DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-1494]

Schedules of Controlled Substances: Temporary Placement of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Temporary amendment; temporary scheduling order.

SUMMARY: The Drug Enforcement Administration issues this temporary order to schedule seven benzimidazole-opioids, as identified in this order, in schedule I of the Controlled Substances Act. DEA bases this action on a finding that placing these substances in schedule I is necessary to avoid imminent hazard to public safety. This order imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess) or propose to handle these substances.

DATES: This temporary order is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER], until October 15, 2027. If this order is extended or made permanent, DEA will publish a document in the *Federal Register*.

ADDRESSES: 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement

Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362–3249.

SUPPLEMENTARY INFORMATION: The Drug Enforcement Administration (DEA) issues a temporary scheduling order[1] (in the form of a temporary amendment) to add the following seven benzimidazole-opioid substances, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible, to schedule I under the Controlled Substances Act (CSA):

- 2-(2-((2,3-dihydrobenzofuran-5-yl)methyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine (commonly known as, ethyleneoxynitazene),
- 2-(2-(benzodioxol-5-ylmethyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine (commonly known as, methylenedioxynitazene or 3′,4′-methylenedioxynitazene),
- 2-(2-(4-ethoxybenzyl)-5-methyl-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine (commonly known as, 5-methyl etodesnitazene),
- 2-(2-(4-ethoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*-ethylethan-1-amine (commonly known as, *N*-desethyl etonitazene),
- *N*-ethyl-2-(5-nitro-2-(4-propoxybenzyl)-1*H*-benzimidazol-1-yl)ethan-1-amine (commonly known as, *N*-desethyl protonitazene),
- 2-(2-(4-ethoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*,*N*-dimethylethan-1-amine (commonly known as, *N*,*N*-dimethylamino etonitazene), and
- 2-(4-isopropoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole (commonly known as, *N*-pyrrolidino isotonitazene).

Legal Authority

[1] Though DEA has used the term "final order" with respect to temporary scheduling orders in the past, this action adheres to the statutory language of 21 U.S.C. 811(h), which refers to a "temporary scheduling order." No substantive change is intended.

Under 21 U.S.C. 811(h)(1), the CSA provides the Attorney General (as delegated to the Administrator of DEA (Administrator) pursuant to 28 CFR 0.100) with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the evaluation requirements of 21 U.S.C. 811(b), if she finds that such action is necessary to avoid an imminent hazard to the public safety.[2] In addition, if proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1) while the substance is temporarily controlled under section 811(h), the Attorney General may extend the temporary scheduling for up to one year.[3]

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under 21 U.S.C. 812, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355.[4]

Background

The CSA requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of an intent to temporarily place a substance in schedule I of the CSA (i.e., to issue a temporary scheduling order).[5] By letter dated April 15, 2025, the then-Acting Administrator transmitted the required notice to place ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in schedule I on a temporary basis to the Acting Assistant Secretary for Health of HHS (Assistant Secretary).[6] On May 20, 2025, the Acting Assistant Secretary responded to this notice and advised DEA that based on a review by

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[2] 21 U.S.C. 811(h)(1).
[3] 21 U.S.C. 811(h)(2).
[4] 21 U.S.C. 811(h)(1); 21 CFR part 1308.
[5] 21 U.S.C. 811(h)(4).
[6] The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. *See Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law 91-513, As Amended; Delegation of Authority*, 58 FR 35460 (July 1, 1993).

the Food and Drug Administration (FDA), there are currently no investigational new drug applications (IND) or approved new drug applications (NDA) for ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene. The Acting Assistant Secretary also stated that HHS had no objection to the temporary placement of these substances in schedule I of the CSA. Ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene currently are not listed in any schedule under the CSA, and no exemptions or approvals under 21 U.S.C. 355 are in effect for these substances.

DEA has taken into consideration the Acting Assistant Secretary's comments as required by 21 U.S.C. 811(h)(4). DEA has found the control of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety.

As required by 21 U.S.C. 811(h)(1)(A), DEA published a notice of intent (NOI) to temporarily schedule ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene on June 26, 2025.[7] That NOI discussed findings from DEA's three-factor analysis dated June 2025, which DEA made available on *www.regulations.gov*.

