DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA- 631]

Schedules of Controlled Substances: Placement of Isotonitazene in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final amendment; final order.

SUMMARY: With the issuance of this final order, the Administrator of the Drug Enforcement Administration is permanently placing *N*,*N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine (commonly known as isotonitazene), including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, in schedule I of the Controlled Substances Act. This scheduling action discharges the United States' obligations under the Single Convention on Narcotic Drugs (1961). This action continues to impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, import, export, engage in research or conduct instructional activities with, or possess), or propose to handle isotonitazene.

DATES: Effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION:

Legal Authority

The United States is a party to the 1961 United Nations Single Convention on Narcotic Drugs (Single Convention), March 30, 1961, 18 U.S.T. 1407, 570 U.N.T.S. 151, as amended by the 1972 Protocol. Article 3, paragraph 7 of the Single Convention requires that if the Commission on Narcotic Drugs (Commission) adds a substance to one of the schedules of such Convention, and the United States receives notification of such scheduling decision from the Secretary-General of the United Nations (Secretary-General), the United States, as a signatory Member State, is obligated to control the substance under its national drug control legislation. Under 21 U.S.C. 811(d)(1)), if control of a substance is required "by United States obligations under international treaties, conventions, or protocols in effect on October 27, 1970," the Attorney General must issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings required by 21 U.S.C. 811(a) or 812(b), and without regard to the procedures prescribed by 21 U.S.C. 811(a) and (b). The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the Drug Enforcement Administration (Administrator of DEA or Administrator). 28 CFR 0.100.

Background

On August 20, 2020, DEA issued a temporary scheduling order, placing isotonitazene (*N*,*N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine), in schedule I of the Controlled Substances Act (CSA). 85 FR 51342. That order was based on findings by the Acting Administrator of DEA (Acting Administrator) that the temporary scheduling of this substance was necessary to avoid an imminent hazard to the public safety; the order was codified at 21 CFR 1308.11(h)(48).

In November 2020, the Director-General of the World Health Organization recommended to the Secretary-General that isotonitazene be placed in Schedule I of the

Single Convention, as this substance has an opioid mechanism of action and similarity to drugs that are controlled in Schedule I of the Single Convention (*i.e.*, isotonitazene is similar to drugs such as morphine and fentanyl), and has dependence and abuse potential. On June 10, 2021, the Secretary-General advised the Secretary of State of the United States, by letter, that during its 64th session in April 2021, the Commission voted to place isotonitazene in Schedule I of the Single Convention (CND Apr/64/1).

Isotonitazene

As discussed in the background section, isotonitazene is temporarily controlled in schedule I of the CSA upon the Acting Administrator's finding it poses imminent hazard to the public safety. Isotonitazene has a pharmacological profile similar to etonitazene (schedule I), fentanyl (schedule II), and other schedule I and II synthetic opioids that act as mu-opioid receptor agonists. Because of the pharmacological similarities of isotonitazene to etonitazene (a potent mu-opioid agonist), the use of isotonitazene presents a high risk of abuse and has negatively affected users and communities. The abuse of isotonitazene has been associated with at least 48[1,2] fatalities in the United States between August 2019 and July 2020. The positive identification of this substance in post-mortem cases is a serious concern to the public safety.

Isotonitazene in the illicit drug market has been reported in Canada, Estonia, Germany, Latvia, Sweden, and the United States since April 2019[3]. Law enforcement reports demonstrate that isotonitazene is being illicitly distributed and abused. The illicit use and distribution of this substance are similar to that of heroin (schedule I) and

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[1] Shover CL, Falasinnu TO, Freedman RB, Humphreys K. Emerging Characteristics of Isotonitazene-Involved Overdose Deaths: A Case-Control Study. J Addict Med. 2020 Nov 23:10.1097/ADM.0000000000000775.

[2] Krotulski AJ, Papsun DM, Kacinko SL, Logan BK. Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. J Anal Toxicol. 2020 Jul 31;44(6):521-530.

[3] European Monitoring Centre for Drugs and Drug Addiction and Europol. (2020). EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1 methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended), Publications Office of the European Union, Luxembourg.

prescription opioid analgesics. According to 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 181 reports for isotonitazene between January 2019 and December 2020[4] (query date: May 28, 2021).

DEA is not aware of any claims or any medical or scientific literature suggesting that isotonitazene has a currently accepted medical use in treatment in the United States. In addition, the Department of Health and Human Services advised DEA, by letter dated March 31, 2020, that there were no investigational new drug applications or approved new drug applications for isotonitazene in the United States. Because isotonitazene is not formulated or available for clinical use as an approved medicinal product, all current use of this substance by individuals is based on their own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer such a drug.

Therefore, consistent with 21 U.S.C. 811(d)(1), DEA concludes that isotonitazene has no currently accepted medical use in treatment in the United States[5] and is most appropriately placed in schedule I of the CSA, the same schedule in which it currently resides. Because control is required under the Single Convention, DEA will not be initiating regular rulemaking proceedings to schedule isotonitazene pursuant to 21 U.S.C. 811(a).

Conclusion

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[4] Reports to NFLIS-Drug are still pending for 2020.

