**DEPARTMENT OF JUSTICE**

**Drug Enforcement Administration**

**21 CFR Part 1308**

**[Docket No. DEA–419N]**

## Schedules of Controlled Substances: Placement of Eluxadoline Into Schedule IV

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration proposes to place the substance eluxadoline (5-[[[(*2S*)-2-amino-3-[4-aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(*1S*)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid), including its salts, isomers, and salts of isomers, into schedule IV of the Controlled Substances Act (CSA). This proposed scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess), or propose to handle eluxadoline.

**DATES:** Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). Electronic comments must be submitted, and written comments must be postmarked, on or before September 10, 2015. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons, defined at 21 CFR 1300.01 as those ''adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811),'' may file a request for hearing, notice of appearance, or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45, 1316.47, 1316.48, or 1316.49, as applicable. Requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before September 10, 2015.

**ADDRESSES:** To ensure proper handling of comments, please reference ''Docket No. DEA–419N'' on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the Web page or to attach a file for lengthier comments. Please go to *http://www.regulations.gov* and follow the online instructions at that site for submitting comments. Upon completion of your submission you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/ODL, 8701 Morrissette Drive, Springfield, Virginia 22152.
- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Federal Register Representative/ODL, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152.

**FOR FURTHER INFORMATION CONTACT:** John R. Scherbenske, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

**SUPPLEMENTARY INFORMATION:**

### Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at *http://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act (FOIA) applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to *http://www.regulations.gov* may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information to this proposed rule are available at *http://www.regulations.gov* for easy reference.

### Request for Hearing, Notice of Appearance at Hearing, Waiver of an Opportunity for a Hearing or To Participate in a Hearing

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking ''on the record after opportunity for a hearing.'' Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. In accordance with 21 CFR 1308.44(a)–(c), requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing may be submitted only by interested persons, defined as those ''adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811).'' 21 CFR 1300.01. Such requests or notices must conform to the requirements of 21 CFR 1308.44(a) or (b), and 1316.47 or 1316.48, as applicable, and include a

statement of interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and 1316.49, including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

Please note that pursuant to 21 U.S.C. 811(a), the purpose and subject matter of a hearing is restricted to: ''find[ing] that such drug or other substance has a potential for abuse, and * * * mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed * * *.'' All requests for hearing and waivers of participation must be sent to the DEA using the address information provided above.

**Legal Authority**

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. 21 U.S.C. 801–971. Titles II and III are referred to as the ''Controlled Substances Act'' and the ''Controlled Substances Import and Export Act,'' respectively, and are collectively referred to as the ''Controlled Substances Act'' or the ''CSA'' for the purpose of this action. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), chapter II. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while ensuring an adequate supply is available for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all scheduled substances is published at 21 CFR part 1308.

Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, ''add to such a schedule or transfer between such schedules any drug or other substance if he * * * finds that such drug or other substance has a potential for abuse, and * * * makes with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed * * *.'' The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA. 28 CFR 0.100.

The CSA provides that scheduling of any drug or other substance may be initiated by the Attorney General (1) on her own motion; (2) at the request of the Secretary of Health and Human Services (HHS); or (3) on the petition of any interested party. 21 U.S.C. 811(a). If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions of schedule IV controlled substances for any person who handles eluxadoline.

**Background**

Eluxadoline is a new molecular entity with central nervous system opioid properties. It has not been marketed in any country. Eluxadoline has mixed mu opioid receptor (MOR) and kappa opioid receptor (KOR) agonist and delta opioid receptor (DOR) antagonist properties. Recently, the Food and Drug Administration (FDA) approved eluxadoline as a prescription drug for the treatment of irritable bowel syndrome with diarrhea (IBS-d). Eluxadoline will be marketed as 75 and 100 milligrams (mg) oral tablets under the trade name of Viberzi.

**Proposed Determination To Schedule Eluxadoline**

Pursuant to 21 U.S.C. 811(a)(1), proceedings to add a drug or substance to those controlled under the CSA may be initiated by request of the Secretary of the HHS.[1] The HHS provided the DEA with a scientific and medical evaluation document (dated May 5, 2015) prepared by the FDA entitled ''Basis for the Recommendation to Place Eluxadoline and Its Salts into schedule IV of the Controlled Substances Act'' and a scheduling recommendation. Pursuant to 21 U.S.C. 811(b), this document contained an eight-factor analysis of the abuse potential of eluxadoline as a new drug, along with the HHS' recommendation to control eluxadoline under schedule IV of the CSA.