To find that temporarily placing a substance in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator must consider three

[7] *Schedules of Controlled Substances: Temporary Placement of Seven Benzimidazole Opioids in Schedule I*, 90 FR 27268 (June 26, 2025).

of the eight factors set forth in 21 U.S.C. 811(c): the substance's history and current pattern of abuse; the scope, duration, and significance of abuse; and what, if any, risk there is to the public health.[8] Considerations of these factors includes any information indicating actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene.[9] Substances meeting the statutory requirements for temporary scheduling may only be placed in schedule I.[10] Substances in schedule I have high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.[11]

Seven Benzimidazole-Opioids: Ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene

The availability of synthetic opioids in the illicit drug market continues to pose an imminent hazard to public safety. Adverse health effects associated with the abuse of synthetic opioids and the continued evolution and increased popularity of these substances have been a serious concern in recent years. As the United States continues to experience an unprecedented epidemic of opioid use and misuse, the presence of new synthetic opioids with no approved medical use exacerbates the epidemic. The trafficking and abuse of new synthetic opioids are deadly new trends. The benzimidazole-opioids have a similar pharmacological profile to fentanyl, morphine, and other mu-opioid receptor agonists.

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[8] 21 U.S.C. 811(h)(3).
[9] 21 U.S.C. 811(h)(3).
[10] 21 U.S.C. 811(h)(1).
[11] 21 U.S.C. 812(b)(1).

Beginning in 2019, this class of synthetic opioids known as benzimidazole-opioids, commonly referred to as "nitazenes," appeared in the United States and have dominated the opioid recreational drug market. Between August 2020 and July 2024, DEA has temporarily controlled 10 benzimidazole-opioids because they posed a threat to public safety.[12] Recently, additional benzimidazole-opioids have been identified within the rapidly expanding class of "nitazene" compounds in the recreational drug market. Ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene etonitazene are some of the recently encountered "nitazene" synthetic opioids identified in the illicit drug market.

Benzimidazole-opioids have contributed to numerous fatalities. The continued trafficking and identification of benzimidazole-opioids in toxicology cases pose a significant threat to public health and safety. The misuse of synthetic opioids has led to devastating consequences including death. Preclinical pharmacology data demonstrate that ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene have pharmacological profiles similar to those of the potent benzimidazole-opioids etonitazene, metonitazene, and protonitazene, schedule I opioid substances. Thus, it is expected that these seven substances will have similar harmful effects in humans. Methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, and *N*-pyrrolidino isotonitazene have been positively identified in at least 37 toxicology cases. As the United States continues to

[12] *Schedules of Controlled Substances: Temporary Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-Pyrrolidino etonitazene, and Protonitazene in Schedule I*, 87 FR 21556 (Apr. 12, 2022); *Schedules of Controlled Substances: Temporary Placement of Isotonitazene in Schedule I*, 85 FR 51342 (Aug. 20, 2020); *Schedules of Controlled Substances: Temporary Placement of N-Desethyl Isotonitazene and N-Piperidinyl Etonitazene in Schedule I*, 89 FR 60817 (Jul. 29, 2024).

experience a high number of opioid-involved overdoses and mortalities, the introduction of new designer opioids further exacerbates the current opioid epidemic.

Available data and information for ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene, summarized below, indicate that these substances have high potentials for abuse, no currently accepted medical uses in treatment in the United States,[13] and a lack of accepted safety for use under medical supervision. DEA's three-factor analysis is available in its entirety under "Supporting and Related Material" of the public docket for this action at www.regulations.gov under Docket Number DEA-1494.

