Common Sense Initiative

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Business Impact Analysis

Agency, Board, or Commission Name: Ohio Board of Pharmacy

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Regulation/Package Title (a general description of the rules' substantive content):

Nitazenes – Schedule I Controlled Substances

Rule Number(s): 4729:9-1-01

Date of Submission for CSI Review: 7/31/24

Public Comment Period End Date: 8/15/24

Rule Type/Number of Rules:

New/___ rules
No Change/____ rules (FYR? ___)
Amended/__1__ rules (FYR? ___)
Rescinded/____ rules (FYR? ___)

The Common Sense Initiative is established in R.C. 107.61 to eliminate excessive and duplicative rules and regulations that stand in the way of job creation. Under the Common Sense Initiative, agencies must balance the critical objectives of regulations that have an adverse impact on business with the costs of compliance by the regulated parties. Agencies should promote transparency, responsiveness, predictability, and flexibility while developing regulations that are fair and easy to follow. Agencies should

prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.

Reason for Submission

1. **R.C. 106.03 and 106.031 require agencies, when reviewing a rule, to determine whether the rule has an adverse impact on businesses as defined by R.C. 107.52. If the agency determines that it does, it must complete a business impact analysis and submit the rule for CSI review.**

   Which adverse impact(s) to businesses has the agency determined the rule(s) create?

   The rule(s):

   a. ☐ **Requires a license, permit, or any other prior authorization to engage in or operate a line of business.**

   b. ☒ **Imposes a criminal penalty, a civil penalty, or another sanction, or creates a cause of action for failure to comply with its terms.**

   c. ☐ **Requires specific expenditures or the report of information as a condition of compliance.**

   d. ☐ **Is likely to directly reduce the revenue or increase the expenses of the lines of business to which it will apply or applies.**

Regulatory Intent

2. **Please briefly describe the draft regulation in plain language.**
   Please include the key provisions of the regulation as well as any proposed amendments.

   4729:9-1-01 – Lists the drugs/compounds that are Schedule I controlled substances. Updates incorporation by reference for substances temporarily scheduled by the Drug Enforcement Administration. Adds 16 nitazene compounds as Schedule I Narcotics-opiates (further justification can be found in the 8-factor analyses included as appendices to this BIA).

3. **Please list the Ohio statute(s) that authorize the agency, board or commission to adopt the rule(s) and the statute(s) that amplify that authority.**

   The proposed rules are authorized by sections 3719.44, 3719.41, 3719.45, and 3719.28 of the Ohio Revised Code.

4. **Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program?**
If yes, please briefly explain the source and substance of the federal requirement.

   These rules do not implement a federal requirement. However, the rules do incorporate the federal controlled substance schedules.

5. **If the regulation implements a federal requirement, but includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.**

   Not applicable.

6. **What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?**

   ORC 4729.41 requires the Board to adopt controlled substance schedules into administrative rule. Additionally, per ORC 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision. In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

   (1) The actual or relative potential for abuse;

   (2) The scientific evidence of the pharmacological effect of the substance;

   (3) The state of current scientific knowledge regarding the substance;

   (4) The history and current pattern of abuse;

   (5) The scope, duration, and significance of abuse;

   (6) The risk to the public health;

   (7) The potential of the substance to produce psychic or physiological dependence liability; and

   (8) Whether the substance is an immediate precursor.

   Further justification for the scheduling of 16 nitazene compounds can be found in the 8-factor analyses included as appendices to this BIA.

7. **How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?**

The success of the regulation will be measured by having rules that are enforceable by state and local jurisdictions as well as crime laboratories who process drug evidence.

8. **Are any of the proposed rules contained in this rule package being submitted pursuant to R.C. 101.352, 101.353, 106.032, 121.93, or 121.931?**
   If yes, please specify the rule number(s), the specific R.C. section requiring this submission, and a detailed explanation.
   No.

Development of the Regulation

9. **Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.**
   If applicable, please include the date and medium by which the stakeholders were initially contacted.

   The proposed nitazene compounds are already Schedule I Controlled Substances in this state. They were either emergency scheduled by the DEA or the Ohio Board of Pharmacy. The Board worked closely with representatives of the Emerging Drug Scientific Working Group (EDSWG) coordinated by the Ohio Department of Public Safety.

10. **What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?**

    Stakeholders such as those representing the EDSWG provided data to support the addition of the 16 nitazene compounds to Schedule I.

11. **What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?**

    Please see the 8-factor analyses included as appendices to this BIA.

12. **What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn't the Agency consider regulatory alternatives?**
    Alternative regulations may include performance-based regulations, which define the required outcome, but do not dictate the process the regulated stakeholders must use to comply.
    The Board determined that regulatory alternatives were not appropriate because the addition of these 16 compounds is intended to safeguard public health and safety.

13. **What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?**

The Board of Pharmacy's Director of Policy and Communications reviewed the proposed rule to ensure that the regulation does not duplicate another Ohio Board of Pharmacy regulation.

14. **Please describe the Agency's plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.**

    The rules will be posted on the Board of Pharmacy's web site, information concerning the rules will be included in materials e-mailed to licensees, and notices will be sent to associations, individuals, and groups. Board of Pharmacy staff are also available via phone or email to answer questions regarding implementation of the rules.

Adverse Impact to Business

15. **Provide a summary of the estimated cost of compliance with the rule(s). Specifically, please do the following:**
    a. **Identify the scope of the impacted business community, and**
       Persons who manufacture, distribute, dispense, and possess Schedule I controlled substances.
    b. **Quantify and identify the nature of all adverse impact (e.g., fees, fines, employer time for compliance, etc.).**
       Violation of these rules could result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.
       The adverse impact can be quantified in terms of dollars, hours to comply, or other factors; and may be estimated for the entire regulated population or for a representative business. Please include the source for your information/estimated impact.

16. **Are there any proposed changes to the rules that will reduce a regulatory burden imposed on the business community? Please identify.** ***(Reductions in regulatory burden may include streamlining reporting processes, simplifying rules to improve readability, eliminating requirements, reducing compliance time or fees, or other related factors).***
    N/A

17. **Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?**

    The Board determined that the regulatory intent justifies the impact on business because the regulations protect and promote public safety by classifying compounds that have no medical use in this state as controlled substances.

Regulatory Flexibility

18. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.

The rule does not provide any exemptions or alternative means of compliance for small businesses. Small businesses are not typically in the business of possessing and distributing Schedule I controlled substances.

19. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?

The possession, manufacture, or distribution of Schedule I controlled substances is not considered a paperwork violation.

20. What resources are available to assist small businesses with compliance of the regulation?

Board of Pharmacy staff is available by telephone and e-mail to answer questions. Board staff members also provide presentations to licensees as well as trade associations who seek updates on current regulations. Additionally, staff are trained to educate licensees on compliance with all Board of Pharmacy rules and regulations.

Please be advised small businesses are not typically in the business of possessing and distributing Schedule I controlled substances.

Rule 4729:9-1-01 | Schedule I controlled substances.

Pursuant to section 3719.41 of the Revised Code, controlled substance schedule I is hereby established, which schedules include the following, subject to amendment pursuant to section 3719.43 or 3719.44 of the Revised Code.

(A) As used in this rule:

(1) "Synthetic" unless specifically excepted or unless listed in another schedule, means any substance, material, compound, mixture, or preparation that contains any quantity of a substance made artificially by chemical reaction.

(2) "Pharmacophore" means the portion of a chemical structure that confers the activity of the substance.

(3) "A report from an established forensic laboratory" means a laboratory report from the bureau of criminal identification and investigation, or a laboratory operated by another law enforcement agency, or a laboratory established by or under the authority of an institution of higher education that has its main campus in this state and that is accredited by the association of American universities or the north central association of colleges and secondary schools, primarily for the purpose of providing scientific services to law enforcement agencies and signed by the person performing the analysis as defined in division (A) of section 2925.51 of the Revised Code.

(4) "Synthetic cannabinoids" are drugs commonly found in herbal incense products (common names include but are not limited to: spice, blaze, devil's advocate, genie, smoke, sense, zohai, spike 99, and K2) that may mimic the effects of delta-9-tetrahydrocannabinol (THC), an active central nervous system constituent compound of marijuana.

(B) Narcotics-opiates

Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term isomer includes the optical and geometric isomers):

(1) Acetyl-alpha-methylfentanyl (N-[1-(1-methyl-2-phenethyl)-4-piperidinyl]-N-phenylacetamide);

(2) Acetylmethadol;

(3) Acetyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide);

(4) Acryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide; other name: acryloylfentanyl);

(5) AH-7921 (3,4-dichloro-N-[(1-dimethylamino) cyclohexylmethyl]benzamide;

(6) Allylprodine;

(7) Alphacetylmethadol (except levo-alphacetylmethadol, also known as levo-alpha-acetylmethadol, levomethadyl acetate, or LAAM);

(8) Alphameprodine;

(9) Alphamethadol;

(10) Alpha-methylfentanyl (N-[1-(alpha-methyl-beta-phenyl)ethyl-4-piperidyl] propionanilide; 1- (1-methyl-2-phenylethyl)-4-(N-propanilido) piperidine);

(11) Alpha-methylthiofentanyl (N-[1-methyl-2-(2-thienyl)ethyl-4-piperidinyl]-N-phenylpropanamide);

(12) Benzethidine;

(13) Betacetylmethadol;

(14) Beta-hydroxyfentanyl (N-[1-(2-hydroxy-2-phenethyl-4-piperidinyl]-N-phenylpropanamide);

(15) Beta-hydroxy-3-methylfentanyl (other name: N-[1-(2-hydroxy-2-phenethyl)-3-methyl-4-piperidinyl]-N- phenylpropanamide);

(16) N-[1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl]-N-phenylpropionamide (other name: beta-Hydroxythiofentanyl);

(17) Betameprodine;

(18) Betamethadol;

(19) Betaprodine;

(20) Butyryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylbutyramide);

(21) Clonitazene;

(22) Dextromoramide;

(23) Diampromide;

(24) Diethylthiambutene;

(25) Difenoxin;

(26) Dimenoxadol;

(27) Dimepheptanol;

(28) Dimethylthiambutene;

(29) Dioxaphetyl butyrate;

(30) Dipipanone;

(31) Ethylmethylthiambutene;

(32) Etonitazene;

(33) Etoxeridine;

(34) 4-Fluoroisobutyryl fentanyl (N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide; other name: para-fluoroisobutyryl fentanyl);

(35) Furanyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylfuran-2-carboxamide);

(36) Furethidine;

(37) Hydroxypethidine;

(38) Ketobemidone;

