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For Immediate Release

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Governor DeWine Authorizes the State of Ohio Board of Pharmacy to Adopt Emergency Rule to Effectively Ban New Opioids

Columbus, Ohio — (COLUMBUS, Ohio) — Ohio Governor Mike DeWine today signed [Executive Order 2022-05D](#) to suspend the normal rulemaking process to allow the State of Ohio Board of Pharmacy to classify the following seven benzimidazole-opioids as Schedule I controlled substances pursuant to OAC [4729:9-1-01.02](#):

- 2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (butonitazene).
- 2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (etodesnitazene; etazene).
- N,N-diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (flunitazene).
- N,N-diethyl-2-(2-(4-methoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (metodesnitazene).
- N,N-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (metonitazene).
- 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzimidazole (N-pyrrolidino etonitazene; etonitazepyne).
- N,N-diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (protonitazene).

After a review of all available data, the Board of Pharmacy found that the above compounds have no accepted medical use in treatment in this state and pose an imminent hazard to the public health, safety, or welfare.

For more information regarding this emergency action, please see the 3-factor analysis conducted by the Board included with this release.

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Emergency Scheduling: Temporary Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, Npyrrolidino etonitazene, and Protonitazene in Schedule I

Section 1: Summary

The State of Ohio Board of Pharmacy (BOP), pursuant to section 3719.45 of the Ohio Revised Code, proposes the placement of the following into Schedule I by emergency rule:

- 2-(2-(4-butoxybenzyl)-5-nitro-1*H*benzimidazol-1-yl)-*N,N*-diethylethan-1-amine (butonitazene),
- 2-(2-(4-ethoxybenzyl)-1*H*benzimidazol-1-yl)-*N,N*-diethylethan-1-amine (etodesnitazene; etazene),
- *N,N*-diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine (flunitazene),
- *N,N*-diethyl-2-(2-(4-methoxybenzyl)-1*H*-benzimidazol-1-yl)ethan-1-amine (metodesnitazene),
- *N,N*-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine (metonitazene),
- 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*benzimidazole (*N*-pyrrolidino etonitazene; etonitazepyne), and
- *N,N*-diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1*H*-benzimidazol-1-yl)ethan-1-amine (protonitazene).

Section 2: Background

Pursuant to section 3719.45 of the Ohio Revised Code, the Board, by emergency rule adopted in accordance with division (G) of section 119.03 of the Revised Code, shall add a previously unscheduled compound, mixture, preparation, or substance to schedule I if the board determines that the compound, mixture, preparation, or substance has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.



In determining whether a previously unscheduled compound, mixture, preparation, or substance poses an imminent hazard to the public health, safety, or welfare, the board shall consider all of the following with respect to the compound, mixture, preparation, or substance:

- (1) Its actual or relative potential for abuse;
- (2) The scope, duration, and significance of that abuse;
- (3) The risk it poses to the public health.

Section 3: Evaluation Under the Emergency Scheduling Criteria

(1) The actual or relative potential for abuse.

In the late 1950s, pharmaceutical research laboratories of the Swiss chemical company CIBA Aktiengesellschaft synthesized a group of benzimidazole derivatives with analgesic properties; however, the research did not lead to any medically approved analgesic products. These benzimidazole derivatives include schedule I substances such as synthetic opioids clonitazene, etonitazene, and isotonitazene. In 2019, isotonitazene emerged on the illicit drug market and was involved in numerous fatal overdose events. In August 2020, DEA temporarily controlled it as a schedule I substance under the CSA ([85 FR 51342](#)).

Subsequently, the benzimidazole-opioids at issue here have emerged on the illicit drug market. Law enforcement agencies have encountered etodesnitazene, flunitazene, metonitazene, and protonitazene in several solid (*e.g.*, powder and rock) and liquid forms. These substances are not approved for medical use anywhere in the world. The Assistant Secretary, by letters dated July 7 and September 10, 2021, informed DEA that there are no FDA-approved NDAs or INDs for them in the United States. Hence, there are no legitimate channels for these substances as marketed drug products. Their appearance on the illicit drug market is similar to other synthetic opioids trafficked for their psychoactive effects. These seven opioid substances are likely to be abused in the same manner as schedule I opioids such as etonitazene, isotonitazene, and heroin. They have been identified as white to beige powders or in liquid forms, typically of unknown purity or concentration.

In 2020 and 2021, butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, and protonitazene emerged on the illicit synthetic drug market as evidenced by their identification in forensic drug seizures or biological samples. In July 2020, metonitazene was first reported seized as a white powdery substance in a North Carolina case. Based on data from the National Forensic Laboratory Information System (NFLIS)ⁱ law enforcement often encounters etodesnitazene, flunitazene, metonitazene,

and protonitazene in mixtures. Substances found in combination with some of these benzimidazole-opioids include cutting agents (caffeine, xylazine, etc.) or other substances of abuse such as heroin, fentanyl (schedule II), fentanyl analogs, and tramadol (schedule IV).