Factor 4. History and Current Pattern of Abuse

[13] When finding schedule I placement on a temporary basis is necessary to avoid imminent hazard to the public, 21 U.S.C 811(h) does not require DEA to consider whether the substance has a currently accepted medical use in treatment in the United States. Nonetheless, there is no evidence suggesting that ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene have a currently accepted medical use in treatment in the United States. To determine whether a drug or other substance has a currently accepted medical use, DEA has traditionally applied a five-part test to a drug or substance that has not been approved by the FDA: (1) The drug's chemistry must be known and reproducible; (2) there must be adequate safety studies; (3) there must be adequate and well-controlled studies proving efficacy; (4) the drug must be accepted by qualified experts; and (5) the scientific evidence must be widely available. *See Marijuana Scheduling Petition; Denial of Petition; Remand*, 57 FR 10499 (Mar. 26, 1992), pet. for rev. denied, *Alliance for Cannabis Therapeutics v. Drug Enforcement Admin.*, 15 F.3d 1131, 1135 (D.C. Cir. 1994). DEA applied the traditional five-part test and concluded the test was not satisfied. In a recent published letter in a different context, HHS applied an additional two-part test to determine currently accepted medical use for substances that do not satisfy the five-part test: (1) whether there exists widespread, current experience with medical use of the substance by licensed health care providers operating in accordance with implemented jurisdiction-authorized programs, where medical use is recognized by entities that regulate the practice of medicine, and, if so, (2) whether there exists some credible scientific support for at least one of the medical conditions for which part (1) is satisfied. On April 11, 2024, the Department of Justice's Office of Legal Counsel (OLC) issued an opinion, which, among other things, concluded that HHS's two-part test would be sufficient to establish that a drug has a currently accepted medical use. Office of Legal Counsel, Memorandum for Merrick B. Garland Attorney General Re: Questions Related to the Potential Rescheduling of Marijuana at 3 (April 11, 2024). For purposes of this temporary order, there is no evidence that health care providers have widespread experience with medical use of these seven substances or that the use of these substances is recognized by entities that regulate the practice of medicine, so the two-part test also is not satisfied. By letter dated May 20, 2025, DEA has been advised by HHS that there are currently no approved new drug applications or investigational new drug applications for seven benzimidazole-opioids. Additionally, HHS communicated no objections to the temporary placement of these substances into schedule I of the CSA.

Benzimidazole-opioids were originally synthesized and studied for their analgesic properties in the 1950s by the pharmaceutical research laboratories of the Swiss chemical company Chemical Industries Basel. The research produced a group of structurally unique benzimidazole derivatives with analgesic properties; however, the research effort did not produce any medically approved analgesic products. Since 2019, there has been an emergence of benzimidazole-opioid compounds on the illicit drug market, which have been positively identified in numerous cases of fatal overdose events. These benzimidazole-opioid derivatives include schedule I substances, such as synthetic opioids clonitazene, etonitazene, and isotonitazene.

Recently, ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene have emerged in the illicit drug market. Law enforcement officers have encountered these seven substances in solid forms (e.g., powder and tablets) and are often mixed with other illicit drugs. Commonly, benzimidazole-opioids are co-detected with designer benzodiazepines, a combination that poses significant risk to users. These substances are not approved pharmaceutical products, and they are not approved for medical use anywhere in the world. In a letter to DEA dated May 20, 2025, the Acting Assistant Secretary stated that there are no FDA-approved NDAs or INDs for ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in the United States; hence, there are no legitimate channels for these substances as marketed drug products.

Reports of detection of benzimidazole-opioids in forensic casework are on the rise. The appearance of benzimidazole-opioids on the illicit drug market is similar to other designer opioid drugs trafficked for their psychoactive effects. In 2023 and 2024, ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl

etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene emerged on the illicit synthetic drug market as evidenced by their identification in forensic drug seizures and in biological samples.[14] According to the National Forensic Laboratory Information System (NFLIS-Drug) and DEA STARLiMS databases, law enforcement encounters of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene have been identified in powder or tablet forms.

Factor 5. Scope, Duration and Significance of Abuse

Ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene, similar to etonitazene, metonitazene, and protonitazene (schedule I substances), have been described as potent synthetic opioids, and evidence suggests they are abused for their opioidergic effects (see Factor 6). The abuse of these benzimidazole-opioids, similar to other synthetic opioids, has resulted in serious adverse health effects. According to the center for forensic science research education (CFSRE) monograph reports published between November 2023 and December 2024, some of these benzimidazole-opioids have been co-identified with designer benzodiazepines, fentanyl, heroin, or other benzimidazole-opioids.[15] Data from law enforcement suggest that ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl

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[14] Gao, G., Yang, S., Wang, X., Xiang, P., Ma, L., Yan, F., & Shi, Y. (2025). UHPLC-MS/MS-based analysis of 17 nitazenes in human hair for practical forensic casework with simultaneous separation of 6 groups of isomers. *Journal of pharmaceutical and biomedical analysis, 257, 116707*