In response, the DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS, and all other relevant data, and completed its own eight-factor review document pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in its proposed scheduling decision. Please note that both the DEA and the HHS analyses are available in their entirety under ''Supporting and Related Material'' in the public docket for this proposed rule at *http://www.regulations.gov,* under Docket Number ''DEA–419N''. Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. *The Drug's Actual or Relative Potential for Abuse:* Eluxadoline is a new chemical entity that has not been marketed in the U.S. or in any other country. As such, there is no information available which details actual abuse of eluxadoline. However, the legislative history of the CSA suggests that the DEA consider the following criteria in determining whether a particular drug or substance has a potential for abuse: [2]

(1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community;

(2) There is significant diversion of the drug or substance from legitimate drug channels;

(3) Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

(4) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that they will have the same potentiality for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Both the HHS and the DEA note that three of the above mentioned four criteria (1, 2, and 3) do not apply to eluxadoline for the following reasons. Eluxadoline is a new molecular entity

[1] As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of the NIDA. 50 FR 9518, Mar. 8, 1985. In addition, because the Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations, for purposes of this document, all subsequent references to ''Secretary'' have been replaced with ''Assistant Secretary.''

[2] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4601.

and has not been marketed in any country. Accordingly, it has not been diverted from legitimate sources, and individuals have not taken this substance in amounts sufficient to create a hazard to public health or safety. Therefore, criterion 4 is the only one that applies to eluxadoline.

Eluxadoline acts as a high affinity agonist at MORs and KORs and as an antagonist at DORs. Eluxadoline produced opioid agonistic effects such as centrally mediated analgesia, sedation, motor impairment, respiratory depression, and death in some animals. Eluxadoline generalized to morphine in a drug discrimination study in monkeys suggesting its MOR agonist properties. Monkeys self-administered eluxadoline indicating its rewarding properties.

Receptor binding and functional profile studies demonstrate that eluxadoline has KOR agonistic activity. Pentazocine (schedule IV opioid analgesic) and butorphanol (schedule IV opioid analgesic) are the two currently marketed opioid drugs with KOR agonist activity. Pentazocine and butorphanol were initially approved for market as non-controlled drugs. However, subsequent reports of their actual abuse supported control as schedule IV drugs under the CSA. Clinical studies indicated that pentazocine and butorphanol have been shown to cause greater dysphoria and to be less abusable than the schedule II opioids.

In human abuse potential studies, eluxadoline produced both positive and negative responses. The maximal effects of eluxadoline on Drug Liking are greater than that of placebo, but less than that of oxycodone (schedule II). Eluxadoline produced small statistically significant increases in several positive subjective responses such as visual analog scale (VAS) scores for Take Drug Again, Subjective Drug Value, Good Drug Effects, High, and the Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI–MBG, Euphoria). The positive subjective responses to eluxadoline were most often statistically significantly less than those produced by oxycodone. Eluxadoline produced a high rate of euphoria in human abuse potential studies. However, these euphoric effects of eluxadoline are less than that of oxycodone.

Eluxadoline at all doses elicited a small but significant increase in the VAS score for Drug Disliking. Eluxadoline also produced a statistically significant increase in VAS Bad Drug Effects, ARCI Lysergic Acid Diethylamide (ARCI–LSD, Dysphoria), but did not cause a significant increase in Drowsiness and Sedation. These results are also similar to those produced by pentazocine in a published study which reported a statistically significant increase in the VAS score for Bad Drug Effects and the score for ARCI–LSD (Dysphoria). Eluxadoline produced dysphoric effects consistent with kappa agonist activity related effects produced by pentazocine and butorphanol.

In summary, eluxadoline appears to be so related in its action to substances already listed as having potential for abuse, and which have been controlled in schedule IV of the CSA, to make it likely that eluxadoline will have the same potential for abuse as those substances.

*2. Scientific Evidence of Its Pharmacological Effects, If Known:* The HHS, in its scientific and medical evaluation document, reviewed data from pre-clinical and clinical studies on eluxadoline. The HHS' findings are summarized below.

Pre-Clinical *In Vitro* Pharmacological Studies

Eluxadoline has high affinity at the MOR, KOR, and DOR. Eluxadoline lacked significant affinity for other binding sites including those associated with abuse potential. Similar to butorphanol (schedule IV), eluxadoline acted as an agonist at both MOR and KOR, but acted as an antagonist at DOR. Pentazocine (schedule IV) also has agonist activity at KOR.

