadoline). Product labeling will warn about the risks of sphincter of Oddi spasm and pancreatitis, and will contraindicate use of eluxadoline in patients with known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction, a history of pancreatitis or a history of alcoholism. In addition, product labeling will contraindicate use of eluxadoline in patients with a history of chronic or severe constipation, or known or suspected mechanical gastrointestinal obstruction, and in patients with severe hepatic impairment.

Product labeling will recommend the eluxadoline 75 mg BID regimen for patients without a gall bladder, for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, and when eluxadoline is used concomitantly with OATP1B1 inhibitors such as cyclosporine.

Although reports of euphoria and feeling drunk were rare in clinical trials of IBS-D patients, supratherapeutic oral doses and intranasal doses of eluxadoline were associated with more frequent reports of euphoria in recreational opioid-experienced subjects. Eluxadoline may produce psychological dependence. The final scheduling of Viberzi (eluxadoline) under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this approval.

Product labeling, including a Medication Guide for patients, adequately addresses the safety concerns identified with use of the drug. Eluxadoline is a controlled substance and will be marketed as a scheduled drug. A Risk Evaluation and Mitigation Strategy (REMS) will not be required. The Applicant's

proposed non-REMS risk minimization strategy is acceptable.

A post-approval clinical pharmacology trial in patients with renal impairment will be required under 505(o) to assess the pharmacokinetic profile of eluxadoline and the occurrence of euphoria and other CNS adverse effects that may be associated with higher eluxadoline exposures in these patients. Several *in vitro* studies will be conducted as post-approval commitments to further assess the metabolic profile of eluxadoline, and to evaluate the dissolution method and acceptance criterion for eluxadoline. There are no inspectional issues that preclude approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Irritable bowel syndrome affects 10 to 20% of the population in developed countries; the diarrhea predominant form of IBS (or IBS-D) is associated with acceleration of colonic transit in 15 to 45% of patients. The diagnosis of IBS is traditionally based on symptoms of recurrent abdominal pain or discomfort with two or more of the following: improvement with defecation, onset associated with a change in the frequency of bowel movements, or onset associated with a change in stool consistency. A variety of luminal and mucosal factors can activate immune, motor, and sensory mechanisms in the small intestine or colon which, in turn, lead to the symptoms and pathophysiological features of IBS. ¹	IBS-D is a common condition; although not life-threatening, recurrent signs and symptoms can be debilitating and negatively impact quality of life.
Current Treatment Options	Initial interventions typically include lifestyle and dietary modifications, and anti-diarrheal agents such as loperamide; patients who do not respond to these approaches should undergo testing to identify potential causative factors. The only FDA-approved therapy for IBS-D is Lotronex (alosetron), a selective 5-HT ₃ receptor antagonist which is indicated only for women with severe IBS-D. Lotronex is marketed with a REMS to mitigate the risks of serious complications of constipation and ischemic colitis.	Additional treatment options for patients with IBS-D are needed, particularly for men with the condition given the lack of approved therapies for men.