[15] Monographs, *N*-Desethyl etonitazene (Nov. 30, 2023), *available at* www.cfsre.org/images/monographs/N-Desethyl-Etonitazene-New-Drug-Monograph-NPS-Discovery-113023.pdf; Monographs, 5Mmethyl etodesnitazene (Aug. 26, 2024), *available at* www.cfsre.org/images/monographs/5-Methyl-Etodesnitazene-New-Drug-Monograph-NPS-Discovery.pdf; Monographs, Methylenedioxynitazene (Aug. 29, 2024), *available at* www.cfsre.org/images/monographs/Methylenedioxynitazene-New-Drug-Monograph-NPS-Discovery.pdf; Monographs- *N*-Pyrrolidino isotonitazene (Dec. 20, 2024), *available at* www.cfsre.org/images/monographs/N-Pyrrolidino-Isotonitazene-New-Drug-Monograph-NPS-Discovery.pdf.

etonitazene, *N*-desethyl protonitazene, *N*-pyrrolidino isotonitazene, and *N*,*N*-dimethylamino etonitazene are being abused in the United States as recreational drugs.[16] Since 2023, there have been 184 exhibits reported to the National Forensic Laboratory Information System (NFLIS-Drug)[17] database pertaining to the trafficking, distribution, and abuse of these substances.[18] NFLIS registered 14 encounters of ethyleneoxynitazene from 5 states; 19 encounters of methylenedioxynitazene from 5 states; four encounters of 5-methyl etodesnitazene from 1 state, 114 encounters of *N*-desethyl etonitazene from 14 states; 9 encounters of *N*-desethyl protonitazene from 6 states; 12 encounters of *N*,*N*-dimethylamino etonitazene from 4 states; and 12 encounters of *N*-pyrrolidino isotonitazene from 9 states. According to data from DEA STARLiMS[19] database, there have been 66 identifications of 6 of these substances.[20] There have been 7 identifications of ethyleneoxynitazene; 2 identifications of methylenedioxynitazene; 24 identifications of *N*-desethyl etonitazene; 7 identifications of *N*-desethyl protonitazene; 4 identifications of *N*-pyrrolidino isotonitazene; and 22 identifications of *N*,*N*-dimethylamino etonitazene in drug seizures.

Because abusers of these substances are likely to obtain these substances through unregulated sources, the identity, purity, and quantity of these substances are uncertain and inconsistent, thus posing significant adverse health risks to the end user. The misuse and use of opioids have been demonstrated and are well-characterized. Individuals who

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[16] While law enforcement data are not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. *See* Schedules of Controlled Substances: Placement of Carisoprodol Into Schedule IV, 76 FR 77330, 77332 (Dec. 12, 2011).

[17] DEA's National Forensic Laboratory Information System (NFLIS) is a comprehensive information system that collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories within the United States. NFLIS-Drug, a component of NFLIS, includes drug chemistry results from completed analyses only. While NFLIS data are not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. *See Schedules of Controlled Substances: Placement of Carisoprodol Into Schedule IV*, 76 FR 77330, 77332 (Dec. 12, 2011).

[18] NFLIS-Drug was queried on May 12, 2025.

[19] On October 1, 2014, DEA implemented STARLiMS (a web-based, commercial laboratory information management system) to replace the System to Retrieve Information from Drug Evidence (STRIDE) as its laboratory drug evidence data system of record. Accessed June 25, 2025.

[20] There is duplication of records between NFLIS and STARLiMS

initiate use (i.e., use a drug for the first time) of these benzimidazole-opioids are likely to be at risk of developing substance use disorder, an overdose event, or death, similar to that of other opioid analgesics (e.g., fentanyl and morphine). The population likely to abuse these benzimidazole-opioids appears to be the same as those misusing prescription opioid analgesics, fentanyl, and other synthetic drugs. This is evidenced by the types of other drugs co-identified in biological samples and law enforcement encounters. Law enforcement and toxicology reports demonstrate that ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene are being illicitly distributed and abused.

Factor 6. What, if Any, Risk There Is to the Public Health

The increase in opioid overdose deaths in the United States has been exacerbated recently by the availability of potent synthetic opioids on the illicit drug market. Data obtained from pre-clinical studies demonstrate that ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene exhibit pharmacological profiles similar to that of etonitazene, metonitazene, protonitazene, and other mu-opioid receptor agonists.[21] It is well established that substances that act as mu-opioid receptor agonists have a high potential for addiction and can induce dose-dependent respiratory depression.