Pre-Clinical *In Vivo* Studies

In the Irwin test (a test of general behavioral responses), there were no noticeable behavioral changes produced by eluxadoline at three subcutaneous doses of 500, 1000, or 2000 mg/kg in mice. Similarly, there were no changes in motor activity, reflexes, excitation, body tone, righting reflex, and rotorod tests or in body temperature in rats following oral administration of eluxadoline (30 or 300 mg/kg). However, intravenous administration of eluxadoline HCl (5, 10 and 20 mg/kg/day) in rats for 14 days followed by a 14-day recovery period produced classic opioid-related behaviors including general arousal, handling reactivity, stereotypy, tail pinch response, touch response, changes in posture, gait, mobility, righting reflex, respiration, and hindlimb splay. In a toxicity study in Cynomolgus monkeys, animals treated with eluxadoline (50, 100, and 200 mg/kg/day) or vehicle via oral gavage for nine months, followed by a four-week recovery period (for the vehicle and 200 mg/kg groups), exhibited no changes in behavior during the 39-week treatment period. In a dose-finding study, daily intravenous administration of 20 mg/kg eluxadoline for seven days produced opioid-associated behaviors (decreased respiration and periods of unconsciousness). These effects were severely pronounced following 40 mg/kg dose. All animals in the highest dose group (40 mg/kg reduced to 30 mg/kg on the second day of the dosing after one animal died) exhibited opioid overdose symptoms such as decreased activity, unresponsiveness, decreased body temperature and respiration rates. Opioid antagonist naloxone (0.1 mg/kg) was administered either subcutaneously or intravenously to more or less severely affected animals, respectively. Upon reducing the eluxadoline dose from 40 mg/kg to 30 mg/kg, all animals continued to respond with opioid overdose symptoms.

In a hot-plate test for studying anti-nociceptive effects in mice, oral administration of eluxadoline up to doses of 1000 mg/kg showed no significant analgesic responses. However, subcutaneous administration of both 10 and 50 mg/kg eluxadoline caused significant increases in hot plate latencies and produced concurrent opioid-associated behaviors such as Straub tail and increased limb tone.

As mentioned in the HHS scientific and medical evaluation and scheduling recommendation, drug discrimination tests in animals serve as an important experimental method for predicting whether the effects of a given test drug will be similar to that of a standard training drug used in the study. In drug discrimination studies conducted in Rhesus monkeys trained to discriminate between subcutaneously administered morphine (1 mg/kg) and vehicle using shock stimulus termination procedure, intravenous administration of 17.8 mg/kg dose of eluxadoline HCl produced full generalization to morphine (1 mg/kg) in the only monkey tested. When this same monkey was tested at 10 mg/kg, there was no generalization. However, the 10 mg/kg dose of eluxadoline produced full generalization in a different monkey. The lowest doses of eluxadoline at 1.0 (n = 1) and 3.2 mg/kg (n = 2) produced no generalization (<20%) to morphine. Eluxadoline, as a mu and kappa opioid agonist, produces an interoceptive cue similar to that of mu opioid agonist, morphine (schedule II). These data are similar to those from several published human studies in which butorphanol (schedule IV, mu and kappa opioid agonist), pentazocine (schedule IV, kappa opioid agonist) and tramadol (schedule IV, mu opioid agonist

prodrug) generalized to hydromorphone (schedule II, mu opioid agonist). Thus, these drug discrimination data demonstrate that mu opioid agonists will be recognized by animals and humans as having similar pharmacological properties to each other.

Drug self-administration tests in animals are used to evaluate the rewarding effects of drugs. There is a good correlation between those drugs that are self-administered by animals and those that are abused by humans. The data from self-administration studies provide a measure for abuse potential. In a self-administration study with monkeys (n = 5) trained to self-administer heroin (0.032 mg/kg/infusion in two monkeys or 0.01 mg/kg/infusion in three monkeys), the 0.32 and 1.0 mg/kg/infusion doses of eluxadoline HCl did not produce self-administration in one monkey trained to self-administer the higher 0.032 mg/kg/infusion dose of heroin, or in three other monkeys trained to self-administer the lower 0.001 mg/kg/infusion dose of heroin. When the highest dose of eluxadoline HCl (3.2 mg/kg/infusion) was tested first in the two monkeys trained at the 0.032 mg/kg/infusion dose of heroin, the self-administration rate of eluxadoline HCl (10–19 infusions/session) was less than that of heroin, but more than that of saline (2–4 infusions/session). The self-administration of eluxadoline in animals seems similar to that of the mu and kappa opioid agonist, butorphanol (schedule IV), a kappa opioid agonist, pentazocine (schedule IV) and another mu opioid agonist prodrug, tramadol (schedule IV).