(39) Levomoramide;

(40) Levophenacylmorphan;

(41) 3-methylfentanyl (N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N- phenylpropanamide);

(42) 3-methylthiofentanyl (N-[3-methyl-1-[2-(thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide);

(43) Morpheridine;

(44) MPPP (1-methyl-4-phenyl-4-propionoxypiperidine);

(45) MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine);

(46) Noracymethadol;

(47) Norlevorphanol;

(48) Normethadone;

(49) Norpipanone;

(50) Ocfentanil (N-(2-fluorophenyl)-2-methoxy-N-(1-phenethylpiperidin-4-yl)acetamide);

(51) Para-fluorofentanyl (N-(4-fluorophenyl)-N-[1-(2-phenethyl)-4-piperidinyl]propanamide;

(52) PEPAP (1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine;

(53) Phenadoxone;

(54) Phenampromide;

(55) Phenomorphan;

(56) Phenoperidine;

(57) Piritramide;

(58) Proheptazine;

(59) Properidine;

(60) Propiram;

(61) Racemoramide;

(62) Tetrahydrofuranyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenyltetrahydrofuran-2-carboxamide);

(63) Thiofentanyl (N-phenyl-N-[1-(2-thienyl)ethyl-4-piperidinyl]-propanamide;

(64) Tilidine;

(65) Trimeperidine;

(66) U-47700 (3,4-Dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide);

(67) Except as otherwise provided in this chapter, any compound that meets all of the following fentanyl pharmacophore requirements to bind at the mu receptor, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of both of the following:

(i) A five, six, or seven member ring structure containing a nitrogen, whether or not further substituted;

(ii) An attached nitrogen to the ring, whether or not that nitrogen is enclosed in a ring structure, including an attached aromatic ring or other lipophilic group to that nitrogen.

(b) A polar functional group attached to the chemical scaffold, including but not limited to, a hydroxyl, ketone, amide, or ester;

(c) An alkyl or aryl substitution off the ring nitrogen of the chemical scaffold; and

(d) The compound has not been approved for medical use by the United States food and drug administration.

(68) N,N-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene).

(69) 2-Methyl-AP-237 (1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one).

(70) AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone).

(71) Tianeptine.

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

(73) 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H -benzimidazole (N -pyrrolidino etonitazene; etonitazepyne).

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

(75) 2-(2-(4-ethoxybenzyl)-1H -benzimidazol-1-yl)- N,N -diethylethan-1-amine (etodesnitazene; etazene).

(76) 2-(2-(4-butoxybenzyl)-5-nitro-1H -benzimidazol-1-yl)- N,N -diethylethan-1-amine (butonitazene).

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

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

(79) N-Pyrrolidino metonitazene (2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate).

(80) N-Pyrrolidino protonitazene (5-nitro-2-(4-propoxybenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole).

(81) Ethyleneoxynitazene (2-(2-((2,3-dihydrobenzofuran-5-yl)methyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid).

(82) N-Desethyl isotonitazene (N-(2-(3-ethyl-2-oxoimidazolidin-1-yl)-5-nitrophenyl)-2-(4-isopropoxyphenyl)acetamide).

(83) 5-Methyl etodesnitazene (2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-5-methyl-1H-benzimidazole-1-ethanamine, 2-hydroxypropane-1,2,3-tricarboxylic acid).

(84) 3', 4'-Methylenedioxynitazene (2-(2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine).

(85) N-Pyrrolidino Isotonitazene (2-(4-isopropoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate).

(86) Ethylene etonitazene (2-(2-(4-ethoxyphenethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid).

(87) N-Desethyl etonitazene (2-[(4-ethoxyphenyl)methyl]-N-ethyl-5-nitro-1H-benzimidazole-1-ethanamine).

(C) Narcotics-opium derivatives

Any of the following opium derivatives, 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) Acetorphine;

(2) Acetyldihydrocodeine;

(3) Benzylmorphine;

(4) Codeine methylbromide;

(5) Codeine-n-oxide;

(6) Cyprenorphine;

(7) Desomorphine;

(8) Dihydromorphine;

(9) Drotebanol;

(10) Etorphine (except hydrochloride salt);

(11) Heroin;

(12) Hydromorphinol;

(13) Methyldesorphine;

(14) Methyldihydromorphine;

(15) Morphine methylbromide;

(16) Morphine methylsulfonate;

(17) Morphine-n-oxide;

(18) Myrophine;

(19) Nicocodeine;

(20) Nicomorphine;

(21) Normorphine;

(22) Pholcodine;

(23) Thebacon;

(24) 6-monoacetylmorphine (6-MAM).

(D) Hallucinogens

Any material, compound, mixture, or preparation that contains any quantity of the following hallucinogenic substances, 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. For the purposes of this division only, "isomer" includes the optical isomers, position isomers, and geometric isomers.

(1) Alpha-ethyltryptamine (some trade or other names: etryptamine; Monase; alpha-ethyl-1H-indole-3-ethanamine; 3-(2-aminobutyl) indole; alpha-ET; and AET);

(2) 4-bromo-2,5-dimethoxyamphetamine (some trade or other names: 4-bromo-2,5-dimethoxy- alpha-methyphenethylamine; 4-bromo-2,5-DMA);

(3) 4-bromo-2,5-dimethoxyphenethylamine (some trade or other names: 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane; alpha-desmethyl DOB; 2C-B, Nexus);

(4) 2,5-dimethoxyamphetamine (some trade or other names: 2,5-dimethoxy-alpha-methylphenethylamine; 2,5-DMA);

(5) 2,5-dimethoxy-4-ethylamphetamine (some trade or other names: DOET);

(6) 2,5-dimethoxy-4-(n)-propylthiophenethylamine (other name: 2C-T-7);

(7) 4-methoxyamphetamine (some trade or other names: 4-methoxy-alpha-methylphenethylamine; paramethoxyamphetamine; PMA);

(8) 5-methoxy-3,4-methylenedioxy-amphetamine;

(9) 4-methyl-2,5-dimethoxy-amphetamine (some trade or other names: 4-methyl-2,5-dimethoxy- alpha-methylphenethylamine; "DOM" and "STP");

(10) 3,4-methylenedioxy amphetamine (MDA);

(11) 3,4-methylenedioxymethamphetamine (MDMA);

(12) 3,4-methylenedioxy-N-ethylamphetamine (also known as N-ethyl-alpha-methyl-3,4(methylenedioxy)phenethylamine, N-ethyl MDA, MDE, MDEA);

(13) N-hydroxy-3,4-methylenedioxyamphetamine (also known as N-hydroxy-alpha-methyl-3,4(methylenedioxy)phenethylamine and N-hydroxy MDA);

(14) 3,4,5-trimethoxy amphetamine;

(15) 5-methoxy-N,N-dimethyltryptamine (some trade or other names: 5-methoxy-3-[2-(dimethylamino)ethyl]indole; 5-MeO-DMT);

(16) Alpha-methyltryptamine (other name: AMT);

(17) Bufotenine (some trade or other names: 3-(beta-dimethylaminoethyl)-5-hydroxyindole; 3-(2- dimethylaminoethyl)-5-indolol; N, N-dimethylserotonin; 5-hydroxy-N, N-dimethyltryptamine; mappine);

(18) Diethyltryptamine (some trade or other names: N, N-diethyltryptamine; DET);

(19) Dimethyltryptamine (some trade or other names: DMT);

(20) 5-methoxy-N,N-diisopropyltryptamine (other name: 5-MeO-DIPT);

(21) Ibogaine (some trade or other names: 7-ethyl-6,6beta,7,8,9,10,12,13-octahydro-2-methoxy- 6,9-methano- 5H-pyrido[1',2':1,2] azepino [5, 4-b] indole; tabernanthe iboga);

(22) Lysergic acid diethylamide;

(23) Marihuana;

(24) Mescaline;

(25) Parahexyl (some trade or other names: 3-hexyl-1- hydroxy-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran; synhexyl);

(26) Peyote (meaning all parts of the plant presently classified botanically as "Lophophora williamsii Lemaire," whether growing or not, the seeds of that plant, any extract from any part of that plant, and every compound, manufacture, salts, derivative, mixture, or preparation of that plant, its seeds, or its extracts);

(27) N-ethyl-3-piperidyl benzilate;

(28) N-methyl-3-piperidyl benzilate;

(29) Psilocybin;

(30) Psilocyn;

(31) Tetrahydrocannabinols (synthetic equivalents of the substances contained in the plant, or in the resinous extractives of Cannabis, sp. and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity such as the following: delta-1- cis or trans tetrahydrocannabinol, and their optical isomers; delta-6-cis or trans tetrahydrocannabinol, and their optical isomers; delta-3,4-cis or trans tetrahydrocannabinol, and its optical isomers. (Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions, are covered.)), excluding any of the following:

(a) Tetrahydrocannabinols found in "hemp" and "hemp products" as those terms are defined in section 928.01 of the Revised Code; and

(b) Any other substance containing tetrahydrocannabinols as authorized in this chapter of the Administrative Code.