Consistent with any mu-opioid receptor agonist, the potential health and safety risks for users of these seven substances are high. Data obtained from trend reports published by CFSRE, which reports on novel psychoactive substances (NPS) opioid positivity in cases and samples types from recreational drug use, medicolegal death

[21] DEA-VA Interagency Agreement. "In Vitro Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA". Binding and Functional Activity at Delta, Kappa and Mu Opioid Receptors. 2022 2024.

investigations, clinical intoxications, and/or driving under the influence of drugs investigations, showed that in 2024, 5-methyl etodesnitazene was identified in 6 toxicology cases; methylenedioxynitazene was identified in 4 toxicology cases; *N*-desethyl etonitazene was identified in 11 cases; *N*-desethyl protonitazene was identified as a metabolite of protonitazene in 11 cases and as a parent compound in 7 cases; and *N*-pyrrolidino isotonitazene was identified in 1 case.[22] A study conducted to develop an analytical method for identifying nitazenes in human hair detected the presence of *N*,*N*-dimethylamino etonitazene in two biological samples obtained from individuals suspected of smoking tobacco products containing nitazenes.[23]

The public health risks attendant to the use of mu-opioid receptor agonists are well established and have resulted in large numbers of drug treatment admissions, emergency department visits, and fatal overdoses. The introduction of potent synthetic opioids, such as ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene, into the illicit market may serve as a portal to problematic opioid use for those seeking these powerful opioids. The United States is currently experiencing an opioid epidemic, and the presence of synthetic opioids on the illicit drug market further exacerbates the problem. The trafficking and abuse of new synthetic opioids are deadly trends which pose imminent hazard to the public safety. Adverse health effects associated with the use of synthetic opioids and the continued evolution and increased popularity of these substances has been a serious concern in recent years.

Because of the pharmacological similarities of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl

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[22] NPS Opioids- 2024 Q1-Q4 reports, *available at* www.cfsre.org/nps-discovery/trend-reports/nps-opioids/report/49?trend_type_id=2.

[23] Gao, G., Yang, S., Wang, X., Xiang, P., Ma, L., Yan, F., & Shi, Y. (2025). UHPLC-MS/MS-based analysis of 17 nitazenes in human hair for practical forensic casework with simultaneous separation of 6 groups of isomers. *Journal of pharmaceutical and biomedical analysis*, *257*, 116707.

protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene to other schedule I opioids such as etonitazene and protonitazene, the use of these substances presents high risk of abuse and may negatively affect users and communities. The positive identification of these substances in toxicology and forensic cases demonstrates that the use of these substances is of serious concern to public safety. Thus, ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene pose imminent hazard to public safety.

Finding of Necessity of Schedule I Placement to Avoid Imminent Hazard to Public Safety

In accordance with 21 U.S.C. 811(h)(3), based on the available data and information summarized above, the uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene pose imminent hazards to public safety. DEA is not aware of any currently accepted medical uses for these substances in the United States. A substance meeting the statutory requirements for temporary scheduling, found in 21 U.S.C. 811(h)(1), may only be placed in schedule I. Substances in schedule I must have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. Available data and information for ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene indicate that these substances meet the three statutory criteria.

As required by 21 U.S.C. 811(h)(4), the then-Acting Administrator transmitted to the Acting Assistant Secretary, via letter dated April 15, 2025, notice of DEA's intent to place ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in schedule I on a temporary basis. By letter dated May 20, 2025, the Acting Assistant Secretary had no objection to the temporary placement of these substances in schedule I. DEA subsequently published this NOI in the *Federal Register* on June 26, 2025.[24]

Conclusion

In accordance with 21 U.S.C. 811(h)(1) and (3), the Administrator considered available data and information, herein set forth the grounds for his determination that it is necessary to temporarily schedule ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in schedule I of the CSA, and finds that placement of these substances in schedule I is necessary to avoid an imminent hazard to the public safety.