Human Behavioral Studies

In a clinical study, the abuse potential, safety, tolerability, and pharmacokinetics of orally administered eluxadoline (100, 300 and 1000 mg) were compared with positive control drug, oxycodone (30 and 60 mg) in healthy non-dependent recreational opioid users. Of the subjects who received any study treatment, a total of 33 subjects completed the study. On the primary subjective measure of VAS Drug Liking, eluxadoline at the two supratherapeutic doses (300 and 1000 mg) produced statistically significant higher maximum (Emax) scores on Drug Liking compared to placebo. When compared to that of either dose of oxycodone on Drug Liking, all three tested doses of eluxadoline (100, 300 and 1000 mg) showed statistically significant lower Emax scores. Eighteen of the 36 subjects who received eluxadoline showed a statistically significant positive response on Drug Liking with at least one of the eluxadoline doses tested. Data from the secondary subjective measures showed that oxycodone (30 and 60 mg) statistically significantly increased scores on other positive subjective responses such as the VAS for Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Drug Effects, High, and ARCI–MBG (Euphoria). At supratherapeutic oral doses (300 and/or 1000 mg), eluxadoline elicited statistically significant increases as compared to the placebo in positive subjective responses such as VAS for Take Drug Again, Subjective Drug Value, Good Drug Effects, High, and ARCI–MBG (Euphoria). The positive subjective responses to eluxadoline were most often statistically significantly less than those produced by either dose of oxycodone (30 and 60 mg). The HHS states that these results are similar to those produced by a kappa opioid agonist, pentazocine (schedule IV). Eluxadoline at all doses elicited a small but significant increase in the VAS score for Drug Disliking, but it happened one to two hours before the peak Drug Liking response. Furthermore, there were no statistically significant differences in Drug Disliking between eluxadoline and oxycodone (60 mg). Eluxadoline also produced a statistically significant increase in VAS Bad Drug Effects, and ARCI–LSD (Dysphoria), but did not cause a significant increase in Drowsiness and Sedation. These results are also similar to those produced by pentazocine in a published study which reported a statistically significant increase in the VAS score for Bad Drug Effects and the score for ARCI–LSD (Dysphoria).

Oral administration of eluxadoline produced an increase in several classical opioid-like adverse events (AEs) associated with mu opioid agonists. Eluxadoline (ranging from 14–28%) produced euphoria in a dose-dependent manner and it was greater than that after placebo (5%) but less than that of oxycodone (ranging from 73–76%). Eluxadoline induced centrally-mediated responses such as somnolence (ranging from 19–42%), and it overlaps with the rate reported for oxycodone (38–41%) and placebo (19%). Peripheral opioid-associated AEs such as dry mouth were also mentioned (11–19% for eluxadoline and 11–13% for oxycodone). Pruritus was also reported with a range of 8–11% for eluxadoline and 54–70% for oxycodone. The above AEs support that eluxadoline produced typical opioid-like effects, although these are less frequent than reported for oxycodone.

Another clinical study evaluated the abuse potential and safety of intranasal administration of crushed eluxadoline (100 and 200 mg) in comparison to crushed oxycodone HCl (crushed, 15 and 30 mg) in 31 healthy adult, non-dependent recreational opioid users. On the primary subjective measure of Drug Liking VAS, eluxadoline (100 and 200 mg) failed to produce Emax scores on Drug Liking that were statistically different from that of placebo while oxycodone at both tested doses (15 and 30 mg) produced statistically significant higher maximum (Emax) scores compared to placebo. Results for the secondary subjective measures show oxycodone (15 and 30 mg) significantly increased scores on positive subjective responses including the VAS for Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Drug Effects, High, and ARCI–MBG (Euphoria). Eluxadoline (100 and 200 mg) produced significant increases compared to placebo in these positive subjective responses. The positive subjective responses to eluxadoline were most often significantly less than those produced by either dose of oxycodone. Intranasal eluxadoline produced a small but statistically significant increase in the VAS for Drug Disliking while oxycodone did not. Eluxadoline also produced a significant increase in VAS Bad Drug Effects, ARCI–LSD (Dysphoria), Drowsiness, and Sedation. Oxycodone at both doses increased each of these negative subjective measurements, to a degree significantly greater than that of placebo but similar to the high dose of eluxadoline. Subjects identified eluxadoline as an opioid to a degree that was less than that of oxycodone. Intranasal administration of eluxadoline caused adverse events such as euphoria after the 100 mg (22%) and the 200 mg doses (19%). Rate of euphoria following eluxadoline was less than that of oxycodone at 15 mg (44%) and 30 mg (67%), and greater than placebo (0%). All incidences of euphoria produced by eluxadoline were mild in intensity.

