DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206940

NDA APPROVAL

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viberzi (eluxadoline) Tablets, 75 mg and 100 mg.

We acknowledge receipt of your amendments dated July 18, 2014, August 12, 2014, August 15, 2014, August 19, 2014, August 22, 2014, August 29, 2014, September 22, 2014, October 9, 2014, October 17, 2014, October 23, 2014, December 2, 2014, December 3, 2014, December 9, 2014, December 12, 2014, December 23, 2014, January 8, 2015, January 9, 2015, January 12, 2015, January 30, 2015, February 11, 2015, February 12, 2015, February 18, 2015, February 20, 2015, February 24, 2015, February 27, 2015, March 11, 2015, March 17, 2015, May 4, 2015, May 7, 2015, May 8, 2015, May 13, 2015, May 18, 2015, May 21, 2015, May 22, 2015, and May 26, 2015.

This new drug application provides for the use of Viberzi (eluxadoline) Tablets, 75 mg and 100 mg for adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

CONTROLLED SUBSTANCE SCHEDULING

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you of your signed agreement on Form 356h dated June 26, 2014 and received June 27, 2014 and your agreement on May 20, 2015 not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of Viberzi in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206940**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Viberzi was not referred to an FDA advisory committee because the clinical trial design is acceptable, outside expertise was not necessary, and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 5 years because necessary studies are impossible or highly impracticable. This is based on the lack of prevalence data on IBS-D in this age group.

We are deferring submission of your pediatric studies for ages 6 through 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2901-1 Conduct a dose ranging study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D). The pharmacokinetics of eluxadoline in these pediatric patients should also be characterized.

Final Protocol Submission:	06/01/2016
Study Completion:	10/15/2019
Final Report Submission:	01/15/2020

2901-2 Conduct a randomized, double-blind study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D).

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2026
Final Report Submission:	06/15/2026

2901-3 Conduct an open-label extension safety study of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D) who participated in the dose ranging (# 2901-1) or efficacy (# 2901-2) studies.

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2027
Final Report Submission:	06/15/2027

Submit the protocols to your IND 079214, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of euphoria and other central nervous system (CNS) adverse effects based on increased drug concentrations in patients with renal insufficiency.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2901-4 A dedicated clinical pharmacology trial to evaluate the impact of renal impairment on eluxadoline pharmacokinetics and the risk for euphoria and other central nervous system (CNS) adverse effects.

The timetable you submitted on May 7, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/01/2016
Trial Completion:	12/31/2017
Final Report Submission:	06/30/2018

Submit the protocol to your IND 079214, with a cross-reference letter to this NDA. Submit the final report to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2901-5 Conduct an *in vitro* study to determine the specific isozymes involved in the metabolism of eluxadoline.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-6 Conduct an *in vitro* study to assess the time-dependent inhibition of CYP3A4 by eluxadoline.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-7 Conduct an *in vitro* study to estimate the IC_{50} (or K_i) value of eluxadoline with respect to P-gp and predict the *in vivo* relevance of this interaction.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-8 Conduct an *in vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-9 Conduct a study of the product dissolution and acceptance criterion to assess post-approval product quality using the following:

- Re-evaluate the dissolution acceptance criterion based on the dissolution data collected from at least 10 batches of commercial drug products (5 batches of 75 mg and 5 batches of 100 mg), manufactured over a maximum period of 1 year post-launch.

- Add 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.

- Assess the dissolution criterion of Q= (b) (4) % at 10, 15, or 20-minute time points and submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

The timetable you submitted on May 14, 2015, states that you will conduct this study according to the following schedule:

Completion of dissolution data assessment:	Launch date + 12 months
Submission of dissolution data assessment:	Launch date + 14 months

Submit clinical protocols to your IND 079214 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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