The temporary placement of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in schedule I of the CSA will take effect on the date the order is published in the *Federal Register* and will remain in effect for two years, with a possible extension of one year, pending completion of the regular (permanent) scheduling process.[25]

The CSA sets forth specific criteria for scheduling drugs or other substances. Regular scheduling actions in accordance with 21 U.S.C. 811(a) are subject to formal

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[24] *Schedules of Controlled Substances: Temporary Placement of Seven Benzimidazole-Opioids in Schedule I*, 90 FR 27268 (June 26, 2025).
[25] 21 U.S.C. 811(h)(1) and (2).

rulemaking procedures "on the record after opportunity for a hearing" conducted pursuant to the provisions of 5 U.S.C. 556 and 557.[26] The permanent scheduling process of formal rulemaking affords interested parties appropriate process and the government any additional relevant information needed to make a determination. Final decisions that conclude the permanent scheduling process of formal rulemaking are subject to judicial review.[27] Temporary scheduling orders are not subject to judicial review.[28]

Requirements for Handling

Upon the effective date of this temporary order, ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene will be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, importation, exportation, possession of, and engagement in research and conduct of instructional activities or chemical analysis with, schedule I controlled substances, including but not limited to the following:

1. *Registration.* Any person who handles (possesses, manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with) or desires to handle, ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene must be registered with 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, as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER]. Any person who currently handles ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl

[26] 21 U.S.C. 811.
[27] 21 U.S.C. 877.
[28] 21 U.S.C. 811(h)(6).

etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene and is not registered with DEA must submit an application for registration and may not continue to handle ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER], unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of these substances in a manner not authorized by the CSA on or after [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER] is unlawful, and those in possession of any quantity of these substances may be subject to prosecution pursuant to the CSA.

2. *Disposal of stocks.* Any person who does not desire or is unable to obtain a schedule I registration to handle ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene must surrender all currently held quantities of these seven substances.

3. *Security*. Ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene are subject to schedule I security requirements and must be handled in accordance with 21 CFR 1301.71-1301.93, as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER].

4. *Labeling and Packaging*. All labels, labeling, and packaging for commercial containers of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-

pyrrolidino isotonitazene must comply with 21 U.S.C. 825 and 958(e) and 21 CFR part 1302. Current DEA registrants will have 30 calendar days from [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER] to comply with all labeling and packaging requirements.

5. *Inventory*. Every DEA registrant who possesses any quantity of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene on the effective date of this order must take an inventory of all stocks of these substances on hand pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11. Current DEA registrants will have 30 calendar days from the effective date of this order to comply with all inventory requirements. After the initial inventory, every DEA registrant must take an inventory of all controlled substances (including ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene) 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.

6. *Records*. All DEA registrants must maintain records with respect to ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene pursuant to 21 U.S.C. 827 and 958(e) and in accordance with 21 CFR parts 1304, 1312, and 1317, and section 1307.11. Current DEA registrants authorized to handle these seven substances shall have 30 calendar days from the effective date of this order to comply with all recordkeeping requirements.

7. *Reports.* All DEA registrants must submit reports with respect to ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl

etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304, 1312, and 1317, and sections 1301.74(c) and 1301.76(b), as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER]. Manufacturers and distributors must also submit reports regarding these seven substances to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312.

8. *Order Forms*. All DEA registrants who distribute ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene must comply with order form requirements pursuant to 21 U.S.C. 828 and in accordance with 21 CFR part 1305 as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER].

9. *Importation and Exportation*. All importation and exportation of ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene must be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312 as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER].

10. *Quota.* Only DEA-registered manufacturers may manufacture ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303, as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER].

11. *Liability*. Any activity involving ethyleneoxynitazene, methylenedioxynitazene, 5-methyl etodesnitazene, *N*-desethyl etonitazene, *N*-desethyl protonitazene, *N*,*N*-dimethylamino etonitazene, and *N*-pyrrolidino isotonitazene not authorized by or in violation of the CSA, occurring as of [INSERT DATE OF PUBLICATION IN FEDERAL REGISTER], is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

The CSA provides for expedited temporary scheduling actions where necessary to avoid an imminent hazard to public safety. Under 21 U.S.C. 811(h)(1), the Administrator, as delegated by the Attorney General, may, by order, temporarily place substances in schedule I. Such orders may not be issued before the expiration of 30 days from: (1) the publication of a notice in the *Federal Register* of the intent to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Assistant Secretary, as delegated by the Secretary of HHS.[29]

