EMERGENCY MEETING NOTICE

May 22, 2020 - 8:40 a.m.

LOCATION:

This meeting is being convened telephonically at **8:40 a.m.**

Dial-in Number: 614-721-2972 | Conference ID: 829962746#

PURPOSE:

The State of Ohio Board of Pharmacy, pursuant to section 3719.45 of the Ohio Revised Code, proposes the placement of isotonitazene into Schedule I as an opium derivative through the adoption of emergency rule 4729:9-1-01.2 of the Ohio Administrative Code.

Pursuant to section 3719.45 the Board may add a previously unscheduled compound, mixture, preparation, or substance to Schedule I by emergency rule if the Board determines the compound has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

In making a determination to add an unscheduled compound by emergency rule, the Board is required to consider the following three criteria:

(1) Its actual or relative potential for abuse;

(2) The scope, duration, and significance of that abuse;

(3) The risk it poses to the public health.

The Board's three-factor analysis starts on the next page of this meeting notice.

PROPOSED EMERGENCY RULE:

4729:9-1-01.2 – Isotonitazene.

Pursuant to section 3719.45 of the Revised Code, the state board of pharmacy hereby adds to controlled substance schedule I the following opium derivative, including its 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:

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

PROPOSAL TO SCHEDULE ISOTONITAZENE

Section 1: Summary

The State of Ohio Board of Pharmacy (Board), pursuant to section 3719.45 of the Ohio Revised Code, proposes the placement of isotonitazene into Schedule I as an opium derivative.

Section 2: Background

Pursuant to section 3719.45 the Board may add a previously unscheduled compound, mixture, preparation, or substance to Schedule I by emergency rule if the Board determines the compound has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

In making a determination to add an unscheduled compound by emergency rule, the Board is required to consider the following three criteria:

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

Section 3: Evaluating Isotonitazene Under the Three Criteria

(1) The actual or relative potential for abuse.

Isotonitazene is a synthetic opioid bearing structural resemblance to etonitazene, a synthetic opioid that is classified as a Schedule I controlled substance in Ohio and nationally. Isotonitazene and similar analogues (e.g. etonitazene, metonitazene, and clonitazene), known as benzimidazole opioids, were first synthesized and reported in the literature in the 1950s.[i] Most recently, isotonitazene was reported to be highly potent and efficacious for activation of μ-opioid receptors.[ii]

A review of U.S. isotonitazene-related deaths found that the drug is being used by individuals who are also currently abusing opioids and other controlled substances. Of the 18 deaths [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)] reported in the U.S., at least six of the decedents included individuals with a documented history of opioid-use disorder.[iii] In addition, isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these individuals.[iv]

Pharmacological data suggest that the group of synthetic opioids that includes isotonitazene (along with etonitazene, metonitazene, and clonitazene) has potency similar to or greater than fentanyl based on their structural modifications. Etonitazene is reported to be the most potent of the group followed by isotonitazene and metonitazene.[v] The toxicity of isotonitazene has not been extensively studied but recent association with drug user deaths leads forensic professionals to believe this new synthetic opioid retains the potential to cause widespread harm and is of public health concern.[vi]

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

Isotonitazene was first reported in August 2019 based on the results from seized drug and toxicology casework in Europe (Belgium) and Canada (Alberta); the Canadian toxicology case was collected in March 2019.[vii] Although the size of the market is unknown, isotonitazene is sold online as a legal replacement to controlled opioids.[viii] In March 2020, isotonitazene was found in 1,900 fake pharmaceutical pills in Nova Scotia and Newfoundland. The drug has been pressed into tablets

to resemble Dilaudid, or hydromorphone. Dilaudid is a much-desired, highly euphoric synthetic opioid similar to oxycodone, aka Oxycontin.[ix]

In the United States, isotonitazene is considered one of the most persistent and prevalent new opioids.[x] Data from the Ohio Bureau of Criminal Investigation finds that isotonitazene has been identified in the state at least 11 times since the start of 2020.[xi]

Isotonitazene has been identified in at least 18 deaths in the United States. The deaths occurred between August 2019 and January 2020 and were from the Midwestern United States [Illinois (n=9), Indiana (n=7), Minnesota (n=1), and Wisconsin (n=1)]. Based on information from the death investigations and forensic toxicology results, at least some of the individuals were high-risk drug users and included people who had a history of injecting opioids such as heroin. Isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these individuals. In particular, many of the cases involved the use of other CNS depressants along with isotonitazene (such as other opioids and/or benzodiazepines).[xii]

(3) The risk to the public health.