The clinical efficacy studies conducted with oral eluxadoline (75 and 100 mg/BID) reported abuse-related AEs. The AE of euphoric mood was reported by only two IBS-d patients in the pooled Phase 2 and 3 safety trials (0.2% of population). The dose of eluxadoline for both these subjects was 100 mg BID. Similarly, the AE of ''feeling drunk'' was reported by only two subjects (0.1% of subjects in the 75 mg group and 0.1% of subjects in the 100 mg group). Other than euphoria, anxiety (1.7%) and somnolence (0.7%)

were the most commonly reported abuse-related AEs. There were a few other central nervous system-associated AEs observed in clinical trials. These included headache (4.0–4.5%), dizziness (2.2–3.2%), and fatigue (1.9–2.6%). Thus there was a very low incidence of euphoria-related AEs in these clinical studies. It is not uncommon for patients participating in clinical studies to exhibit a low rate of euphoria-related AEs compared to participants in Phase I human abuse potential studies. This difference may be due to the underlying disease state of the patient population in clinical studies versus the healthy subject population in human abuse potential studies.

*3. The State of Current Scientific Knowledge Regarding Eluxadoline:* The chemical name of eluxadoline is 5-[[[(*2S*)-2-amino-3-[4-aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(*1S*)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid. The molecular formula of eluxadoline is $C_{32}H_{35}N_5O_5$ and its molecular weight is 569.65. Eluxadoline has two asymmetric carbons, and there are at least four different optical isomers. Because eluxadoline contains a primary amine and a carboxylic acid in its structure, the pH of the solution will determine whether the primary amine will be protonated (positively charged) and the carboxylic acid will be deprotonated (negatively charged). The synthesis of eluxadoline requires a high level of expertise and knowledge in organic chemistry. The tablets could be cracked and easily crushed by users with a tablet crusher or a mortar and pestle. However, the unique physicochemical properties of eluxadoline may present a challenge to isolate eluxadoline for purposes of abuse.

The half-life of eluxadoline is approximately five hours, with high inter-subject variability. Eluxadoline has a low oral bioavailability due to poor GI permeability and moderate hepatic first-pass extraction involving OATP1B1-mediated hepatic uptake of eluxadoline. Co-administration with food lowered systemic exposures. Biliary excretion accounted for over 80% of overall elimination, while there is a minimal elimination by renal excretion.

*4. History and Current Pattern of Abuse:* Because eluxadoline is a new molecular entity and has not been marketed in any country, information as to the history and current pattern of its abuse is not available. Data from pre-clinical and clinical studies indicated that eluxadoline shares pharmacological similarities with schedule IV drugs such as pentazocine and butorphanol and has similar abuse potential (see factors 1 and 2). Pentazocine and butorphanol were initially approved for market as non-controlled drugs. However, subsequent reports of actual abuse of pentazocine and butorphanol supported control as schedule IV drugs under the CSA. It is likely that eluxadoline, upon approval for marketing, will be abused for its rewarding effects.

Eluxadoline generalized to the stimulus effects of morphine (schedule II) in animal drug discrimination studies. These discriminative stimulus effects are similar to that for butorphanol, a schedule IV mu and kappa opioid receptor agonist and for pentazocine, a schedule IV kappa opioid receptor agonist. In two human abuse potential studies, eluxadoline produced both positive and negative subjective responses. The maximal effects of eluxadoline on Drug Liking are greater than that of placebo, but less than that of oxycodone (schedule II). Eluxadoline at all doses elicited a small but significant increase in the VAS score for Drug Disliking. The negative subjective responses of eluxadoline may be reflective of its kappa opioid receptor agonist properties and these are similar to those of schedule IV opioids, butorphanol and pentazocine. These dysphoric effects may indicate a lower abuse potential of a substance. In human abuse potential studies oral or intranasal administration of eluxadoline produced euphoria with a degree less than that of oxycodone.

As of May 20, 2015, no reports for eluxadoline were identified in either the National Forensic Laboratory Information System (NFLIS),[3] or System to Retrieve Information on Drug Evidence (STRIDE).[4]

*5. The Scope, Duration, and Significance of Abuse:* Because eluxadoline is a new molecular entity and has not been marketed in any country, information as to the scope, duration and significance of its abuse is not available. Both pre-clinical and clinical studies indicate that eluxadoline shares pharmacological similarities with schedule IV drugs such as butorphanol and pentazocine and has similar abuse potential. Pentazocine and butorphanol were initially marketed as uncontrolled drugs. However subsequent reports of abuse of butorphanol and pentazocine led to their control as schedule IV drugs under the CSA. Thus, if eluxadoline were to be marketed as a non-controlled drug, it is likely to be abused for its rewarding properties. If uncontrolled, it is also likely that individuals seeking opioids will abuse eluxadoline as a substitute for other opioids that are controlled under the CSA.

In human abuse potential studies, eluxadoline produced both positive and negative subjective responses. The maximal effects of eluxadoline on Drug Liking are greater than that of placebo, but less than that of oxycodone (schedule II). Eluxadoline at all doses elicited a small but significant increase in the VAS score for Drug Disliking. The negative subjective responses of eluxadoline may be reflective of its kappa opioid receptor agonist properties and these are similar to those of schedule IV opioids, butorphanol and pentazocine. These dysphoric effects may indicate a lower abuse potential of eluxadoline.