(32) N-ethyl-1- phenylcyclohexylamine (1-phenylcyclohexyl)ethylamine; N-(1-phenylcyclohexyl)ethylamine; cyclohexamine; PCE);

(33) 1-(1- phenylcyclohexyl)pyrrolidine (PCPy; PHP);

(34) 1-[1-(2-thienyl)-cyclohexyl]- piperidine (2-thienyl analog of phencyclidine; TPCP; TCP);

(35) 1-[1-(2-thienyl)cyclohexyl]pyrrolidine (some other names: TCPy);

(36) 4-methylmethcathinone (mephedrone);

(37) 3,4-methylenedioxypyrovalerone (MDPV);

(38) 3,4-Methylenedioxy-N-methylcathinone (Methylone);

(39) Hashish;

(40) Salvia divinorum;

(41) Salvinorin A;

(42) (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144);

(43) 1-pentyl-3-(1-adamantoyl)indole (AB-001);

(44) N-adamantyl-1-pentylindole-3-carboxamide (APICA, 2NE1);

(45) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB- FUBINACA);

(46) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA);

(47) N-adamantyl-1-pentylindazole-3-carboxamide (APINACA, AKB48);

(48) 2-ethylamino-2-(3-methoxyphenyl)cyclohexanone (methoxetamine);

(49) N,N-diallyl-5-methoxytryptamine (5MeO-DALT);

(50) [1-(5-fluoropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoropentyl-UR-144; XLR11);

(51) [1-(5-chloropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-chloropentyl-UR-144);

(52) [1-(5-bromopentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-bromopentyl-UR-144);

(53) {1-[2-(4-morpholinyl)ethyl]indol-3-yl}-(2,2,3,3-tetramethylcyclopropyl) methanone (A-796,260);

(54) 1-[(N-methylpiperidin-2-yl)methyl]-3-(1-adamantoyl)indole (AM1248);

(55) N-adamantyl-1-(5-fluoropentylindole)-3-carboxamide (5F-APICA, STS135);

(56) 5-(2-aminopropyl)benzofuran (5-APB);

(57) 6-(2-aminopropyl)benzofuran (6-APB);

(58) 5-(2-aminopropyl)-2,3-dihydrobenzofuran (5-APDB);

(59) 6-(2-aminopropyl)-2,3-dihydrobenzofuran (6-APDB);

(60) Benzothiophenylcyclohexylpiperidine (BTCP);

(61) 2-(2,5-Dimethoxy-4-ethylphenyl)ethanamine (2C-E);

(62) 2-(2,5-Dimethoxy-4-methylphenyl)ethanamine (2C-D);

(63) 2-(4-Chloro-2,5-dimethoxyphenyl)ethanamine (2C-C);

(64) 2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine (2C-I);

(65) 2-[4-(Ethylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-2);

(66) 2-[4-(Isopropylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-4);

(67) 2-(2,5-Dimethoxyphenyl)ethanamine (2C-H);

(68) 2-(2,5-Dimethoxy-4-nitro-phenyl)ethanamine (2C-N);

(69) 2-(2,5-Dimethoxy-4-(n)-propylphenyl)ethanamine (2C-P);

(70) 4-methoxymethamphetamine (PMMA);

(71) 5,6 - Methylenedioxy-2-aminoindane (MDAI);

(72) 5-iodo-2-aminoindiane (5-IAI);

(73) 2-(4-iodo-2,5-dimethoxyphenyl)-N- [(2-methoxyphenyl)methyl]ethanamine(25I-NBOMe);

(74) 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25C-NBOMe, 2C-C-NBOMe);

(75) 2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25B-NBOMe, 2C-B-NBOMe);

(76) 4-methyl-N-ethylcathinone (4-MEC);

(77) 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP);

(78) Alpha-pyrrolidinopentiophenone (alpha-PVP);

(79) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one (butylone, bk-MBDB);

(80) 2-(methylamino)-1-phenylpentan-1-one (pentedrone);

(81) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)pentan-1- one (pentylone, bk-MBDP);

(82) 4-fluoro-N-methylcathinone (4-FMC; flephedrone);

(83) 3-fluoro-N-methylcathinone (3-FMC);

(84) 1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)pentan-1-one (naphyrone);

(85) Alpha-pyrrolidinobutiophenone (alpha-PBP);

(86) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA);

(87) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA);

(88) [1-(5-fluoropentyl)-1H-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201);

(89) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: MAB- CHMINACA; ADB-CHMINACA);

(90) Diphenylprolinol (diphenyl(pyrrolidin-2-yl)methanol, D2PM);

(91) Desoxypipradrol (2-benzhydrylpiperidine);

(92) Synthetic cannabinoids - unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of a synthetic cannabinoid found to be in any of the following chemical groups or any of those groups which contain any synthetic cannabinoid salts, isomers, or salts of isomers, whenever the existence of such salts, isomers, or salts of isomers is possible within the specific chemical groups:

(a) Naphthoylindoles: any compound containing a 3-(1-naphthoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylindoles include, but are not limited to, 1-[2-(4- morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200); 1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM2201), 1-pentyl-3-(1-naphthoyl)indole (JWH-018), and 1-butyl-3-(1-naphthoyl)indole (JWH- 073).

(b) Naphthylmethylindoles: any compound containing a 1H-indol-3-yl-(1-naphthyl)methane structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N- methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindoles include, but are not limited to, (1-pentylindol-3-yl)(1-naphthyl)methane (JWH-175).

(c) Naphthoylpyrroles: any compound containing a 3-(1-naphthoyl)pyrrole structure with or without substitution at the nitrogen atom of the pyrrole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the pyrrole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylpyrroles include, but are not limited to, 1-hexyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-147).

(d) Naphthylmethylindenes: any compound containing a naphthylmethylideneindene structure with or without substitution at the 3-position of the indene ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the indene group to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindenes include, but are not limited to, (1-[(3-pentyl)-1H-inden-1-ylidene)methyl]naphthalene (JWH-176).

(e) Phenylacetylindoles: any compound containing a 3-phenylacetylindole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Phenylacetylindoles include, but are not limited to, 1-pentyl-3-(2-methoxyphenylacetyl)indole (JWH-250), and 1-(2-cyclohexylethyl)-3-(2-methoxyphenylacetyl)indole (RCS-8); 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203).

(f) Cyclohexylphenols: any compound containing a 2-(3-hydroxycyclohexyl)phenol structure with or without substitution at the 5-position of the phenolic ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the cyclohexyl group to any extent. Cyclohexylphenols include, but are not limited to, 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3- hydroxycyclohexyl]-phenol (some trade or other names: CP-47,497) and 5-(1,1-dimethyloctyl)-2- [(1R,3S)-3-hydroxycyclohexyl]-phenol (some trade or other names: cannabicyclohexanol; CP- 47,497 C8 homologue).

(g) Benzoylindoles: any compound containing a 3-(1-benzoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Benzoylindoles include, but are not limited to, 1-pentyl-3-(4- methoxybenzoyl)indole (RCS-4), 1-[2-(4-morpholinyl)ethyl]-2-methyl-3-(4-methoxybenzoyl)indole (Pravadoline or WIN 48, 098).

(93) Quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate (PB-22; QUPIC);

(94) Quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22);

(95) Except as otherwise provided in this rule, any compound that meets at least three of the following cannabinoid pharmacophore requirements to bind at the CB1 and CB2 receptors, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of substituted or non-substituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles or other ring types);

(b) Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors;

(c) Carbonyl or ester or equivalent for hydrogen bonding;

(d) Cyclohexane, naphthalene ring, substituted butanamide or equivalent for steric requirements for CB1 and CB2 receptor binding.

(E) Depressants

Any material, compound, mixture, or preparation that contains any quantity of the following substances having a depressant effect on the central nervous system, 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) Mecloqualone;

(2) Methaqualone;

(3) Except as listed in rule 4729:9-1-03 of the Administrative Code, gamma-hydroxybutyric acid (some other names include GHB; gamma-hydroxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid; sodium oxybate; sodium oxybutyrate);

(4) Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine);

(5) Except as otherwise provided in this chapter, any compound that contains the following structural requirements of a benzodiazepine pharmacophore, as identified by a report from an established forensic laboratory:

A core structure consisting of a benzene ring fused to the seven-membered diazepine ring with a 5-aryl substituent aka 5-aryl-1,4-benzodiazepine for binding to the GABA receptor. Regardless of impact on the lipophilic properties of the compound, a benzodiazepine pharmacophore may contain a variety of functional groups including, but not limited to, aldehydes, ketones, esters, and amides.

This paragraph only applies to a compound that has not been approved for medical use by the United States food and drug administration.

(F) Stimulants

Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of the following substances having a stimulant effect on the central nervous system, including their salts, isomers, and salts of isomers:

(1) Aminorex (some other names: aminoxaphen; 2-amino-5-phenyl-2-oxazoline; or 4,5-dihydro-5- phenyl-2-oxazolamine);

(2) N-Benzylpiperazine (some other names: BZP, 1-benzylpiperazine);

(3) Cathinone (some trade or other names: 2-amino-1-phenyl-1-propanone, alpha-aminopropiophenone, 2-aminopropiophenone, and norephedrone);

(4) Fenethylline;

(5) Methcathinone (some other names: 2-(methylamino)-propiophenone; alpha-(methylamino)propiophenone; 2-(methylamino)-1-phenylpropan-1-one; alpha-N-methylaminopropiophenone; monomethylpropion; ephedrone; N-methylcathinone; methylcathinone; AL-464; AL-422; AL-463 and UR1432), its salts, optical isomers and salts of optical isomers;

(6) (+/-)cis-4-methylaminorex ((+/-)cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine);

(7) N-ethylamphetamine;

(8) N,N-dimethylamphetamine (also known as N,N-alpha-trimethyl-benzeneethanamine; N,N-alpha-trimethylphenethylamine);

(9) N-methyl-1-(thiophen-2-yl) propan-2-amine (methio-propamine);

(10) Substituted cathinones - any compound except bupropion or compounds listed under a different schedule, structurally derived from 2-aminopropan-1-one by substitution at the 1-position with either phenyl, naphthyl, or thiophene ring systems, whether or not the compound is further modified in any of the following ways:

(a) By substitution in the ring system to any extent with alkyl, alkylenedioxy, alkoxy, haloalkyl, hydroxyl, or halide substituents, whether or not further substituted in the ring system by one or more other univalent substituents;

(b) By substitution at the 3-position with an acyclic alkyl substituent;

(c) By substitution at the 2-amino nitrogen atom with alkyl, dialkyl, benzyl, or methoxybenzyl groups;

(d) By inclusion of the 2-amino nitrogen atom in a cyclic structure.

(11) Except as otherwise provided in this rule, any compound that contains the structural requirements of the cathinone pharmacophore, as identified by a report from an established forensic laboratory.

(G) For the purpose of complying with federal law, all materials, compounds, mixtures or preparations which contain any substance temporarily placed in schedule I pursuant to 21 U.S.C. 811 by the United States drug enforcement administration (~~**4/14/2023**~~ **7/19/2024**).

Placement of Benzimidazole Opioids (Nitazenes) in Schedule I (1 of 2) – DRAFT FOR CSI REVIEW

Section 1: Summary

The Ohio Board of Pharmacy (BOP), pursuant to sections 3719.44 and 3719.41 of the Ohio Revised Code, proposes the placement of the following seven compounds into Schedule I:

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

Compounds are currently listed in Schedule I under federal drug abuse laws. These compounds are being incorporated into OAC 4729:9-1-01 pursuant to ORC 3719.41 and 3719.43.

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Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluation Under the Eight Criteria

(1) The actual or relative potential for abuse.

DEA and HHS eight-factor analyses found that butonitazene, flunitazene, and metodesnitazene have pharmacological profiles similar to those of the synthetic opioids etonitazene and isotonitazene, which are both schedule I controlled substances under state and federal law and have high potential for abuse. **NOTE:** These compounds are currently temporarily listed as schedule I controlled substances under federal and state drug abuse laws.