Inasmuch as section 811(h) directs that temporary scheduling actions be issued by order (as distinct from a rule) and sets forth the procedures by which such orders are to be issued, DEA believes the notice-and-comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, which are applicable to rulemaking, do not apply to this temporary scheduling order. The APA expressly differentiates between orders and rules, as it defines an "order" to mean a "final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency *in a matter other than rule making*." [30] (Emphasis added). This contrasts with permanent scheduling actions, which are subject to formal rulemaking procedures done "on the record after

[29] 21 U.S.C. 811(h)(1).
[30] 5 U.S.C. 551(6).

opportunity for a hearing," and final decisions that conclude the scheduling process and are subject to judicial review. 21 U.S.C. 811(a) and 877. The specific language chosen by Congress indicates its intent that DEA issue *orders* instead of proceeding by rulemaking when temporarily scheduling substances. Given that Congress specifically requires the Administrator (as delegated by the Attorney General) to follow rulemaking procedures for *other* kinds of scheduling actions, *see* 21 U.S.C. 811(a), it is noteworthy that, in section 811(h)(1), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

Even assuming that this action is subject to section 553 of the APA, the Acting Administrator finds that there is good cause to forgo its notice-and-comment requirements pursuant to 5 U.S.C. 553(b)(B), as any further delays in the process for issuing temporary scheduling orders would be impracticable and contrary to the public interest given the manifest urgency to avoid an imminent hazard to public safety.

Although DEA believes this temporary scheduling order is not subject to the notice-and-comment requirements of section 553 of the APA, DEA notes that in accordance with 21 U.S.C. 811(h)(4), the Administrator took into consideration comments submitted by the Acting Assistant Secretary in response to the notices that DEA transmitted to the Acting Assistant Secretary pursuant to such subsection.

Further, DEA believes that this temporary scheduling action is not a "rule" as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act (RFA). The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, DEA is not required by section 553 of the APA or any other law to publish a general notice of proposed rulemaking. Therefore, in this instance, since DEA believes this temporary scheduling action is not a "rule," it is not subject to the requirements of the RFA when issuing this temporary action.

In accordance with the principles of Executive Orders (E.O.) 12866, 13563, and 14192, this action is not a significant regulatory action. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866, sec. 3(f), provides the definition of a "significant regulatory action," requiring review by the Office of Management and Budget. Because this is not a rulemaking action, this is not a significant regulatory action as defined in Section 3(f) of E.O. 12866. DEA scheduling actions are not subject to either E.O. 14192, Unleashing Prosperity Through Deregulation, or E.O. 14294, Fighting Overcriminalization in Federal Regulations.

This action will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with E.O. 13132, it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

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, DEA amends 21 CFR part 1308 as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

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

Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

2. In § 1308.11, add paragraphs (h)(79) through (85) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(h) * * *

* * * * * * *	
(79) 2-(2-((2,3-dihydrobenzofuran-5-yl)methyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: Ethyleneoxynitazene)	9770
(80) 2-(2-(benzodioxol-5-ylmethyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other names: Methylenedioxynitazene; 3',4'-methylenedioxynitazene)	9766
(81) 2-(2-(4-ethoxybenzyl)-5-methyl-1*H*-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: 5-methyl etodesnitazene)	9767
(82) 2-(2-(4-ethoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*-ethylethan-1-amine, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: *N*-desethyl etonitazene)	9768
(83) *N*-ethyl-2-(5-nitro-2-(4-propoxybenzyl)-1*H*-benzimidazol-1-yl)ethan-1-amine its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: *N*-desethyl protonitazene)	9769
(84) 2-(2-(4-ethoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*,*N*-dimethylethan-1-amine, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: *N*,*N*-dimethylamino etonitazene)	9771
(85) 2-(4-isopropoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole, its isomers, esters, ethers, salts, and salts of isomers, esters and ethers (Other name: *N*-pyrrolidino isotonitazene)	9772

SIGNING AUTHORITY

This document of the Drug Enforcement Administration was signed on October 9, 2025, by Administrator Terrance Cole. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register

Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

Heather Achbach,
Federal Register Liaison Officer,
Drug Enforcement Administration.

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