¹ Camilleri M. Peripheral Mechanisms in Irritable Bowel Syndrome. NEJM 2012; 367:1626-1635.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<p>Eluxadoline is a mu opioid receptor agonist, and also a delta opioid receptor antagonist and a kappa opioid receptor agonist. In animals, eluxadoline interacts with opioid receptors in the gut.</p> <p>The efficacy of Viberzi (eluxadoline) was established in two randomized, double-blind, placebo-controlled trials, IBS-3001 and IBS-3002.</p> <ul style="list-style-type: none"> A total of 1280 adult patients with IBS-D in Study IBS-3001 and 1145 patients in Study IBS-3002 were randomized 1:1:1 to either eluxadoline 75 mg BID, eluxadoline 100 mg BID or placebo. All patients met Rome III criteria for IBS-D. The mean age of participants was 45 years (range 18 to 80 years); 66% were female and 86% were Caucasian. Information regarding disease-related symptoms and signs, and use of loperamide rescue medication, was collected using a daily electronic diary. Endpoints: The primary endpoint was the proportion of composite responders over the initial 12 week double-blind period. Response was defined as the simultaneous improvement in Worst Abdominal Pain (WAP) score by at least 30% relative to the baseline weekly average score, and a reduction in the Bristol Stool Score to less than 5 on the same day for at least 50% of days. The individual components of the composite response (stool consistency and abdominal pain) were also evaluated. Results: In both trials, a significantly higher proportion of patients in the eluxadoline 100 mg BID and eluxadoline 75 mg BID groups were composite responders compared to placebo over the first 12 weeks of treatment. The proportion of composite responders in both eluxadoline treatment groups was also higher than placebo over 26 weeks of treatment and higher at each 4-week interval for months 1 through 6. In both trials, composite responses in both eluxadoline treatment groups exceeded that of placebo in men and women, and in patients 65 years and older as well as patients aged 18-64 years. Regarding 	<p>Two Viberzi (eluxadoline) treatment regimens, 75 mg and 100 mg BID, were found to be efficacious for the treatment of adults with IBS-D in two randomized, double-blind, placebo-controlled trials. Composite responses assessed simultaneous changes in abdominal pain and stool consistency. In both trials, composite responses in both eluxadoline treatment groups exceeded that of placebo in men and women, and in patients 65 years and older as well as patients aged 18-64 years. Regarding effects on the individual components of the composite response, a greater treatment effect was noted in stool consistency than in abdominal pain.</p> <p>The efficacy of eluxadoline has not been established in pediatric patients with IBS-D; this will be further assessed in a post-approval clinical study.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>effects on the individual components of the composite response, the proportion of stool consistency responders in both eluxadoline treatment groups was higher than that for placebo; the proportion of pain responders in both eluxadoline treatment groups was also higher than that for placebo, but the treatment differences were small.</p> <p>The efficacy of eluxadoline has not been established in pediatric patients; this will be further assessed in a post-approval clinical study.</p>	
Risk	<p>Over 1700 adults with IBS-D have received oral eluxadoline 75 mg or 100 mg BID twice daily in placebo-controlled clinical trials. A total of 1391 patients received treatment for 3 months, 1001 patients received treatment for 6 months, and 488 patients completed 12 months of treatment.</p> <p>Consistent with eluxadoline’s mu opioid receptor agonism, sphincter of Oddi spasm was reported in clinical trials. Product labeling will include Warnings regarding the risks of sphincter of Oddi spasm and pancreatitis, and will contraindicate use of eluxadoline in patients with known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction, a history of pancreatitis or a history of alcoholism based on the following findings:</p> <ul style="list-style-type: none"> • Sphincter of Oddi spasm: In clinical trials, sphincter of Oddi spasm resulting in pancreatitis, hepatic enzyme elevations and acute biliary-type abdominal pain occurred in < 1% of patients receiving twice daily eluxadoline. In patients without a gall bladder (due to a prior cholecystectomy or congenital absence of a gallbladder), 1% and 4% of patients receiving eluxadoline 75 mg and 100 mg, respectively, experienced sphincter of Oddi spasm; spasm was not reported in any patient with a gallbladder. Most patients who experienced sphincter of Oddi spasm reported onset of symptoms within the first week of treatment; symptoms resolved upon discontinuation of eluxadoline. 	<p>The overall safety profile of eluxadoline for the treatment of adults with IBS-D is acceptable. The most common adverse reactions reported with eluxadoline use were constipation, nausea and abdominal pain. Severe constipation occurred rarely. Product labeling will contraindicate use of eluxadoline in patients with a history of chronic or severe constipation, or known or suspected mechanical gastrointestinal obstruction.