In the United States, butonitazene, etodesnitazene, flunitazene, metonitazene, *N*-pyrrolidino etonitazene, and protonitazene have been identified alone or in combination with other substances such as designer benzodiazepines and fentanyl (see Evaluation Criteria 2 and 3). Evidence suggests that individuals are using these substances as a replacement for other opioids, either knowingly or unknowingly. Information gathered from case histories and autopsy findings show that deaths involving metonitazene were similar to those of opioid-related deaths. Identified material or paraphernalia from death-scene investigations also were consistent with opioid use. The seven substances are likely to be abused in the same manner as schedule I opioids such as isotonitazene and heroin.

(2) The scope, duration, and significance of abuse.

The subject substances have been described as synthetic opioids, and evidence suggests they are abused for their opioidergic effects (see Evaluation Criterion 3). Their abuse has resulted in their identification in toxicology and post-mortem cases. Between January and February of 2021, metonitazene has been positively identified in 20 forensic post-mortem cases from seven different states: Tennessee (10), Illinois (5), Florida (1), Iowa (1), Ohio (1), South Carolina (1), and Wisconsin (1). Most (18) of the decedents were male, with ages ranging from 19 to 63 years and an average age of 41 years. Metonitazene was identified as the sole drug detected in only three cases, and the only opioid in six cases.

Detection of *N*-pyrrolidino etonitazene in a toxicology case first was reportedⁱⁱ in May 2021. It has been identified in a total of eight post-mortem cases from five different states (Colorado (1), Florida (1), New York (1), Pennsylvania (1), and West Virginia (4)) between January and April 2021. The decedents' ages spanned their 20s to 50s. *N*-Pyrrolidino etonitazene was the only drug of interest in one of these cases. In the other cases, it was co-identified with designer benzodiazepines (7), fentanyl (4), and methamphetamine (4). Data from law enforcement encounters suggests that etodesnitazene, flunitazene, metonitazene, and protonitazene are abusedⁱⁱⁱ in the United States as recreational drugs. Law enforcement encounters of etodesnitazene, flunitazene, metonitazene, and protonitazene as reported to NFLIS (Federal, State, and local laboratories) includes 270 exhibits since 2020 (queried by DEA, 08/04/2021). NFLIS registered one encounter of etodesnitazene from one state, five encounters of flunitazene from four states, 262 encounters of metonitazene from eight states, and two encounters of protonitazene from two states. Data from NFLIS show that 561.55 grams of metonitazene has been encountered by law enforcement since 2020, and it was often

suspected as heroin or fentanyl. This suggests that metonitazene might be presented as a substitute for heroin or fentanyl and likely abused in the same manner as either of these substances. The lack of identification of butonitazene, metodesnitazene, and *N*-pyrrolidino etonitazene in law enforcement reports might be due to the rapid appearance of these benzimidazole-opioids and under-reporting as forensic laboratories try to secure reference standards for these substances. However, butonitazene, metodesnitazene, and *N*-pyrrolidino etonitazene have been identified in toxicology cases.

The population likely to abuse these seven benzimidazole-opioids appears to be the same as those abusing other opioid substances such as heroin, tramadol, fentanyl, and other synthetic opioids. This is evidenced by the types of other drugs co-identified in biological samples and law enforcement encounters. Because abusers are likely to obtain these substances through unregulated sources, their identity, purity, and quantity are uncertain and likely to be inconsistent, thus posing significant adverse health risks to the end user. The misuse and abuse of opioids have been demonstrated and are well-characterized. According to the most recent data from the National Survey on Drug Use and Health (NSDUH),^{iv} as of 2019, an estimated 10.1 million people aged 12 years or older misused opioids in the past year, including 9.7 million prescription pain reliever misusers and 745,000 heroin users. In 2019, an estimated 1.6 million people had an opioid use disorder, including 1.4 million people with a prescription pain reliever use disorder and 438,000 people with heroin use disorder. This population likely is at risk of abusing butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, *N*-pyrrolidino etonitazene, and protonitazene. Individuals who initiate (*i.e.*, use a drug for the first time) use of these benzimidazole-opioids are likely to be at risk of developing substance use disorder, overdose, and death similar to that of other opioid analgesics (*e.g.*, fentanyl, morphine, etc.). Law enforcement or toxicology reports demonstrate that the seven substances at issue are being distributed illicitly and abused. The presence of unscheduled nitazenes has been relayed by five separate forensic lab systems in Ohio. This includes the presence of at the following indicated in at least one submission to an Ohio crime lab: metonitazene, etodesnitazene, butonitazene, *N*-pyrrolidino etonitazene, and flunitazene.^v

(3) The risk 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 in the illicit drug market. Data obtained from pre-clinical studies demonstrate that butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, *N*-pyrrolidino etonitazene, and protonitazene exhibit pharmacological profiles similar to that of schedule I substances such as etonitazene, isotonitazene, and other mu-opioid receptor agonists. These seven benzimidazole-opioids bind to and act as agonists at the mu-opioid receptors. It is well established that

substances that act as mu-opioid receptor agonists have a high potential for abuse and addiction and can induce dose-dependent respiratory depression.