According to HHS, butonitazene, flunitazene, and metodesnitazene have no approved medical uses in the United States, and they have been encountered on the illicit drug market with adverse outcomes on the public health and safety. Because there are no Food and Drug Administration (FDA)-approved or FDA-exempted products for butonitazene, flunitazene, and metodesnitazene in the United States or in any other country, a practitioner may not legally prescribe them, and they cannot be dispensed to an individual. However, these nitazenes substances are available for purchase from legitimate chemical companies because they can be used in scientific research. There is no known diversion from research activities for these substances.

Because butonitazene, flunitazene, and metodesnitazene are not formulated or available for clinical use as approved medicinal products, it is inferred that all current use of these substances by individuals are based on their own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs.

According to drug seizure data from 2020 and 2023 from the National Forensic Laboratory Information System (NFLIS-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 130 reports for butonitazene, flunitazene, or metodesnitazene. Forensic laboratories in Ohio have also identified these three compounds as part of criminal drug seizures.

Individuals may be using these nitazenes on their own initiative because of their opioidergic effects like other Schedule I or II opioids. Consequently, law enforcement encounters of butonitazene, flunitazene, and metodesnitazene demonstrate that these substances are being abused, and thus pose safety hazards to the health of users or the community.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

EDSWG Quarterly Meetings, Cols. OH, (2021, 2022, 2023, and 2024).

(2) The scientific evidence of the pharmacological effect of the substance.

According to DEA and HHS, the pharmacological activity of butonitazene, flunitazene, and metodesnitazene in humans is unknown. Preclinical studies show that these nitazenes exhibit a pharmacological profile similar to that of morphine and fentanyl. As explained in detail in both DEA and HHS eight-factor analyses, data from binding studies show that these substances, similar to morphine and fentanyl, selectively bound to mu-opioid receptors.

In opioid receptor functional assays, butonitazene, flunitazene, and metodesnitazene, similar to fentanyl and morphine, acted as mu-opioid receptor agonists. Further, data from preclinical studies using rodents showed that butonitazene, flunitazene, and metodesnitazene, similar to morphine and fentanyl, produced analgesic effects that can be attenuated by an opioid antagonist pre-treatment. HHS concluded that, similar to morphine and fentanyl, butonitazene, flunitazene, and metodesnitazene produced analgesic effects via activation of mu-opioid receptors.

Additionally, behavioral effects of butonitazene, flunitazene, and metodesnitazene were assessed using the drug discrimination model. Drug discrimination studies can be used to determine whether a test drug produces pharmacological effects (*i.e.,* interoceptive stimulus effects) similar to those produced by a known drug of abuse. Drugs that produce stimulus effects similar to known drugs of abuse in animals are also likely to be abused by humans.

As explained in detail in both DEA and HHS eight-factor analyses, data from drug discrimination studies demonstrate that butonitazene, flunitazene, and metodesnitazene have stimulus properties that are similar to both morphine and fentanyl, schedule II drugs. Taken together, data from preclinical studies demonstrate that butonitazene, flunitazene, and metodesnitazene share similarities in their pharmacological effects and mechanism of action to the schedule II opioid drugs morphine and fentanyl.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and

Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

World Health Organization. Critical review report: Butonitazene. https://cdn.who.int/media/docs/default-source/46th-ecdd/butonitazene_46th-ecdd-critical-review_public-version.pdf?sfvrsn=77ca1954_1

(3) The state of current scientific knowledge regarding the substance.

Butonitazene, flunitazene, and metodesnitazene belong to the 2-benzylbenzimidazole structural class. The chemical structures of these 2-benzylbenzimidazoles contain a benzimidazole ring and a benzyl group at the benzimidazole 2-position. These nitazenes are structurally related to several schedule I substances, including etonitazene. There are no FDA-approved marketing applications for drug products containing butonitazene, flunitazene, and metodesnitazene for any therapeutic indication in the United States or medical use in any other country. Further, there are no well-controlled clinical studies that have demonstrated the safety or efficacy of these substances.

According to HHS, FDA concluded that butonitazene, flunitazene, and metodesnitazene have no currently accepted medical use in the United States.

Similarly, DEA concludes that butonitazene, flunitazene, and metodesnitazene have no currently accepted medical use according to established DEA procedure and case law.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

(4) The history and current pattern of abuse.

In the late 1950s, 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 the synthetic opioids clonitazene, etonitazene, and isotonitazene.

In 2019, isotonitazene emerged on the illicit drug market and was involved in numerous fatal overdose events; in May 2020, it was temporarily controlled as a schedule I substance by the Board. Subsequently, an additional six nitazenes emerged on the illicit opioid drug market. In April 2022, DEA and the Ohio Board of Pharmacy temporarily controlled these six nitazenes as schedule I substances due, in part, to their involvement in numerous postmortem and toxicology cases. Law enforcement agencies have encountered butonitazene, flunitazene, and metodesnitazene in several solid (*e.g.,* powder, rock, and tablet) forms. These substances are not approved for medical use anywhere in the world.

According to HHS, there are no FDA-approved drug products for butonitazene, flunitazene, and metodesnitazene in the United States. The appearance of these nitazenes on the illicit drug market is similar to other synthetic opioids that are trafficked for their psychoactive effects. These three benzimidazole-opioid substances are likely to be abused in the same manner as schedule I opioids, such as etonitazene, isotonitazene, and heroin. These substances have been identified as powders or tablets, typically of unknown purity or concentration. Between 2020 and 2021, butonitazene, flunitazene, and metodesnitazene emerged on the illicit synthetic drug market as evidenced by their identification in forensic drug seizures and in biological samples. Based on NFLIS-Drug data, law enforcement encounters of butonitazene, flunitazene, and metodesnitazene often included mixtures. Substances found in combination with some of these nitazenes include other substances of abuse, such as heroin, fentanyl, fentanyl analogues, designer benzodiazepines, and cocaine.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and

Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

World Health Organization. Critical review report: Butonitazene. https://cdn.who.int/media/docs/default-source/46th-ecdd/butonitazene_46th-ecdd-critical-review_public-version.pdf?sfvrsn=77ca1954_1

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

Butonitazene, flunitazene, and metodesnitazene, similar to schedule I substances, such as etonitazene and isotonitazene, are synthetic opioids, and evidence suggests they are abused for their opioidergic effects. The abuse of these nitazenes, similar to other synthetic opioids, has resulted in their identification in toxicology, post-mortem cases, and law enforcement encounters. Data from the toxicology analysis showed that butonitazene has been positively identified in three postmortem cases, flunitazene in four post mortem cases, and metodesnitazene in one case.

Data from law enforcement suggest that butonitazene, flunitazene, and metodesnitazene are being abused in the United States as recreational drugs. The law enforcement encounters of these nitazenes, as reported to NFLIS-Drug, included 130 exhibits since 2020. NFLIS-Drug registered 66 encounters of butonitazene from 7 states, 60 encounters of flunitazene from 11 states, and 4 encounters of metodesnitazene from 3 states. Of the 66 reports involving butonitazene, fentanyl was co-identified in 24 cases. Flunitazene was commonly co-identified with metonitazene (n = 30) in fifty percent of the cases. Metodesnitazene was co-reported with diphenhydramine (n = 2), fentanyl (n = 2), and heroin (n = 2). Forensic laboratories in Ohio have also identified these three compounds as part of criminal drug seizures.

The identification of these nitazenes in forensic and toxicology cases suggests they may be presented as a substitute for heroin or fentanyl and likely abused in the same manner as either of those substances. The population likely to be harmed by these nitazenes appears to be the same as that harmed by other opioid substances, such as heroin, tramadol, fentanyl, and other synthetic opioid substances. 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 butonitazene, flunitazene, and metodesnitazene are being abused, and that their use can produce serious adverse events that can lead to death. Because users of butonitazene, flunitazene, and metodesnitazene are likely to obtain these substances through unregulated sources, the identity, purity, and quantity of these substances are uncertain and likely to be inconsistent, thus posing significant adverse health risks to the end user. Individuals who initiate use of one or more of these nitazenes are likely to be at risk of developing a substance use disorder, fatal or non-fatal overdose, similar to that of other opioid analgesics (*e.g.,* fentanyl, morphine, etc.).

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I.

https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

EDSWG Quarterly Meetings, Cols. OH, (2021, 2022, 2023, and 2024).

(6) 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 on the illicit drug market. 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, flunitazene, and metodesnitazene are high. Consistently, these three nitazenes have been positively identified in toxicology cases in Ohio. The public health risks associated with the abuse of mu-opioid receptor agonists are well established.

The introduction of synthetic opioids, such as butonitazene, flunitazene, and metodesnitazene, into the illicit drug market may serve as a portal to problematic opioid use for those seeking these opioids. Evidence from toxicology reports show that poly-substance abuse remains common in fatalities associated with the abuse of some of these nitazenes.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

Department of Health and Human Services. Basis for the Recommendation to Control Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, N-Pyrrolidino Etonitazene, and Protonitazene and Their Salts in Schedule I of the Controlled Substances Act (November 2023).

EDSWG Quarterly Meetings, Cols. OH, (2021, 2022, 2023, and 2024).

(7) The potential of the substance to produce psychic or physiological dependence liability; and

Butonitazene, flunitazene, and metodesnitazene have pharmacological effects similar to those of schedule I nitazenes such as clonitazene, etonitazene, and isotonitazene. According to HHS, analgesic studies conducted on these nitazenes show that they produce effects like that of either morphine or fentanyl, both schedule II narcotic drugs. Although there are no clinical studies that have evaluated the dependence potential of these substances, they are mu-opioid receptor agonists, and it is well known that the discontinuation of the use of mu-opioid receptor agonists, such as fentanyl and morphine, causes withdrawal symptoms indicative of physical dependence. The similarities in the pharmacological profile and pattern of abuse of these nitazenes, heroin, and fentanyl are indicative of their similar potential to have psychic and physiological dependence liability.

References:

United States Drug Enforcement Administration. Schedules of Controlled Substances: Placement of Butonitazene, Flunitazene, and Metodesnitazene Substances in Schedule I. https://www.federalregister.gov/documents/2024/04/11/2024-07694/schedules-of-controlled-substances-placement-of-butonitazene-flunitazene-and-metodesnitazene

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(8) Whether the substance is an immediate precursor.

These compounds are not immediate precursors of a substance controlled under the CSA, as defined by 21 U.S.C. 802(23).

Section 4: Finding of the Board

Section 3719.44 of the Ohio Revised Codes authorizes the Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a thorough review of all available data, the Ohio Board of Pharmacy finds that the compounds listed in Section 1 of this document:

1. Have a high potential for abuse;
2. Have no accepted medical use in treatment in this state;
3. Lack accepted safety for use in treatment under medical supervision; and
4. Pose a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that these compounds warrant control in Schedule I and authorizes the filing of amended rule 4729:9-1-01 of the Administrative Code to place these compounds in Schedule I as narcotics-opiates.