*6. What, If Any, Risk There Is To the Public Health:* Data from pre-clinical and clinical studies indicate that eluxadoline has abuse potential similar to schedule IV opioids such as butorphanol and pentazocine. Abuse potential of a drug is considered a risk to the public health. Available information suggests that if eluxadoline were to be marketed as a non-controlled drug, it would be abused for its rewarding properties. The major concern regarding eluxadoline's risk to public health is based on animal studies in monkeys treated with eluxadoline, where the animals exhibited opioid overdose symptoms such as decreased activity, unresponsiveness, decreased body temperature, and decreased respiration rates. Severe sedation and slumping were also observed in monkeys following self-administration with eluxadoline. Furthermore, opioid-like effects of eluxadoline may not be reversible unless adequate or repeated administration of opioid antagonists such as naloxone or naltrexone is performed.

*7. Its Psychic or Physiological Dependence Liability:* Several pre-clinical studies both on Cynomolgus monkeys and rats treated with different doses of eluxadoline followed by various recovery or drug discontinuation periods showed no behavioral changes during the treatment period. There were also no behaviors suggestive of withdrawal during the observed recovery periods. Thus, chronic administration of eluxadoline

[3] NFLIS is a program of the DEA that collects drug identification results from drug cases analyzed by other Federal, State, and local forensic laboratories.

[4] STRIDE collected the results of drug evidence analyzed at DEA laboratories and reflects evidence submitted by the DEA, other Federal law enforcement agencies, and some local law enforcement agencies. On October 1, 2014, STARLiMS replaced STRIDE as the DEA laboratory drug evidence data system of record.

did not result in withdrawal signs in laboratory monkeys and rats. However, monkeys self-administered eluxadoline. This suggests that eluxadoline has sufficient rewarding effects to induce reinforcement. In human subjects, the abuse-related AEs reported in clinical studies found that eluxadoline produced a low incidence of euphoria, ''feeling drunk,'' anxiety, somnolence, headache, abdominal pain, dizziness, and fatigue, which are suggestive of its ability to produce psychic dependence.

*8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:* Eluxadoline is not an immediate precursor of any substance controlled under the CSA.

*Conclusion:* Based on consideration of the scientific and medical evaluation conducted by the HHS and its recommendation, and after considering its own eight-factor analysis, the DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of eluxadoline. As such, the DEA hereby proposes to schedule eluxadoline as a controlled substance under the CSA.

**Findings for Schedule Placement**

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The statute outlines the findings required in placing a drug or other substance in any schedule. 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of the HHS and review of all available data, the Administrator of the DEA, pursuant to 21 U.S.C. 812(b), finds that:

(1) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III. Eluxadoline has a low potential for abuse relative to the drugs or other substances in schedule III. The overall abuse potential of eluxadoline is comparable to the schedule IV substances such as pentazocine and butorphanol.

(2) The drug or other substance has a currently accepted medical use in treatment in the United States. Recently, the FDA approved eluxadoline as a prescription drug for the treatment of irritable bowel syndrome with diarrhea (IBS-d). Therefore, eluxadoline has a currently accepted medical use in treatment in the United States.

(3) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III. Abuse of eluxadoline may lead to limited psychological dependence similar to that of schedule IV drugs, but less than that of schedule III drugs.

Based on these findings, the Administrator of the DEA concludes that eluxadoline, including its salts, isomers and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, warrants control in schedule IV of the CSA (21 U.S.C. 812(b)(4)).

**Requirements for Handling Eluxadoline**

If this rule is finalized as proposed, eluxadoline would be subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, research, and conduct of instructional activities involving schedule IV substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities with) eluxadoline, or who desires to handle eluxadoline, would be required to be registered with the DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958 and in accordance with 21 CFR parts 1301 and 1312. Any person who currently handles eluxadoline, and is not registered with the DEA, would need to submit an application for registration and may not continue to handle eluxadoline as of the effective date of the final rule, unless the DEA has approved that application for registration, pursuant to 21 U.S.C. 822, 823, 957, 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Security.* Eluxadoline would be subject to schedule III–V security requirements and would need to be handled and stored pursuant to 21 U.S.C. 821, 823, 871(b) and in accordance with 21 CFR 1301.71–1301.93.

3. *Labeling and Packaging.* All labels and labeling for commercial containers of eluxadoline on or after finalization of this proposed rule would need to comply with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302.

4. *Inventory.* Every DEA registrant who possesses any quantity of eluxadoline on the effective date of the final rule would be required to take an inventory of all stocks of eluxadoline on hand as of the effective date of the rule, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who becomes registered with the DEA after the effective date of the final rule must take an initial inventory of all stocks of controlled substances (including eluxadoline) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b).

