U.S. Department of Justice

Drug Enforcement Administration

Temporary Schedule I Placement of

N-pyrrolidino metonitazene (2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole); *N*-pyrrolidino protonitazene (5-nitro-2-(4-propoxybenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole)

Background, Data, and Analysis:

Three Factor Analysis Pursuant to 21 U.S.C. 811(h)(3)

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I. Introduction

The continued encounter of novel synthetic opioids in the recreational drug market poses a threat to public safety. Following the class-wide scheduling of fentanyl-related substances, there has been an increase in the emergence of synthetic opioids, which are not structurally related to fentanyl. Beginning in 2019, a new class of synthetic opioids known as benzimidazole-opioids, commonly referred to as "nitazenes," emerged on the recreational drug market. This class of substances was first synthesized in the 1950s by CIBA Aktiengesellschaft in Switzerland and have a similar pharmacological profile to fentanyl, morphine, and other mu-opioid receptor agonists. Between August 2020 and March 2024, the Drug Enforcement Administration (DEA) has temporarily controlled ten benzimidazole-opioids because they posed a threat to public safety. Recently, additional benzimidazole-opioids have been identified within the rapidly expanding class of "nitazene" compounds on the recreational drug market. *N*-Pyrrolidino metonitazene (chemical name: 2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole) and *N*-pyrrolidino protonitazene (chemical name: 5-nitro-2-(4-propoxybenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzimidazole) are some of the recently encountered "nitazene" synthetic opioids identified on the illicit drug market.

The continued trafficking and identification of benzimidazole-opioids in toxicology cases pose a significant threat to public health and safety. Adverse health effects associated with the misuse and abuse of synthetic opioids have led to devastating consequences including death. Preclinical pharmacology data demonstrates that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene have pharmacological profiles similar to those of the potent benzimidazole-opioids metonitazene and protonitazene, schedule I opioid substances. Both substances have been positively identified in at least 26 toxicology cases. As the United States continues to experience a high number of opioid-involved overdoses and mortalities, the introduction of new designer opioids further exacerbates the current opioid epidemic.

In a letter to the Department of Health and Human Services (HHS) dated December 15, 2023, the DEA Administrator notified the Assistant Secretary for Health (Assistant Secretary) of her intention to publish in the *Federal Register* (FR) a Notice of Intent to temporarily place *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene in schedule I of the Controlled Substances Act (CSA) pursuant to the temporary scheduling provision of the CSA, 21 U.S.C.

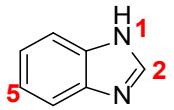
811(h). The Assistant Secretary responded to this notice by letter dated December 22, 2023, and advised that based on a review by the Food and Drug Administration (FDA), there are no approved new drug applications or investigational new drug applications for *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene. The Assistant Secretary also stated that HHS has no objection to the temporary placement *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene into schedule I of the CSA.

Law enforcement data indicates that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene have appeared on the United States illicit drug market. Encounters of *N*-pyrrolidino protonitazene have been reported in Canada and the United Kingdom. According to DEA's National Forensic Laboratory Information System (NFLIS)[1] Drug database, which collects drug identification results from drug cases submitted to and analyzed by Federal, State, and local forensic laboratories, there have been a total of 23 encounters of *N*-pyrrolidino metonitazene or *N*-pyrrolidino protonitazene in the United States since 2023 (queried February 13, 2024).

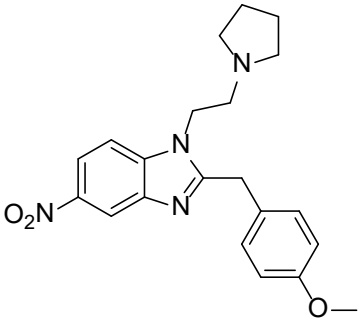
In light of the law enforcement encounters and detection of these substances in toxicology cases, DEA reviewed the available scientific, medical, law enforcement, and all other relevant data on *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene. These substances have pharmacological effects similar to those of schedule I benzimidazole-opioids such as clonitazene, etonitazene, and isotonitazene. With no approved medical use, the abuse and identification of these benzimidazole-opioids in toxicology casework and law enforcement reporting underscores the public health threat associated with their presence in the illicit drug market. Thus, to protect the public health and to avoid an imminent hazard to public safety, DEA intends to temporarily place *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene in schedule I of the CSA. The data presented in this document supports the determination by DEA to control these substances under the temporary scheduling provision of the CSA.[2] With

[1] NFLIS-Drug represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle the nation's drug analysis cases. NFLIS-Drug participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS-Drug, is currently 98.5 percent. NFLIS-Drug includes drug chemistry results from completed analyses only. While NFLIS-Drug 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, December 12, 2011. NFLIS-Drug data was queried on February 13, 2024.
[2] 21 U.S.C. 811(h)(1).