Placement of Benzimidazole Opioids (Nitazenes) in Schedule I (2 of 2) – DRAFT FOR CSI REVIEW

Section 1: Summary

The Ohio Board of Pharmacy (BOP), pursuant to sections 3719.44 and 3719.41 of the Ohio Revised Code, proposes the placement of the following nine compounds into Schedule I:

1. N-Pyrrolidino metonitazene (2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate);
2. N-Pyrrolidino protonitazene (5-nitro-2-(4-propoxybenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole);
3. Ethyleneoxynitazene (2-(2-((2,3-dihydrobenzofuran-5-yl)methyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid);
4. N-Desethyl isotonitazene (N-(2-(3-ethyl-2-oxoimidazolidin-1-yl)-5-nitrophenyl)-2-(4-isopropoxyphenyl)acetamide);
5. 5-Methyl etodesnitazene (2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-5-methyl-1H-benzimidazole-1-ethanamine, 2-hydroxypropane-1,2,3-tricarboxylic acid);
6. 3', 4'-Methylenedioxynitazene (2-(2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine);
7. N-Pyrrolidino Isotonitazene (2-(4-isopropoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole, 2-hydroxy-1,2,3-propanetricarboxylate);
8. Ethylene etonitazene (2-(2-(4-ethoxyphenethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine, 2-hydroxypropane-1,2,3-tricarboxylic acid);
9. N-Desethyl etonitazene (2-[(4-ethoxyphenyl)methyl]-N-ethyl-5-nitro-1H-benzimidazole-1-ethanamine).

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Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluation Under the Eight Criteria

(1) The actual or relative potential for abuse.

As previously recognized by the Board, the availability and abuse of novel psychoactive substances[1] (NPSs) has significantly increased over the past decade. A subset of NPSs are new synthetic opioids (NSOs). Attributed by some to 2018 control measures in China aimed at reducing the availability of fentanyl-related compounds, new non-fentanyl NSOs, known as "nitazenes" (sometimes referred to as benzimidazole-opioids), continue to appear in the illicit market.

Many of the NSOs illicitly available today were synthesized by pharmaceutical companies in the second half of the twentieth century. These syntheses were designed to identify compounds that are safer and more effective alternatives to morphine. Published literature related to these efforts—including patents—serve as a database for underground chemists to manufacture gray market NSOs.

Apart from occasional identifications of etonitazene between 1966 and 2003, it was not until 2019 that the first nitazene (isotonitazene) was identified on the recreational drug market. Following the introduction of laws targeting isotonitazene, various other nitazenes were identified on recreational drug markets and eventually scheduled. Currently, a number of nitazenes are subject to international control (i.e., etonitazene, clonitazene, isotonitazene, metonitazene, protonitazene, butonitazene, etodesnitazene ('etazene'), and *N*-pyrrolidino etonitazene ('etonitazepyne')). In the U.S., different nitazenes such as *N*-piperidinyl etonitazene ('etonitazepipne'), *N*-desethyl isotonitazene, metodesnitazene, and flunitazene were individually scheduled and are temporarily designated as Schedule I substances by the U.S. Drug Enforcement Administration (DEA).

Nitazenes have a high potential for abuse. As early as 1975, Alexander Shulgin suggested that nitazenes were "a fertile field for the search for heroin substitutes that can be domestically synthesized and are potent at levels that would encourage illicit investigation." Moreover, Blanckaert and others (2019) warn that, "[s]ince multiple substances in the [nitazene] class trump morphine's potency by at least an order of magnitude, the number of future possible [nitazene] opioids cannot be underestimated." This is reinforced by the fact that the number of new nitazene compounds identified has grown each year since 2021.

[1] NPSs are defined by the United Nations Office on Drugs and Crime (UNODC) as, "substance of abuse, either in pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat."

Actual abuse of nitazene compounds has grown in both the United States and abroad. The presence of such nitazenes has been relayed by several forensic lab systems in Ohio. This includes the confirmed presence of *N*-Pyrrolidino metonitazene; *N*-Pyrrolidino protonitazene; Ethyleneoxynitazene; *N*-Desethyl Isotonitazene; 5-Methyl etodesnitazene; 3', 4'-Methylenedioxynitazene; *N*-Pyrrolidino isotonitazene; Ethylene etonitaze; N-Desethyl etonitazene.

Although these nitazene compounds may be found to be controlled substance analogs (with four listed federally under Schedule I), inconsistent reporting across lab systems renders quantifying actual abuse elusive. For instance, case law in certain court jurisdictions may create barriers to prosecution for trafficking analogs or labs may not target their analysis for the identification of the non-controlled substance when a more common controlled substance is present. Further compounding this issue for these compounds is that many nitazenes are highly potent and the concentration of some may fall below standard laboratory detection levels.

According to DEA, nitazenes have pharmacological profiles similar to those of the synthetic opioids etonitazene and isotonitazene, which are both schedule I controlled substances and have high potential for abuse. The nitazenes listed in this document are not approved for medical use in the United States by the United States Food and Drug Administration.

References:

Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 94(11):3819-3830. (2020).

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Schedules of Controlled Substances: Temporary Placement of Butonitozene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-pyrrolidino etonitazene, and Protonitazene in Schedule I; Drug Enforcement Administration; 86 Fed. Reg. 69,182 (Dec. 7, 2021).

UNODC, February 2024 – UNDOC EWA: Nitazenes – a new group of synthetic opioids emerges, 2024, available at https://www.unodc.org/LSS/Announcement/Details/cbec8f4c-73aa-49ee-9e2b-75620af8a910 (last visited May 14, 2024).

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United States Drug Enforcement Administration. Nitazenes. January 2024. https://www.deadiversion.usdoj.gov/drug_chem_info/nitazenes.pdf

De Vrieze, L.M., Walton, S.E., Pottie, E. *et al.* In vitro structure–activity relationships and forensic case series of emerging 2-benzylbenzimidazole 'nitazene' opioids. *Arch Toxicol* (2024). https://doi.org/10.1007/s00204-024-03774-7

(2) The scientific evidence of the pharmacological effect of the substance(s).

Data obtained from pre-clinical studies demonstrate that nitazenes exhibit pharmacological profiles similar to that of etonitazene (a Schedule I controlled substance in Ohio) and other mu-opioid receptor agonists. Antinociceptive studies conducted in rodents using known nitazenes, demonstrate that, similar to morphine and fentanyl, these substances produced analgesic effects with varying potencies.

Data from in vitro studies showed that known nitazenes, similar to fentanyl and morphine, bound to and activated the mu-opioid receptor, and thus acted as mu-opioid receptor agonists. It is well established that mu-opioid receptor agonists have a high potential for addiction and can produce dose-dependent respiratory depression and arrest. Abuse of these nitazenes has led to their positive identification in toxicological cases in the United States, including Ohio. Some of these nitazenes have been positively identified in numerous post-mortem cases.

Data suggest that several of the nitazenes listed in this analysis have potency that exceeds fentanyl:

Compound	Relative Strength Compared to Fentanyl
N-Pyrrolidino Metonitazene	2 times more potent
N-Pyrrolidino Protonitazene	25 times more potent
N-Desethyl Isotonitazene	20 times more potent
***N*-Pyrrolidino isotonitazene**	25 times more potent
N-Desethyl etonitazene	10 times more potent

Source: The Center for Forensic Science Research & Education (https://www.cfsre.org/)

References:

United States Drug Enforcement Administration. Nitazenes. January 2024. https://www.deadiversion.usdoj.gov/drug_chem_info/nitazenes.pdf

(3) The state of current scientific knowledge regarding the substance(s).

The chemical structures of the 2-benzylbenzimidazole opioids vary in three positions of the molecule:

(a) the *para*-benzyl position, with typically either a differing alkoxy chain length (e.g., meto-, eto-, proto-, isoto-, and butonitazene) or halogen substitution (e.g., flunitazene) (R_1);

(b) the 5-position of the benzimidazole ring containing or lacking a nitro moiety (e.g., etodesnitazene vs. etonitazene) (R_2); and

(c) the substituted ethyl amino side chain attached to the benzimidazole ring, typically containing a tertiary amine with an *N*,*N*-diethyl moiety (R_3).

Examples of modifications of the latter include *N*-desethyl analogues (e.g., *N*-desethyl etonitazene and *N*-desethyl isotonitazene) and 'ring' analogues with either a pyrrolidine (e.g., *N*-pyrrolidino etonitazene ('etonitazepyne')) or piperidine substitution (e.g., *N*-piperidinyl etonitazene ('etonitazepipne')).

Opioids with diverse chemical structures have emerged in response to class-wide bans on fentanyl analogues in the U.S. and China, and NSOs with a 2-benzyl-benzimidazole core have become the most dominant class of non-fentanyl-related opioids in the last 4 years.

References:

De Vrieze, L.M., Walton, S.E., Pottie, E. *et al.* In vitro structure–activity relationships and forensic case series of emerging 2-benzylbenzimidazole 'nitazene' opioids. *Arch Toxicol* (2024). https://doi.org/10.1007/s00204-024-03774-7

(4) The history and current pattern of abuse.

Actual abuse of nitazenes has grown in both the United States and abroad. The presence of such nitazenes has been relayed by several forensic lab systems in Ohio. This includes the confirmed presence of *N*-Pyrrolidino metonitazene; *N*-Pyrrolidino protonitazene; Ethyleneoxynitazene; *N*-Desethyl Isotonitazene; 5-Methyl etodesnitazene; 3', 4'-Methylenedioxynitazene; *N*-Pyrrolidino isotonitazene; Ethylene etonitaze; N-Desethyl etonitazene.

Since 2019, there have been over 4,300 reports of nitazenes to NFLIS-Drug. Furthermore, substances in this class have been co-identified with other psychoactive substances, including illicit opioids, stimulants, and benzodiazepines, in biological fluids. With no approved medical use, the positive identification of these substances in toxicology cases underscores the public health threat associated with their presence in the illicit drug market.

The population likely to abuse nitazenes appears to be the same as those abusing prescription opioid analgesics, heroin, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in benzimidazole-opioid drug seizures and in fatal overdose cases. Toxicology analyses co-identified some of these nitazenes with other opioids, stimulants, and benzodiazepines.

As individuals using these nitazenes are likely to obtain them through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the users. Similar to other mu-opioid receptor agonists, the potential health and safety risks for users of these nitazenes are high. The positive identification of nitazenes in toxicology and post-mortem cases is a serious concern to the public safety.