After the initial inventory, every DEA registrant would be required to take an inventory of all controlled substances (including eluxadoline) on hand, on a biennial basis, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

5. *Records.* All DEA registrants would be required to maintain records with respect to eluxadoline pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR parts 1304, 1307, and 1312.

6. *Prescriptions.* All prescriptions for eluxadoline or products containing eluxadoline would need to comply with 21 U.S.C. 829, and be issued in accordance with 21 CFR parts 1306 and 1311, subpart C.

7. *Importation and Exportation.* All importation and exportation of eluxadoline would need to be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

8. *Criminal Liability.* Any activity involving eluxadoline not authorized by, or in violation of, the CSA, occurring on or after finalization of this proposed rule, would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

**Regulatory Analyses**

*Executive Orders 12866 and 13563*

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures performed ''on the record after opportunity for a hearing,'' which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

*Executive Order 12988*

This proposed regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

*Executive Order 13132*

This proposed rulemaking does not have federalism implications warranting the application of Executive Order

13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

*Executive Order 13175*

This proposed rule will not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

*Regulatory Flexibility Act*

The Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601–612, has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this proposed rule is to place eluxadoline, including its salts, isomers, and salts of isomers, into schedule IV of the CSA. No less restrictive measures (*i.e.,* non-control, or control in schedule V) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Eluxadoline is a new molecular entity which has not yet been marketed in the United States or any other country. Although the manufacturer is expected to enjoy market exclusivity for many years, the DEA has no basis to determine the level of contracted or outsourced manufacturing activities or the breadth of the distribution network. Furthermore, due to the wide variety of unidentifiable and unquantifiable variables that could potentially influence the dispensing and distribution rates of new pharmaceutical drugs, the DEA is unable to determine the number of potential small entities that might handle eluxadoline. However, the DEA estimates that all persons who would handle, or propose to handle, eluxadoline are currently registered with the DEA to handle schedule IV controlled substances, because it is a pharmaceutical controlled substance intended for medical treatment. Accordingly, the number of DEA registrations authorized to handle schedule IV controlled substances is a reasonable estimate for the maximum number of eluxadoline handlers. Therefore, the DEA estimates that 1.6 million (1,554,254 as of June 2015) controlled substance registrations, representing approximately 427,584 entities, would be the maximum number of entities affected by this rule. The DEA estimates that 418,141 (97.8%) of 427,584 affected entities are ''small entities'' in accordance with the RFA and SBA size standards.

The DEA anticipates that prospective eluxadoline handlers already handle other schedule IV controlled substances and that the cost impact as a result of placing eluxadoline in schedule IV would be nominal. As the anticipated eluxadoline handlers already handle other scheduled IV controlled substances, they already have DEA registrations and the required security and recordkeeping processes, equipment, and facilities in place, and would only require a nominal increase in security, inventory, recordkeeping and labeling costs.

As discussed above, while the DEA does not have a basis to estimate the number of affected entities, the DEA estimates that the maximum number of affected entities is 427,584 of which 418,141 are estimated to be small entities. Since the affected entities are expected to handle other schedule IV controlled substances and maintain security and recordkeeping facilities and processes consistent with schedule IV controlled substances, the DEA estimates any economic impact will be nominal. Because of these facts, this proposed rule will not result in a significant economic impact on a substantial number of small entities.

*Unfunded Mandates Reform Act of 1995*

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.,* the DEA has determined and certifies that this action would not result in any Federal mandate that may result ''in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year.'' Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

*Paperwork Reduction Act of 1995*

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995, 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**List of Subjects in 21 CFR Part 1308**

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, the DEA proposes to amend 21 CFR part 1308 as follows:

## PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

■ 1. The authority citation for 21 CFR part 1308 continues to read as follows:

**Authority:** 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

■ 2. Amend § 1308.14 by adding paragraph (g)(3) to read as follows:

**§ 1308.14 Schedule IV.**

* * * * *

(g) * * *

(3) Eluxadoline (5-[[[(*2S*)-2-amino-3-[4-aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(*1S*)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid) (including its optical isomers) and its salts, isomers, and salts of isomers (9725)

Dated: August 5, 2015.