Isotonitazene is not approved for medical use by the United States Food and Drug Administration. Additionally, researchers have issued warnings about the drug's potency and efficacy, stating:

> *The high potency and efficacy of isotonitazene, combined with the fact that this compound was being sold undiluted, represents an imminent danger to anyone aiming to use this powder.*[xiii]

Pharmacological data suggest that the group of synthetic opioids that includes isotonitazene (along with etonitazene, metonitazene, and clonitazene) has potency similar to or greater than fentanyl based on their structural modifications. Etonitazene is reported to be the most potent of the group followed by isotonitazene and metonitazene. The toxicity of isotonitazene has not been extensively studied but recent association with drug user death leads forensic professionals to believe this new synthetic opioid retains the potential to cause widespread harm and is of public health concern.[xiv]

Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in overdose could lead to apnea, respiratory arrest, and death. This risk may be greater due to the fact that isotonitazene is the first of the benzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this family of opioids, including a lack of information on what doses to use and what effects the substance can have. The timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics. [xv]

Section 4: Finding of the Board

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

After a review of all available data, the State of Ohio Board of Pharmacy finds that isotonitazene:

1. Has no accepted medical use in treatment in this state; and
2. Poses an imminent hazard to the public health, safety, or welfare.

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

Section 5: Proposed Emergency Rule

4729:9-1-01.2 – Isotonitazene.

Pursuant to section 3719.45 of the Revised Code, the state board of pharmacy hereby adds to controlled substance schedule I the following opium derivative, including its 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:

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

---

[i] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Research & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[ii] Blanckaert, P. Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S. and Stove C. (2019), 'Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene', Drug Testing and Analysis. https://doi.org/10.1002/dta.2738

[iii] Krotulski, A., Papsun, D.M., Kacinko, S.L. and Logan, B.K., (2020), 'Isotonitazene quantitation and metabolite discovery in authentic forensic casework', Journal of Analytical Toxicology. https://doi.org/10.1093/jat/bkaa016

[iv] Krotulski, A., Papsun, D.M., Kacinko, S.L. and Logan, B.K., (2020), 'Isotonitazene quantitation and metabolite discovery in authentic forensic casework', Journal of Analytical Toxicology. https://doi.org/10.1093/jat/bkaa016

[v] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Research & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[vi] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Research & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[vii] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Research & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[viii] EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). April 2020. https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en

[ix] Dangerous new street drug found in two Maritime provinces: police. CTV News. March 6, 2020. https://atlantic.ctvnews.ca/dangerous-new-street-drug-found-in-two-maritime-provinces-police-1.4839958

[x] https://www.vice.com/en_us/article/wxebjb/40-americans-are-dying-every-month-from-taking-this-new-legal-opioid

[xi] Sprague, Jon. "Re: Isotonitazene." Message to Cameron McNamee. May 18, 2020. E-mail.

[xii] EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). April 2020. https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en

[xiii] Blanckaert, P. Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S. and Stove C. (2019), 'Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene', Drug Testing and Analysis. https://doi.org/10.1002/dta.2738

[xiv] "Potent Synthetic Opioid - Isotonitazene - Recently Identified in the Midwestern United States." The Center for Forensic Science Research & Education. November 2019. https://www.npsdiscovery.org/wp-content/uploads/2019/11/Public-Alert_Isotonitazene_NPS-Discovery_111919-1.pdf

[xv] EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). April 2020. https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en