</p> <p>Consistent with eluxadoline’s mu opioid receptor agonism, sphincter of Oddi spasm was reported in clinical trials. The risk of sphincter of Oddi spasm was increased in patients without a gall bladder. Product labeling will recommend that alternative therapies be considered in such patients; if eluxadoline is administered, a dose of 75 mg BID is recommended. The use of eluxadoline in patients with known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction is contraindicated.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> Pancreatitis: Cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in < 1% of patients receiving eluxadoline twice daily in clinical trials. The majority of cases were associated with excessive alcohol intake. All cases resolved upon drug discontinuation. <p>The most common adverse reactions reported in > 2% of eluxadoline-treated patients at an incidence greater than placebo were constipation, nausea and abdominal pain. Constipation occurred in a higher percentage of patients in eluxadoline treatment groups (7% in the 75 mg BID, and 8% in the 100 mg BID treatment group) than on placebo (3%). Rates of severe constipation were less than 1% in eluxadoline-treated patients.</p> <p>Eluxadoline is a controlled substance. In clinical trials of IBS-D patients, euphoria was reported in no patient receiving 75 mg and in 0.2% of patients receiving eluxadoline 100 mg BID. Feeling drunk was reported in 0.1% of patients in both treatment groups. In human abuse potential studies conducted in recreational opioid-experienced subjects, supratherapeutic oral doses and intranasal eluxadoline doses were associated with euphoria in 14-28% of subjects as compared to 0-5% of subjects on placebo. In addition, increased responses to positive subjective measures (e.g., Drug Liking) and negative subjective measures (e.g., Drug Disliking) relative to placebo were noted. In these studies, responses to subjective measures and reports of euphoria were greater for oxycodone than for eluxadoline. In monkeys, the ability of eluxadoline hydrochloride to induce self-administration suggests that the drug is sufficiently rewarding to produce reinforcement.</p> <p>The safety of eluxadoline use in specific populations can be summarized as follows:</p> <ul style="list-style-type: none"> Pregnancy: There are no studies in pregnant women to inform any risks associated with eluxadoline use. There are no data available regarding the presence of eluxadoline in human breast milk, although the drug is present in rat milk. No teratogenic effects were seen in rats and rabbits during organogenesis that were administered oral and subcutaneous eluxadoline at doses 	<p>Cases of pancreatitis, not associated with sphincter of Oddi spasm, were also reported. The use of eluxadoline in patients with a history of pancreatitis or alcoholism is contraindicated.</p> <p>The use of eluxadoline in patients with severe hepatic impairment (Child-Pugh Class C) is contraindicated due to the high drug exposures that can occur in these patients. High drug exposures may result in euphoria or other CNS adverse effects. Drug exposures were elevated to a lesser extent in patients with mild or moderate hepatic impairment. Therefore, eluxadoline dosing is permitted in these patients, albeit at the reduced dose of eluxadoline 75 mg BID.</p> <p>Concomitant use of eluxadoline with cyclosporine, an inhibitor of the OATP1B1 transporter, resulted in elevated eluxadoline exposures, similar in magnitude to those observed in patients with mild or moderate hepatic impairment. A similarly reduced eluxadoline dose is recommended (i.e., 75 mg BID) for patients taking concomitant OATP1B1 inhibitors.</p> <p>Eluxadoline is a controlled substance. Euphoria was reported rarely in clinical trials of IBS-D patients, however, supratherapeutic oral doses and intranasal eluxadoline doses were associated with more frequent reports of euphoria in recreational opioid-experienced subjects. Eluxadoline may produce psychological dependence. The final</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>approximately 51 and 115 times the human AUC after a single oral dose of 100 mg, respectively.</p> <ul style="list-style-type: none"> Pediatrics: The safety of eluxadoline in pediatric patients has not been established. The PREA pediatric study requirement for ages 0 through 5 years is waived due to the lack of prevalence of IBS-D in this age group. Pediatric studies will be required under PREA for IBS-D patients 6 through 17 years to assess 1) the pharmacokinetics of eluxadoline, 2) the safety and effectiveness of eluxadoline (b) (4), and 3) the safety of eluxadoline administered up to (b) (4) Elderly: There were no overall differences in the types of adverse reactions observed between elderly and younger patients; however, a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs. 59%), serious adverse reactions (9% vs. 4%), and gastrointestinal adverse reactions (39% vs. 28%). Hepatic Impairment: Plasma concentrations of eluxadoline following a single 100 mg dose increased 16-fold in patients with severe hepatic impairment (Child-Pugh Class C) and use in this population is contraindicated. Plasma concentrations of eluxadoline following a single 100 mg dose increased 4- and 6-fold in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment, respectively. A dose of eluxadoline 75 mg BID is recommended for these patients. Co-administration with OATP1B1 inhibitors: Co-administration of a single oral dose of eluxadoline 100 mg with a single oral dose of cyclosporine 600 mg, an inhibitor of the OATP1B1 transporter, increased the AUC of eluxadoline by 4.4-fold and C_{max} by 6.2-fold compared to a single oral dose of eluxadoline 100 mg. These results suggest that the OATP1B1 transporter plays a role in the disposition of eluxadoline. A dose of eluxadoline 75 mg BID is recommended for patients taking concomitant OATP1B1 inhibitors. 	<p>scheduling of eluxadoline under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this approval.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	<p>Labeling: Product labeling will address the safety concerns identified, including that:</p> <ul style="list-style-type: none"> • Eluxadoline use is contraindicated in selected populations (i.e., patients with known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction; patients with alcoholism or a history of pancreatitis; patients with severe hepatic impairment; and patients with a history of chronic or severe constipation or known or suspected mechanical gastrointestinal obstruction); • A reduced dose of eluxadoline (75 mg BID) should be administered to patients who do not have a gall bladder, who have mild or moderate hepatic impairment, or are taking concomitant OATP1B1 inhibitors; and • Eluxadoline use has been associated with euphoria rarely at recommended doses, but more frequently with supratherapeutic doses, and that eluxadoline may produce psychological dependence. <p>Risk Mitigation: The Applicant submitted a non-REMS risk minimization strategy which included the following goals:</p> <ul style="list-style-type: none"> • To inform prescribers of the risks of pancreatitis and hepatobiliary events related to sphincter of Oddi spasm events, and to educate them on appropriate patient selection in order to minimize the occurrence of these events; • To closely monitor these events following market launch <p>The Applicant’s risk minimization strategy including product labeling, a Medication Guide, and a risk communication guide is acceptable.</p> <p>Post-approval studies and trials: A post-approval clinical pharmacology trial in IBS-D patients with renal impairment will be required under 505(o) to assess the pharmacokinetic profile of eluxadoline and the occurrence of euphoria and other CNS adverse effects that may be associated with increased eluxadoline exposure in these patients. The Applicant has also agreed to conduct several <i>in vitro</i> studies to further assess the metabolic profile of eluxadoline, and to evaluate the dissolution method and acceptance criterion for eluxadoline.</p>	<p>Product labeling adequately addresses the safety concerns identified. A Medication Guide for patients will be included as part of labeling. Eluxadoline is a controlled substance and will be marketed as a scheduled drug.</p> <p>A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Viberzi (eluxadoline). The Applicant’s proposed non-REMS risk minimization strategy is acceptable.</p> <p>A post-approval clinical pharmacology trial in patients with renal impairment will be required under 505(o) to assess the pharmacokinetic profile of eluxadoline and the occurrence of euphoria and adverse CNS effects that may be associated with higher drug exposures in these patients.</p> <p>The Applicant has agreed to conduct several <i>in vitro</i> studies to further assess the metabolic profile of eluxadoline, and to evaluate the dissolution method and acceptance criterion for eluxadoline.</p>

2. Postmarketing Requirements and Commitments

In addition to the pediatric study requirements under PREA and the clinical pharmacology trial in patients with renal impairment required under 505(o) noted above, the Applicant has agreed to conduct the following postmarketing studies:

- 1) An *in vitro* study to determine the specific isozymes involved in the metabolism of eluxadoline;
- 2) An *in vitro* study to assess the time-dependent inhibition of CYP3A4 by eluxadoline;
- 3) An *in vitro* study to estimate the IC₅₀ (or K_i) value of eluxadoline with respect to P-gp and predict the *in vivo* relevance of this interaction; and
- 4) An *in vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

The Applicant has also agreed to evaluate the dissolution method and acceptance criterion for eluxadoline by:

- 1) Re-evaluating the dissolution acceptance criterion based on dissolution data collected from at least 10 batches of commercial drug product (5 batches of 75 mg and 5 batches of 100 mg), manufactured over a maximum period of 1 year post-launch;
- 2) Adding a 15- minute time point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes; and
- 3) Assessing the dissolution criterion of Q= (b) (4) % at 10, 15, or 20-minute time points and submitting the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
05/27/2015