As with any mu-opioid receptor agonist, the potential health and safety risks for users of butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, *N*-pyrrolidino etonitazene, and protonitazene are high. Consistently, these substances have been identified in toxicology cases. The public health risks attendant to the abuse of mu-opioid receptor agonists are well established. These risks include large numbers of drug treatment admissions, emergency department visits, and fatal overdoses. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids other than methadone, are predominantly responsible for drug overdose deaths in recent years. According to CDC data, synthetic opioid-related overdose deaths in the United States increased from 36,359 in 2019, to 56,688 in 2020 (CDC, 2021).^{vi} Of the drug overdose death data (70,630) for 2019, synthetic opioids were involved in about 51.4 percent (36,359) of all drug-involved overdose deaths.

According to recent reports, butonitazene (1 instance), etodesnitazene (5), flunitazene (4), metodesnitazene (1), metonitazene (20), protonitazene (5), and *N*-pyrrolidino etonitazene (10) have been identified in toxicology cases in the United States.^{vii} For cases involving *N*-pyrrolidino etonitazene, it was co-identified with fentanyl in four cases and with novel benzodiazepines (*e.g.*, flualprazolam, etizolam, and clonazepam) in six others.

Section 4: Finding of the Board

Section 3719.45 of the Ohio Revised Codes authorizes the State of Ohio Board of Pharmacy, by emergency rule adopted in accordance with division (G) of section 119.03 of the Revised Code, to add a previously unscheduled compound, mixture, preparation, or substance to schedule I if the board determines that the compound, mixture, preparation, or substance has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

After a review of all available data, the State of Ohio Board of Pharmacy finds that the compounds listed in [Section 1](#) of this document have no accepted medical use in treatment in this state and pose an imminent hazard to the public health, safety, or welfare.

Based on these findings, the Board hereby issues a resolution requesting the Governor to issue an order pursuant to division (G) of section [119.03](#) of the Revised Code to file emergency rule 4729:9-1-01.2 of the Administrative Code.

Section 5: Proposed Rule

4729:9-1-01.2 – Benzimidazole-opioids

Pursuant to section 3719.45 of the Revised Code, the state board of pharmacy hereby classifies as schedule I any of the following opiates, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) 2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)- N,N -diethylethan-1-amine (butonitazene).

(2) 2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)- N,N -diethylethan-1-amine (etodesnitazene; etazene).

(3) N,N -diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1 H -benzimidazol-1-yl)ethan-1-amine (flunitazene).

(4) N,N -diethyl-2-(2-(4-methoxybenzyl)-1 H -benzimidazol-1-yl)ethan-1-amine (metodesnitazene).

(5) N,N -diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1 H - benzimidazol-1-yl)ethan-1-amine (metonitazene).

(6) 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1 H -benzimidazole (N -pyrrolidino etonitazene; etonitazepyne).

(7) N,N -diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1 H -benzimidazol-1-yl)ethan-1-amine (protonitazene).

ⁱ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual state and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011.

ⁱⁱ Center for Forensic Science Research and Education. Public Alert: New High Potency Synthetic Opioid N -Pyrrolidino Etonitazene (Etonitazepyne) Linked to Overdoses across United States. June 17, 2021.

ⁱⁱⁱ While law enforcement data are not direct evidence of abuse, they can lead to an inference that drugs have been diverted and abused. See [76 FR 77330, 77332](#), Dec. 12, 2011.

^{iv} NSDUH, formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of non-medical use of pharmaceutical drugs, illicit drugs,

alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The NSDUH provides yearly national and state level estimates of drug abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year, and past month abuse or dependence. The 2019 NSDUH Annual Report: <https://www.samhsa.gov/data/report/2019-nsduh-annual-national-report>

^v EDSWG Quarterly Meetings, Cols. OH, (2021).

^{vi} 12 Month-ending Provisional Number of Drug Overdose Deaths. Reported provisional data as of July 4, 2021. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>.

^{vii} Center for Forensic Science Research and Education. NPS Opioids in the United States—Trend Report Q1 and Q2, 2021.