Nitazenes are also becoming increasingly involved in overdose deaths in Ohio. As recently as 2020, just three overdose deaths involving nitazene compounds were confirmed and reported to the Ohio Department of Health (ODH). However, a significant jump occurred in 2021 and 2022, which saw an average of 57 such deaths per year. Although 2023 data is not yet complete, ODH has recorded 77 nitazene-involved overdose deaths for the year – and this number only represents confirmed cases. Due to under reporting, the true number of overdose deaths involving nitazene compounds is expected to be much higher.

References:

United States Drug Enforcement Administration. Nitazenes. January 2024. https://www.deadiversion.usdoj.gov/drug_chem_info/nitazenes.pdf

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Governor DeWine Authorizes Emergency Ban of Nine Synthetic Opioids. June 4, 2024. https://governor.ohio.gov/media/news-and-media/governor-dewine-authorizes-emergency-ban-of-nine-synthetic-opioids

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

The scope, duration, and significance of opioid abuse is well-characterized. Illicitly available NSOs deviate from the classical fentanyl and morphinan chemical structures. The vast variety of molecular modifications render the identification of NSOs in both drug seizure and toxicology evidence difficult.

Although these nine nitazene compounds may be found to be controlled substance analogs, inconsistent reporting across lab systems renders quantifying actual abuse elusive. For instance, case law in certain court jurisdictions may create barriers to prosecution for trafficking analogs or labs may not target their analysis for the identification of the non-controlled substance when a more common controlled substance is present. Nonetheless, it is known that as opioid abuse continues to rise, so too do efforts by clandestine chemists to synthesize and distribute NSOs that skirt chemical control policies.

Following the pattern of other NPSs before them, nitazenes are a public health concern that are continuing to grow. This is due in no small part to the efforts of clandestine chemists to undermine prohibitions on the possession and trafficking of nitazenes. These efforts merit additional counter-control measures.

Moreover, data from law enforcement suggests that these nine compounds are being abused recreationally in Ohio. Each has been confirmed by an Ohio crime lab. Although law enforcement data are not direct evidence of abuse, they are used to establish an inference that drugs are being diverted and abused.

Data from Ohio crime labs suggest that etodesnitazene reached peak positivity in 2021 with 17 positive cases that year, and its positivity decreased in 2022 (7 cases) and 2023 (Q1-Q3, 1 case). Notably, Q4 2022 marked the emergence of *N*-desethyl isotonitazene, *N*-pyrrolidino metonitazene, and *N*-pyrrolidino protonitazene, with their respective positivities further increasing through the first quarter of 2023. Since then, the prevalence of *N*-pyrrolidino protonitazene has largely remained stable, while the positivities for *N*-desethyl isotonitazene and *N*-pyrrolidino metonitazene have fluctuated and decreased, respectively. *N*-Desethyl etonitazene was identified for the first time in Q3 2023 (1 case).

Evidence from the dark web compiled by the Ohio Narcotics Intelligence Center (ONIC), demonstrates the availability and interest in nitazene compounds for illicit use. Of note, dark web users and vendors often refer to N-pyrro compounds as “pyne” drugs. Examples of such posts can be found in Appendix I of this document.

Nitazenes are also becoming increasingly involved in overdose deaths in Ohio. As recently as 2020, just three overdose deaths involving nitazene compounds were confirmed and reported to the Ohio Department of Health (ODH). However, a significant jump occurred in 2021 and 2022, which saw an average of 57 such deaths per year. Although 2023 data is not yet complete, ODH has recorded 77 nitazene-involved overdose deaths for the year – and this number only represents confirmed cases. Due to under reporting, the true number of overdose deaths involving nitazene compounds is expected to be much higher.

References:

Schedules of Controlled Substances: Temporary Placement of N-Desethyl Isotonitazene and N-Piperidinyl Etonitazene in Schedule I; Drug Enforcement Administration; 88 Fed. Reg. No. 205, 73293, 73294 (Oct. 25, 2023).

Ohio Narcotics Intelligence Center. Dark Web Research. Completed May 21, 2024 (documentation on file with ONIC).

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(6) The risk to the public health.

Synthetic opioids are the primary cause of deaths related to unintentional drug poisonings in the United States. Nitazene compounds contribute to those poisonings. Indeed, in its October 25, 2023, Notice of Intent to Schedule new nitazene compounds, the DEA stated that, "the continued trafficking and identification of nitazenes 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."

Nitazenes have a high abuse potential. In 1975, Alexander Shulgin suggested that nitazenes were "a fertile field for the search for heroin substitutes that can be domestically synthesized and are potent at levels that would encourage illicit investigation." Moreover, Blanckaert and others (2019) warn that, "[s]ince multiple substances in the [nitazene] class trump morphine's potency by at least an order of magnitude, the number of future possible [nitazene] opioids cannot be underestimated."

Several nitazene compounds are known to be highly potent and to present an elevated risk of death caused by unintentional drug poisonings. In multiple unintentional drug poisonings, nitazenes have been the only compounds reported and assessed to be causal or contributory to the negative health outcome.

Data suggest that several compounds in this group have potency that exceeds fentanyl:

Compound	Relative Strength Compared to Fentanyl
N-Pyrrolidino Metonitazene	2 times more potent
N-Pyrrolidino Protonitazene	25 times more potent
N-Desethyl Isotonitazene	20 times more potent
***N*-Pyrrolidino isotonitazene**	25 times more potent
N-Desethyl etonitazene	10 times more potent

Source: The Center for Forensic Science Research & Education (https://www.cfsre.org/)

Nitazenes are becoming increasingly involved in overdose deaths in Ohio. As recently as 2020, just three overdose deaths involving nitazene compounds were confirmed and reported to the Ohio Department of Health (ODH). However, a significant jump occurred in 2021 and 2022, which saw an average of 57 such deaths per year. Although 2023 data is not yet complete, ODH has recorded 77 nitazene-involved overdose deaths for the year – and this number only represents confirmed cases. Due to under reporting, the true number of overdose deaths involving nitazene compounds is expected to be much higher.

References:

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Governor DeWine Authorizes Emergency Ban of Nine Synthetic Opioids. June 4, 2024. https://governor.ohio.gov/media/news-and-media/governor-dewine-authorizes-emergency-ban-of-nine-synthetic-opioids

(7) The potential of the substance to produce psychic or physiological dependence liability; and

Nitazenes have a high potential for abuse. As early as 1975, Alexander Shulgin suggested that nitazenes were "a fertile field for the search for heroin substitutes that can be domestically synthesized and are potent at levels that would encourage illicit investigation." Moreover, Blanckaert and others (2019) warn that, "[s]ince multiple substances in the [nitazene] class trump morphine's potency by at least an order of magnitude, the number of future possible [nitazene] opioids cannot be underestimated."

Data from in vitro studies showed that known benzimidazole-opioids, similar to fentanyl and morphine, bound to and activated the mu-opioid receptor, and thus acted as mu-opioid receptor agonists. It is well established that mu-opioid receptor agonists have a high potential for addiction and can produce dose-dependent respiratory depression and arrest. Abuse of these benzimidazole-opioids has led to their positive identification in several toxicological cases in the United States. Some of these benzimidazole-opioids have been positively identified in numerous post-mortem cases.

This is reinforced by the fact that nitazenes are becoming increasingly involved in overdose deaths in Ohio. As recently as 2020, just three overdose deaths involving nitazene compounds were confirmed and reported to the Ohio Department of Health (ODH). However, a significant jump occurred in 2021 and 2022, which saw an average of 57 such deaths per year. Although 2023 data is not yet complete, ODH has recorded 77 nitazene-involved overdose deaths for the year – and this number only represents confirmed cases. Due to under reporting, the true number of overdose deaths involving nitazene compounds is expected to be much higher.

References:

Vandeputte MM, Uytfanghe KV, Layle NK, St. Germaine DM, Iula DM, Stove CP. Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of 'Nitazene' 2-Benzylbenzimidazole Synthetic Opioids. ACS Chem. Neurosci. 2021, 12, 1241–1251.

Blanckaert P, Cannaert A, Van Uytfanghe K, Hulpia F, Deconick E, Van Calenbergh S, Stove C. Report on a Novel Emerging Class of Highly Potent Benzimidazole NPS Opioids: Chemical and In Vitro Functional Characterization of Isotonitazene. Drug Test Anal. 2020; 12:422–430.

Governor DeWine Authorizes Emergency Ban of Nine Synthetic Opioids. June 4, 2024. https://governor.ohio.gov/media/news-and-media/governor-dewine-authorizes-emergency-ban-of-nine-synthetic-opioids

United States Drug Enforcement Administration. Nitazenes. January 2024. https://www.deadiversion.usdoj.gov/drug_chem_info/nitazenes.pdf

(8) Whether the substance is an immediate precursor.

These compounds are not immediate precursors of a substance controlled under the CSA, as defined by 21 U.S.C. 802(23).

Section 4: Finding of the Board

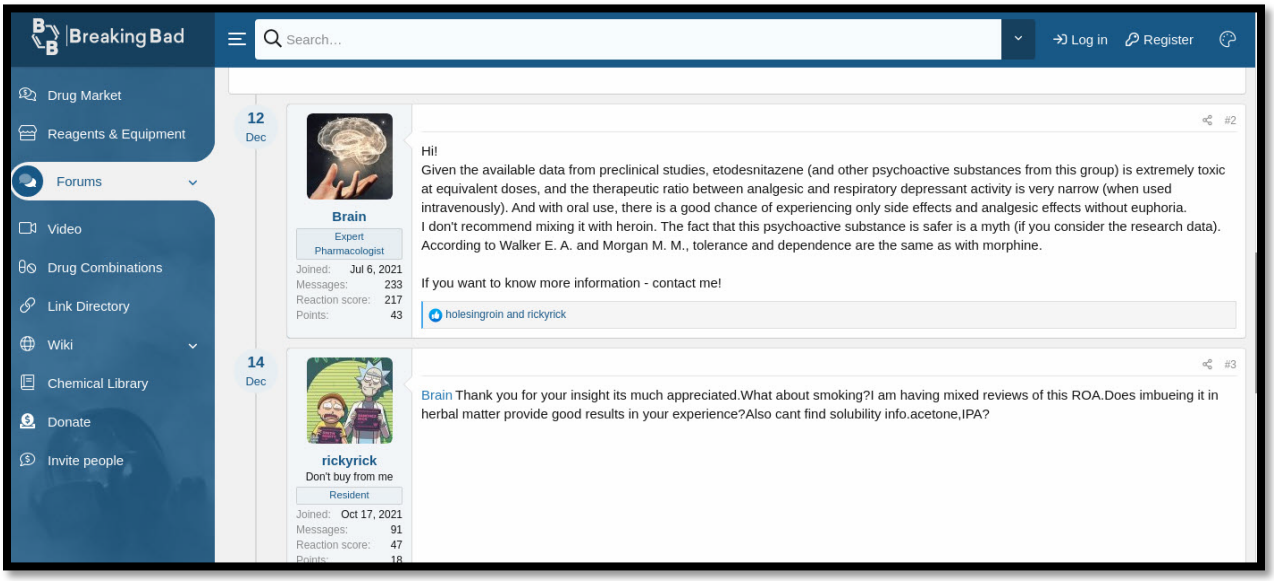
Section 3719.44 of the Ohio Revised Codes authorizes the Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