**Chuck Rosenberg,**

*Acting Administrator.*

[FR Doc. 2015–19655 Filed 8–10–15; 8:45 am]

**BILLING CODE 4410–09–P**

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 52

**[EPA–R04–OAR–2015–0248; FRL–9932–19–Region 4]**

### Approval and Promulgation of Implementation Plans; Georgia; Atlanta; Requirements for the 2008 8-Hour Ozone Standard

**AGENCY:** Environmental Protection Agency.

**ACTION:** Proposed rule.

**SUMMARY:** The Environmental Protection Agency (EPA) is proposing to approve a state implementation plan revision submitted by the State of Georgia, through Georgia Environmental Protection Division on February 6, 2015, to address the base year emissions inventory and emissions statements requirements for the 2008 8-hour ozone national ambient air quality standards for the Atlanta, Georgia 2008 8-hour ozone nonattainment area (hereinafter referred to as the ''Atlanta Area''). These requirements apply to all ozone nonattainment areas. The Atlanta Area is comprised of 15 counties in Atlanta (Bartow, Cherokee, Clayton, Cobb, Coweta, DeKalb, Douglas, Fayette, Forsyth, Fulton, Gwinnett, Henry, Newton, Paulding, and Rockdale). This proposed action is being taken pursuant to the Clean Air Act and its implementing regulations.

In the Final Rules Section of this **Federal Register,** EPA is approving the State's SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial submittal and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule. If no adverse comments are received in response to this rule, no further activity is contemplated. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this document. Any parties interested in commenting on this document should do so at this time.

**DATES:** Written comments must be received on or before September 10, 2015.

**ADDRESSES:** Submit your comments, identified by Docket ID No. EPA–R04–OAR–2015–0248 by one of the following methods:

1. *www.regulations.gov:* Follow the on-line instructions for submitting comments.

2. *Email: R4-ARMS@epa.gov*.

3. *Fax:* (404) 562–9019.

4. *Mail:* ''EPA–R04–OAR–2015–0248,'' Air Regulatory Management Section (formerly the Regulatory Development Section), Air Planning and Implementation Branch (formerly the Air Planning Branch), Air, Pesticides and Toxics Management Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303–8960.

5. *Hand Delivery or Courier:* Lynorae Benjamin, Chief, Air Regulatory Management Section, Air Planning and Implementation Branch, Air, Pesticides and Toxics Management Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303–8960. Such deliveries are only accepted during the Regional Office's normal hours of operation. The Regional Office's official hours of business are Monday through Friday, 8:30 a.m. to 4:30 p.m., excluding Federal holidays. Please see the direct final rule which is located in the Rules section of this **Federal Register** for detailed instructions on how to submit comments.

**FOR FURTHER INFORMATION CONTACT:** Tiereny Bell, Air Regulatory Management Section, Air Planning and Implementation Branch, Air, Pesticides and Toxics Management Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303–8960. Ms. Bell can be reached at (404) 562–9088 and via electronic mail at *bell.tiereny@epa.gov*.

**SUPPLEMENTARY INFORMATION:** For additional information see the direct final rule which is published in the Rules Section of this **Federal Register**. A detailed rationale for the approval is set forth in the direct final rule and incorporated herein by reference. If no adverse comments are received in response to this rule, no further activity is contemplated. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this document. Any parties interested in commenting on this document should do so at this time.

Dated: July 30, 2015.

**Heather McTeer Toney,**

*Regional Administrator, Region 4.*

[FR Doc. 2015–19727 Filed 8–10–15; 8:45 am]

**BILLING CODE 6560–50–P**

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 52

**[EPA–R04–OAR–2015–0384; FRL–9932–22–Region 4]**

### Approval and Promulgation of Implementation Plans; Kentucky: New Sources in or Impacting Nonattainment Areas

**AGENCY:** Environmental Protection Agency

**ACTION:** Proposed rule.

**SUMMARY:** The Environmental Protection Agency (EPA) is proposing to approve the Commonwealth of Kentucky's September 23, 2011, State Implementation Plan (SIP) revision, submitted through the Kentucky Division for Air Quality (KY DAQ), which modifies the SIP by making changes to Kentucky regulation, ''*Review of new sources in or impacting upon nonattainment areas.*'' EPA has preliminarily determined that Kentucky's requested SIP revision meets the applicable provisions of the Clean Air Act (CAA or Act) and EPA regulations regarding Nonattainment New Source Review (NNSR) permitting.

**DATES:** Written comments must be received on or before September 10, 2015.

**ADDRESSES:** Submit your comments, identified by Docket ID Number EPA–R04–OAR–2015–0384 by one of the following methods:

1. *www.regulations.gov:* Follow the on-line instructions for submitting comments.

2. *Email: R4-ARMS@epa.gov*.

3. *Fax:* (404) 562–9019.

4. *Mail:* ''EPA–R04–OAR–2015–0384'', Air Regulatory Management Section, Air Planning and Implementation Branch, Air, Pesticides and Toxics Management Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303–8960.

5. *Hand Delivery or Courier:* Ms. Lynorae Benjamin, Chief, Air Regulatory Management Section, Air Planning and Implementation Branch, Air, Pesticides and Toxics Management Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303–8960. Such