[5] Although, as discussed above, there is no evidence suggesting that isotonitazene has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by the Food and Drug Administration, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated: i. the drug's chemistry must be known and reproducible; ii. there must be adequate safety studies; iii. there must be adequate and well-controlled studies proving efficacy; iv. the drug must be accepted by qualified experts; and v. the scientific evidence must be widely available. 57 FR 10499 (1992), pet. for rev. denied, Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

In order to meet the United States' obligations under the Single Convention and because isotonitazene has no currently accepted medical use in treatment in the United States, the Administrator has determined that isotonitazene, including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, should remain in schedule I of the CSA.

Requirements for Handling

Isotonitazene has been controlled as a schedule I controlled substance since August 20, 2020. Upon the effective date of the final order contained in this document, isotonitazene will be permanently subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture of, distribution of, importation of, exportation of, engagement in research or conduct of instructional activities with, and possession of, schedule I controlled substances, including the following:

1. *Registration*. Any person who handles (manufactures, distributes, imports, exports, engages in research or conducts instructional activities with, or possesses), or who desires to handle, isotonitazene must be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of these substances in a manner not authorized by the CSA is unlawful and those in possession of any quantity of these substances may be subject to prosecution pursuant to the CSA.

2. *Disposal of stocks.* Isotonitazene must be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable federal, state, local, and tribal laws.

3. *Security*. Isotonitazene is subject to schedule I security requirements and must be handled and stored pursuant to 21 U.S.C. 821 and 823, and in accordance with 21 CFR

1301.71–1301.76. Non-practitioners handling isotonitazene must also comply with the employee screening requirements of 21 CFR 1301.90–1301.93.

4. *Labeling and packaging*. All labels, labeling, and packaging for commercial containers of isotonitazene must be in compliance with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302.

5. *Quota.* Only registered manufacturers are permitted to manufacture isotonitazene in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303.

6. *Inventory*. Every DEA registrant who possesses any quantity of isotonitazene has been required to keep an inventory of all stocks of this substance on hand as of August 20, 2020, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

7. *Records and Reports.* DEA registrants must maintain records and submit reports with respect to isotonitazene pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR parts 1304, 1312, and 1317, and § 1307.11. Manufacturers and distributors must submit reports regarding isotonitazene to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312.

8. *Order Forms*. All DEA registrants who distribute isotonitazene must continue to comply with order form requirements pursuant to 21 U.S.C. 828 and in accordance with 21 CFR part 1305.

9. *Importation and Exportation*. All importation and exportation of isotonitazene must continue to be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR parts 1304, 1312, and 1317.

10. *Liability*. Any activity involving isotonitazene not authorized by, or in violation of the CSA, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866 (Regulatory Planning and Review) and 13563 (Improving Regulation and Regulatory Review)

This action is not a significant regulatory action as defined by Executive Order (E.O.) 12866 (Regulatory Planning and Review), section 3(f), and the principles reaffirmed in E.O. 13563 (Improving Regulation and Regulatory Review); and, accordingly, this action has not been reviewed by the Office of Management and Budget (OMB).

Executive Order 12988, Civil Justice Reform

This action meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This action does not have federalism implications warranting the application of E.O. 13132. This action does not have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

This action does not have tribal implications warranting the application of E.O. 13175. The action does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the

distribution of power and responsibilities between the Federal Government and Indian tribes.

Administrative Procedure Act

The CSA provides for an expedited scheduling action where control is required by the United States' obligations under international treaties, conventions, or protocols. 21 U.S.C. 811(d)(1). If control is required pursuant to such international treaty, convention, or protocol, the Attorney General, as delegated to the Administrator, must issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings or procedures otherwise required for scheduling actions. *Id.*

In accordance with 21 U.S.C. 811(d)(1), scheduling actions for drugs that are required to be controlled by the United States' obligations under international treaties, conventions, or protocols in effect on October 27, 1970, shall be issued by order (as compared to scheduling by rule pursuant to 21 U.S.C. 811(a)). Therefore, DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, do not apply to this scheduling action. In the alternative, even if this action does constitute "rule making" under 5 U.S.C. 551(5), this action is exempt from the notice and comment requirements of 5 U.S.C. 553 pursuant to 5 U.S.C. 553(a)(1) as an action involving a foreign affairs function of the United States because it is being done pursuant to 21 U.S.C. 811(d)(1), which requires that the United States comply with its obligations under the specified international agreements.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601–612) applies to rules that are subject to notice and comment under section 553(b) of the APA or any other law. As explained above, the CSA exempts this final order from notice and comment. Consequently, the RFA does not apply to this action.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501–3521. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.*, DEA has determined and certifies that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Congressional Review Act

This order is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. However, DEA is submitting the required reports to the Government Accountability Office, the House, and the Senate under the CRA.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

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

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

2. In § 1308.11:

a. Redesignate paragraphs (b)(46) through (90) as paragraphs (b)(47) through (91);

b. Add new paragraph (b)(46); and

c. Remove and reserve paragraph (h)(48).

The addition reads as follows:

§ 1308.11 Schedule I.

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(b) * * *

(46) Isotonitazene (*N*,*N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine)…….....9614

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Anne Milgram,
Administrator.
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