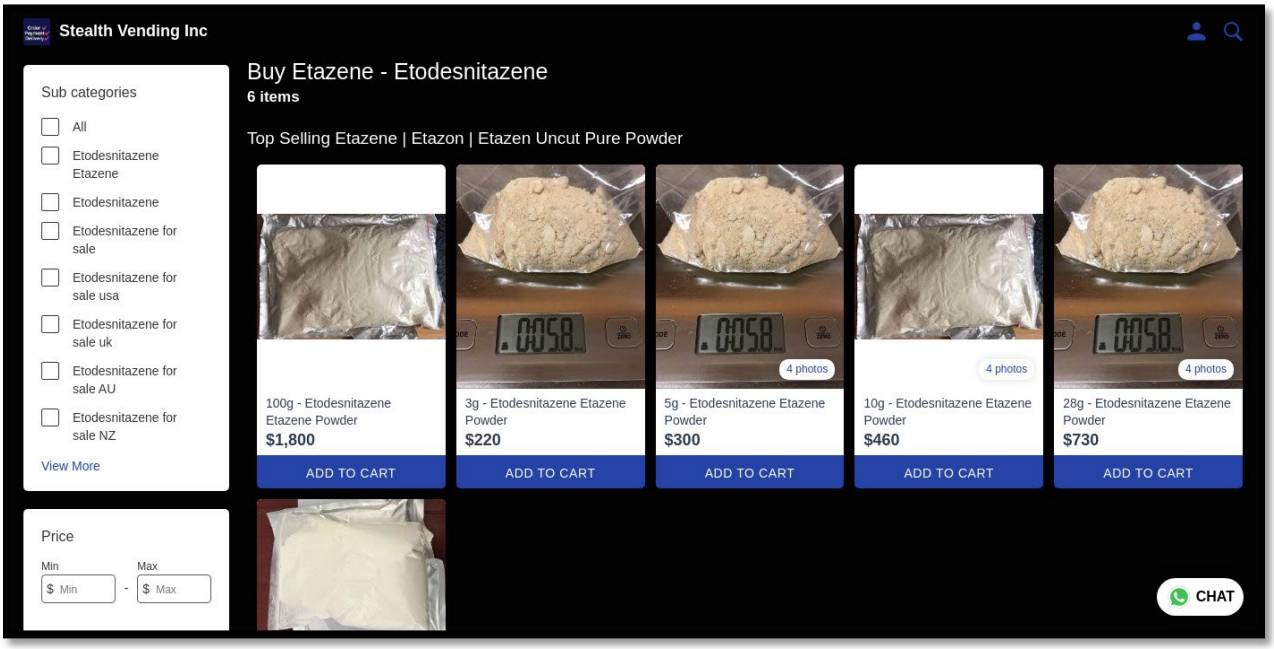
After a thorough review of all available data, the Ohio Board of Pharmacy finds that the compounds listed in Section 1 of this document:

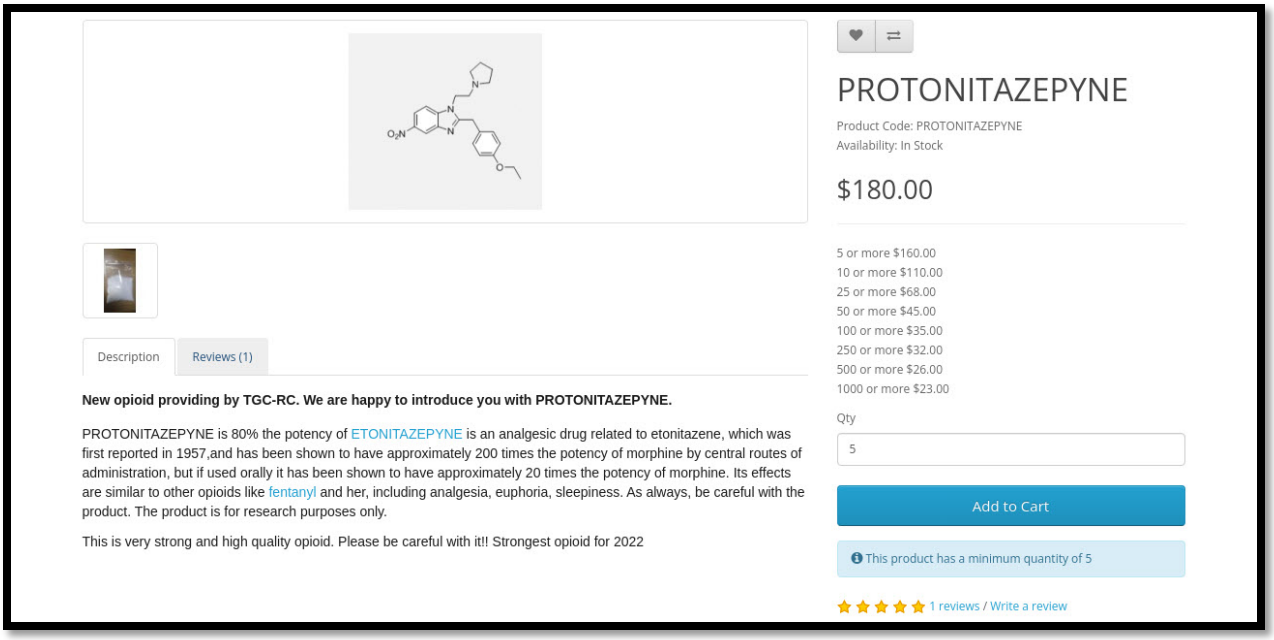
1. Have a high potential for abuse;
2. Have no accepted medical use in treatment in this state;
3. Lack accepted safety for use in treatment under medical supervision; and
4. Pose a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that these compounds warrant control in Schedule I and authorizes the filing of amended rule 4729:9-1-01 of the Administrative Code to place these compounds in Schedule I as narcotics-opiates.

Appendix I – ONIC Dark Web Research







PROTONITAZEPYNE

Product Code: PROTONITAZEPYNE
Availability: In Stock

$180.00

5 or more $160.00
10 or more $110.00
25 or more $68.00
50 or more $45.00
100 or more $35.00
250 or more $32.00
500 or more $26.00
1000 or more $23.00

Qty

5

Add to Cart

This product has a minimum quantity of 5

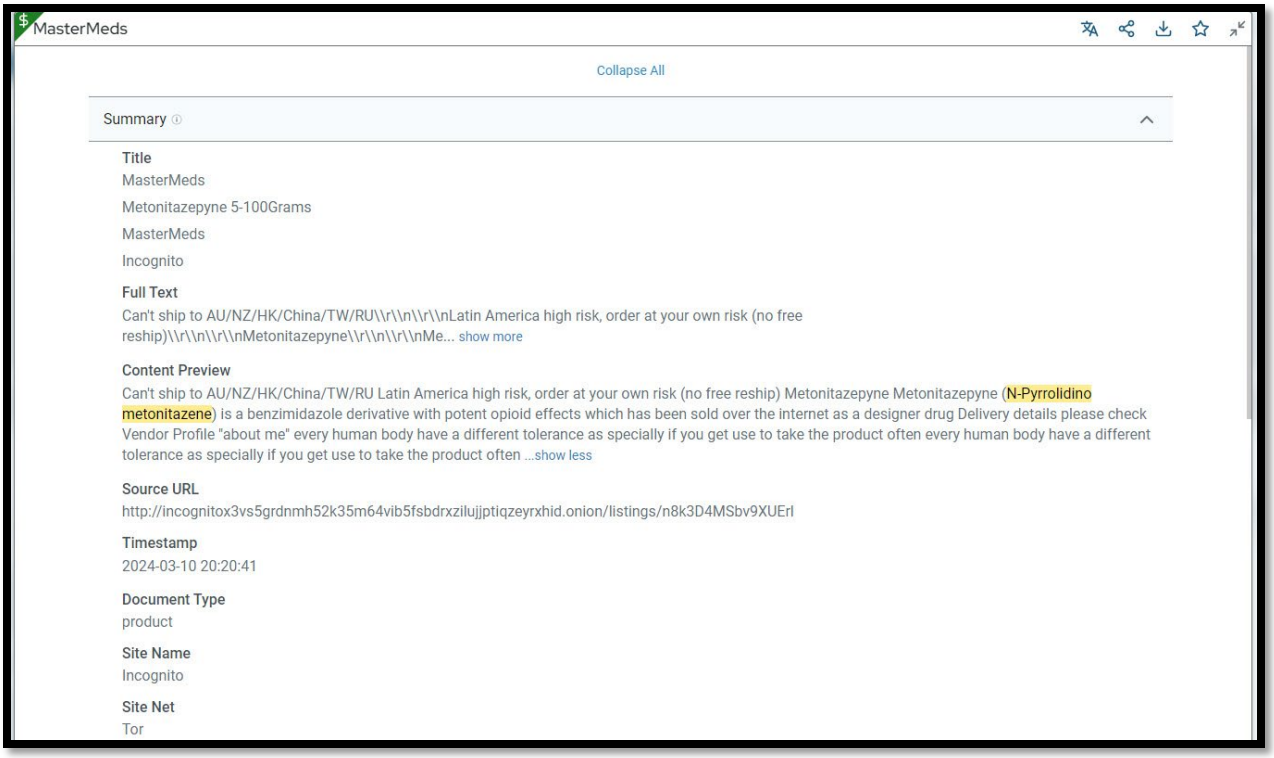
1 reviews / Write a review

Description | Reviews (1)

New opioid providing by TGC-RC. We are happy to introduce you with PROTONITAZEPYNE.