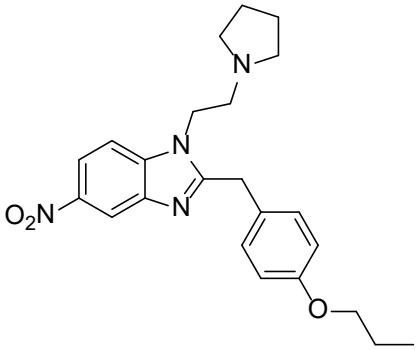
respect to finding that control of these substances is necessary to avoid imminent hazard to the public safety, DEA has considered the three factors required under the CSA for the temporary scheduling of *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene.[3]



Benzimidazole core structure



N-pyrrolidino metonitazene



N-pyrrolidino protonitazene

Figure 1: *N*-Pyrrolidino metonitazene and *N*-pyrrolidino protonitazene chemical structures

Factor 4. History and Current Pattern of Abuse

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. The benzimidazole-opioids were originally synthesized and studied in the late 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. These benzimidazole derivatives include schedule I substances, such as synthetic opioids clonitazene, etonitazene, and isotonitazene. In August

[3] 21 U.S.C. 811(c)(4)–(6) and (h)(3).

2020, isotonitazene was placed in schedule I of the CSA (85 FR 51342). Subsequently, seven[4] additional benzimidazole-opioids have been placed in schedule I of the CSA (87 FR 21556). Further, two additional benzimidazole-opioids were placed in schedule 1 of the CSA (89 FR 60817) because they posed threat to public safety. Recently, law enforcement has encountered *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene in solid forms (powder and tablets) on the illicit drug market. These substances are not approved pharmaceutical products and are not approved for medical use anywhere in the world. The Assistant Secretary of HHS in a letter to DEA dated December 22, 2023, stated that there are no FDA-approved New Drug Application or Investigational New Drug applications for *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene in the United States; hence, there are no legitimate channels for these substances as marketed drug products.

The appearance of benzimidazole-opioids on the illicit drug market is similar to other designer opioid drugs trafficked for their psychoactive effects. These substances are likely to be abused in the same manner as schedule I opioids such as etonitazene, isotonitazene, and heroin. In 2023, *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene emerged on the illicit synthetic drug market as evidenced by their identification in forensic drug seizures and in biological samples.[5] Based on NFLIS-Drug data, law enforcement encounters of *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene were found in combination with other substances of abuse such as heroin, designer benzodiazepines, cocaine, fentanyl, methamphetamine, and xylazine.

Factor 5. Scope, Duration and Significance of Abuse

N-Pyrrolidino metonitazene and *N*-pyrrolidino protonitazene, 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

[4] Butonitazene, etodesnitazene, flunitazene, metodesnitazene, metonitazene, *N*-pyrrolidino etonitazene, and protonitazene

[5] NMS Labs, in collaboration with the Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation and the Organized Crime Drug Enforcement Task Force at the United States Department of Justice, has received funding from the Centers for Disease Control and Prevention to develop systems for the early identification and notification of novel psychoactive substances in the drug supply within the United States.

adverse health effects. According to a public alert report[6] published in August 2023, *N*-pyrrolidino protonitazene has been positively confirmed in 20 medico-legal death investigation cases in the United States (n =16) and United Kingdom (n = 4). The cases that occurred in the United States originated from seven states including California, Illinois, Maine, Massachusetts, Minnesota, Wisconsin, and Wyoming. *N*-Pyrrolidino metonitazene has been identified in six toxicology cases as of June 2023 in the United States. The cases occurred in at least three states including Ohio, Illinois, and West Virginia.[7]

Data from law enforcement suggest that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene are being abused in the United States as recreational drugs.[8] Since 2023, there have been 23 exhibits reported to the NFLIS-Drug (Federal, State and local laboratories) database pertaining to the trafficking, distribution, and abuse of these substances. There were seven encounters of *N*-pyrrolidino metonitazene from two states in NFLIS-Drug: Missouri (n = 2) and Ohio (n = 5). *N*- Pyrrolidino protonitazene has been identified in 16 NFLIS-Drug exhibits from five states: Florida (n =1), Iowa (n = 1), Missouri (n =1), Ohio (n = 12), and Texas (n =1).[9]

The population likely to abuse these benzimidazole-opioids appears to be the same as those abusing 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. Because abusers of *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene 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 abuse of opioids have been demonstrated and are well-characterized (Jones *et al*., 2015). According to the most recent data from the National Survey on Drug Use and Health (NSDUH),[10] as of 2022, an estimated 8.9 million people aged 12 years or older

[6] New Nitazene Analogue N-Pyrrolidino Protonitazene Impacting Drug Markets In North America and Europe (cfsre.org)
[7] N-Pyrrolidino-Metonitazene-New-Drug-Monograph-NPS-Discovery-230623.pdf (cfsre.org)
[8] 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* 76 FR 77330, 77332, Dec. 12, 2011.
[9] NFLIS-Drug was queried on February 13, 2024.
[10] 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 nonmedical 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

misused opioids in the past year, including 8.5 million prescription pain reliever misusers and 1 million heroin users. In 2022, an estimated 6.1 million people had an opioid use disorder in the past year, which included 5.6 million people with a prescription pain reliever use disorder and 900,000 people with heroin use disorder. This population abusing opioids is likely to be at risk of abusing *N*-pyrrolidino metonitazene and *N*-pyrrolidino 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, an overdose event, and/or death, similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). Law enforcement and toxicology reports demonstrate that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene 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 *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene exhibit pharmacological profiles similar to that of etonitazene, metonitazene, protonitazene, and other mu (μ)-opioid receptor agonists. These two benzimidazole-opioids bind to and act as an agonist at the μ-opioid receptors (DEA-VA, 2022). It is well established that substances that act as μ-opioid receptor agonists have a high potential for addiction and can induce dose-dependent respiratory depression (Fox *et al*., 2018).

Consistent with any μ-opioid receptor agonist, the potential health and safety risks for users of *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene are high. *N*-Pyrrolidino metonitazene and *N*-pyrrolidino protonitazene have been positively identified in forensic toxicology and post mortem cases. According to a pubic alert publication by center for forensic science research and education (CFSRE) *N*-pyrrolidino protonitazene has been positively identified in 20 medico-legal death investigations in the United States and United Kingdom as of August 2023. Of the cases, 16 occurred across seven states in the United States. Decedent

abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year, and past month abuse or dependence. Substance Abuse and Mental Health Services Administration. (2023). Key substance use and mental health indicators in the United States: Results from the 2022 National Survey on Drug Use and Health (HHS Publication No. PEP23-07-01-006, NSDUH Series H-58). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2022-nsduh-annual-national-report.

ages ranged mid-20s to mid-70s. *N*-Pyrrolidino protonitazene was co-identified with additional NPS (70 percent), quinine (60 %), other benzimidazole-opioids (55 percent), methamphetamine/cocaine (55 percent), fentanyl (55 %), xylazine (35 percent) and designer benzodiazepines (30 percent). [11] Also, *N*-pyrrolidino metonitazene has been identified in six toxicology cases in the United States as of June 2023. The public health risks attendant to the abuse of μ-opioid receptor agonists are well established and have resulted in large numbers of drug treatment admissions, emergency department visits, and fatal overdoses (Brunton *et al.*, 2010; SAMSHA, 2022; CDC, 2023). According to the drug abuse warning network preliminary findings from drug-related emergency department (ED) visits, in 2021, 1.03 million visits involved opioids (fentanyl, heroin, and other opioid pain medications taken alone or in combination with other opioids and/or other drugs). [12] The introduction of potent synthetic opioids such as *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene into the illicit market may serve as a portal to problematic opioid use for those seeking these powerful opioids. As documented by toxicology reports, polysubstance abuse remains common in fatalities associated with the abuse of some of these benzimidazole-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 abuse 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 *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene to metonitazene 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 cases is of serious concern to the public safety. Thus, *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene pose imminent hazard to public safety.

[11] New Nitazene Analogue N-pyrrolidino protonitazene Impacting Drug Markets in North America and Europe. CFSRE Public Alert. August 2023.
[12] Drug Abuse Warning Network. Preliminary Findings from Drug-Related Emergency Department Visits, 2021. Preliminary Findings from Drug-Related Emergency Department Visits, 2021 (DAWN) (samhsa.gov). Accessed January 25, 2023.

Conclusion of 3-Factor Analysis

After a careful review of the scientific literature, Factors 4, 5, and 6, NFLIS-Drug, law enforcement data and other relevant data, it is evident that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene are trafficked, abused, and pose an imminent hazard to public safety. DEA has considered the three factors for temporary placement of a substance under schedule I of the CSA (21 U.S.C. 812). Available data indicates that *N*-pyrrolidino metonitazene and *N*-pyrrolidino protonitazene, 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, pose an imminent hazard to public safety, have no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. Further, the trafficking of these synthetic opioids poses a high risk for overdose and life-threatening events.

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