PROTONITAZEPYNE is 80% the potency of ETONITAZEPYNE is an analgesic drug related to etonitazene, which was first reported in 1957,and has been shown to have approximately 200 times the potency of morphine by central routes of administration, but if used orally it has been shown to have approximately 20 times the potency of morphine. Its effects are similar to other opioids like fentanyl and her, including analgesia, euphoria, sleepiness. As always, be careful with the product. The product is for research purposes only.

This is very strong and high quality opioid. Please be careful with it!! Strongest opioid for 2022



MasterMeds

Collapse All

Summary

Title
MasterMeds
Metonitazepyne 5-100Grams
MasterMeds
Incognito

Full Text
Can't ship to AU/NZ/HK/China/TW/RU\\r\\n\\r\\nLatin America high risk, order at your own risk (no free reship)\\r\\n\\r\\nMetonitazepyne\\r\\n\\r\\nMe... show more

Content Preview
Can't ship to AU/NZ/HK/China/TW/RU Latin America high risk, order at your own risk (no free reship) Metonitazepyne Metonitazepyne (N-Pyrrolidino metonitazene) is a benzimidazole derivative with potent opioid effects which has been sold over the internet as a designer drug Delivery details please check Vendor Profile "about me" every human body have a different tolerance as specially if you get use to take the product often every human body have a different tolerance as specially if you get use to take the product often ...show less

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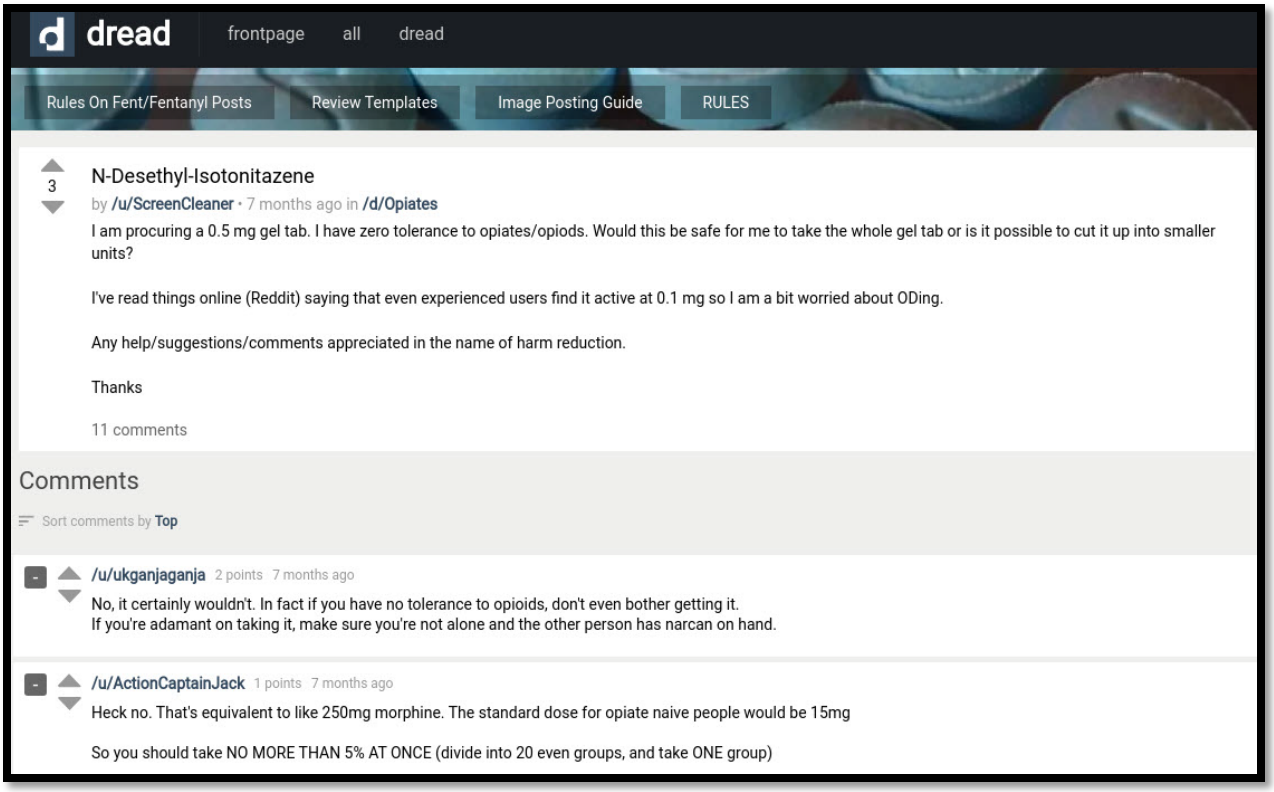
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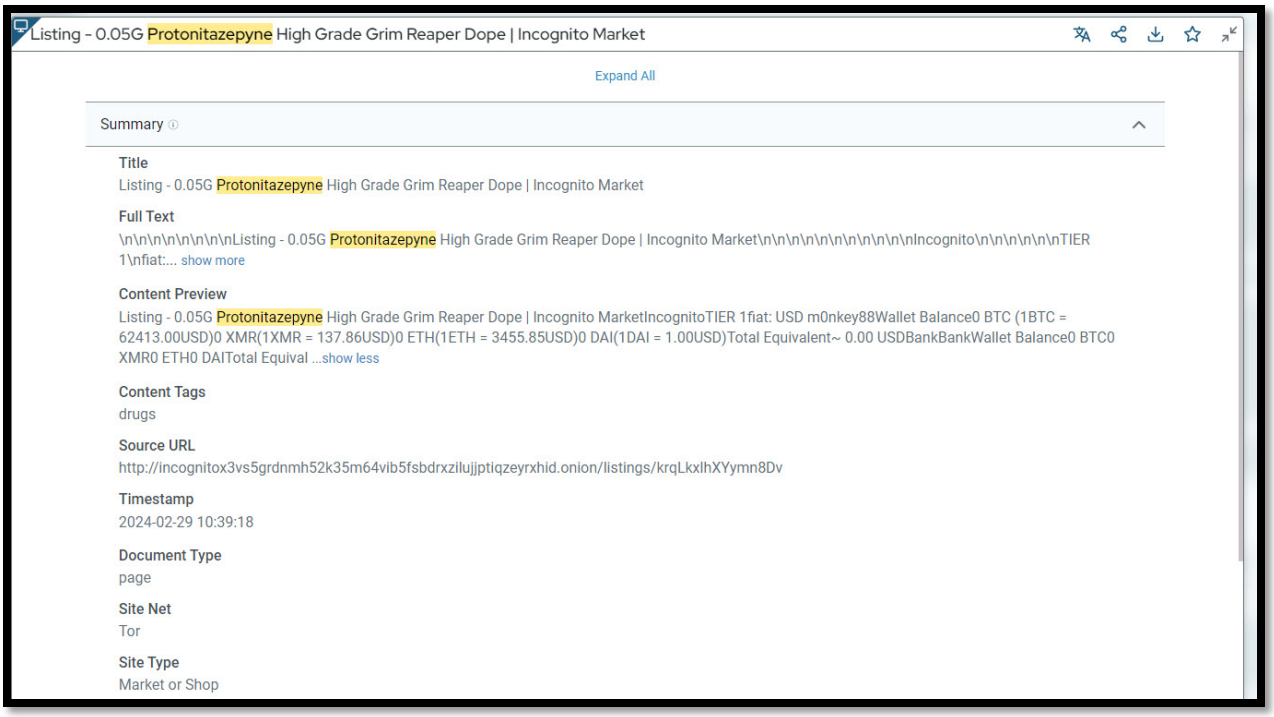
Rules On Fent/Fentanyl Posts
Review Templates
Image Posting Guide
RULES
3
N-Desethyl-Isotonitazene
by /u/ScreenCleaner • 7 months ago in /d/Opiates
I am procuring a 0.5 mg gel tab. I have zero tolerance to opiates/opiods. Would this be safe for me to take the whole gel tab or is it possible to cut it up into smaller units?
I've read things online (Reddit) saying that even experienced users find it active at 0.1 mg so I am a bit worried about ODing.
Any help/suggestions/comments appreciated in the name of harm reduction.
Thanks
11 comments
Comments
Sort comments by Top
/u/ukganjaganja 2 points 7 months ago
No, it certainly wouldn't. In fact if you have no tolerance to opioids, don't even bother getting it.
If you're adamant on taking it, make sure you're not alone and the other person has narcan on hand.
/u/ActionCaptainJack 1 points 7 months ago
Heck no. That's equivalent to like 250mg morphine. The standard dose for opiate naive people would be 15mg
So you should take NO MORE THAN 5% AT ONCE (divide into 20 even groups, and take ONE group)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Full Text
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Content Preview
Listing - 0.05G Protonitazepyne High Grade Grim Reaper Dope | Incognito MarketIncognitoTIER 1fiat: USD m0nkey88Wallet Balance0 BTC (1BTC = 62413.00USD)0 XMR(1XMR = 137.86USD)0 ETH(1ETH = 3455.85USD)0 DAI(1DAI = 1.00USD)Total Equivalent~ 0.00 USDBankBankWallet Balance0 BTC0 XMR0 ETH0 DAITotal Equival ...show less
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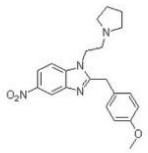

METONITAZEPYNE

Product Code: METONITAZEPYNE
Availability: In Stock

$180.00

5 or more $120.00
10 or more $90.00
25 or more $60.00
50 or more $40.00
100 or more $33.00
250 or more $22.00
500 or more $18.00
1000 or more $15.00

Qty

5

Add to Cart

This product has a minimum quantity of 5

0 reviews / Write a review

Description | Reviews (0)

New opioid providing by TGC-RC. We are happy to introduce you with METONITAZEPYNE.

METONITAZEPYNE is around 80% the potency of ETONITAZEPYNE is an analgesic drug related to etonitazene, which was first reported in 1957,and has been shown to have approximately 200 times the potency of morphine by central routes of administration, but if used orally it has been shown to have approximately 20 times the potency of morphine. Its effects are similar to other opioids like fentanyl and her, including analgesia, euphoria, sleepiness. As always, be careful with the product. The product is for research purposes only.

IUPAC NAME: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)benzimidazole
Chemical formula: C21H24N4O3
Molar mass: 380.448 g•mol−1

Metonitazepyne (N-Pyrrolidino metonitazene) is a benzimidazole derivative with potent opioid effects which has been sold over the internet as a designer drug...
This product is intended for laboratory research purposes only and are not to be used for any other purposes.

This is very strong and high quality opioid. Please be careful with it!! STRONGER AND BETTER THAN METONITAZENE!!

Please note, shipping to Canada limited to 250 grams only! All other countries, can order up to 2kg.