



DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-716]

Schedules of Controlled Substances: Temporary Placement of Brorphine in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Proposed amendment; notice of intent.

SUMMARY: The Acting Administrator of the Drug Enforcement Administration is issuing this notice of intent to publish a temporary order to schedule 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (commonly known as brorphine), 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, in schedule I of the Controlled Substances Act. When it is issued, the temporary scheduling order will impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess) or propose to handle brorphine.

DATES: [INSERT 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; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152;

Telephone: (571) 362-8207.

SUPPLEMENTARY INFORMATION: This document is issued pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The Drug Enforcement Administration (DEA) intends to issue a temporary scheduling order (in the form of a temporary amendment) to add brophine to schedule I under the Controlled Substances Act (CSA).¹ The temporary scheduling order will be published in the *Federal Register* on or after [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Legal Authority

The CSA provides the Attorney General (as delegated to the Administrator of DEA (Administrator) pursuant to 28 CFR 0.100) with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b), if he finds that such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). In addition, if proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1) while the substance is temporarily controlled under section 811(h), the Administrator may extend the temporary scheduling for up to one year. 21 U.S.C. 811(h)(2).

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under 21 U.S.C. 812, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355. 21 U.S.C. 811(h)(1); 21 CFR part 1308.

Background

¹ Though DEA has used the term “final order” with respect to temporary scheduling orders in the past, this notice of intent adheres to the statutory language of 21 U.S.C. 811(h), which refers to a “temporary scheduling order.” No substantive change is intended.

Section 811(h)(4) requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance in schedule I of the CSA.² The Acting Administrator transmitted notice of his intent to place bupropion in schedule I on a temporary basis to the Assistant Secretary for Health of HHS (Assistant Secretary) by letter dated September 22, 2020. The Assistant Secretary responded to this notice by letter dated October 27, 2020, and advised that based on a review by the Food and Drug Administration (FDA), there are currently no investigational new drug applications or approved new drug applications for bupropion. The Assistant Secretary also stated that HHS had no objection to the temporary placement of bupropion in schedule I of the CSA. Bupropion is not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for bupropion under 21 U.S.C. 355.

To find that placing a substance temporarily in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator is required to consider three of the eight factors set forth in 21 U.S.C. 811(c): The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(h)(3). Consideration of these factors includes actual abuse; diversion from legitimate channels; and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. 21 U.S.C. 811(h)(1). Substances in schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. 21 U.S.C. 812(b)(1).

² The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

Brorphine

The availability of synthetic opioids on the illicit drug market continues to pose an imminent hazard to the public safety. Adverse health effects associated with the abuse of synthetic opioids and the increased popularity of these substances have been serious concerns in recent years. The presence of new synthetic opioids with no approved medical use exacerbates the unprecedented opioid epidemic the United States continues to experience. The trafficking and abuse of new synthetic opioids are deadly new trends.

The identification of brorphine on the illicit drug market has been reported in the United States, Canada, Belgium, and Sweden. Data obtained from preclinical pharmacology studies show that brorphine has a pharmacological profile similar to that of other potent opioids such as morphine and fentanyl, schedule II controlled substances. Because of the pharmacological similarities between brorphine and other potent opioids, the use of brorphine presents a high risk of abuse and may negatively affect users and their communities. The positive identification of this substance in law enforcement seizures and post-mortem toxicology reports is a serious concern to the public safety. The abuse of brorphine has been associated with at least seven fatalities between June 2020 and July 2020 in the United States. Thus, brorphine poses an imminent hazard to public safety.

Available data and information for brorphine, as summarized below, indicates that this substance has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. DEA's three-factor analysis is available in its entirety under "Supporting and Related Material" of the public docket for this action at www.regulations.gov under Docket Number DEA-716.

Factor 4. History and Current Pattern of Abuse

Brorphine is part of a structural class of compounds known as substituted piperidine benzimidazolones. The general synthesis of brorphine was first reported in the literature in 2018. Brorphine is not an approved pharmaceutical product and is not approved for medical use anywhere in the world. The Assistant Secretary, by a letter to DEA dated October 27, 2020, stated that there are no FDA-approved new drug applications or investigational new drug applications for brorphine in the United States; hence, there is no legitimate channel for brorphine as a marketed drug product. The appearance of brorphine on the illicit drug market is similar to other designer drugs trafficked for their psychoactive effects.

Since 2014, numerous synthetic opioids structurally related to fentanyl and several synthetic opioids from other structural classes have begun to emerge on the illicit drug market as evidenced by the identification of these drugs in forensic drug exhibits and toxicology samples. Beginning in June 2019, brorphine emerged in the U.S. illicit, synthetic drug market as evidenced by brorphine's identification in drug seizures. Between July and September of 2019, brorphine was first reported in drug casework in Canada and was first reported in police seizures in Sweden in March 2020.³

Brorphine has been encountered by U.S. law enforcement in powder form. In the United States, brorphine has been identified as a single substance and in combination with other substances. Twenty reports of brorphine have been reported in the National Forensic Laboratory Information System (NFLIS) in 2019 and 2020 from three different states (see Factor 5).⁴ In several NFLIS encounters, brorphine was found in combination with heroin (a schedule I substance) and fentanyl (a schedule II substance). In reports from the

³ Health Canada Drug Analysis Service (2019); Analyzed Drug Report Canada 2019 – Q3 (July to September); European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2020); EU Early Warning System Situation Report, Situation report 1 – June 2020.

⁴ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle the nation's drug analysis cases. NFLIS-Drug participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is currently 98.5 percent. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, December 12, 2011. NFLIS data was queried on August 18, 2020.

Northeastern Illinois Regional Crime Laboratory, suspected heroin/fentanyl powders were analyzed and found to be bromphine in combination with flualprazolam, a non-scheduled benzodiazepine, and diphenhydramine, an over-the-counter antihistamine.⁵

Post-mortem toxicology samples collected and submitted to National Medical Services (NMS) Laboratory⁶ in June and July 2020 verified the appearance of bromphine. Bromphine was first reported by the Center for Forensic Science Research and Education (CFSRE) – Novel Psychoactive Substance (NPS) Discovery Program (under the novel psychoactive substances discovery program, in collaboration with NMS Labs) in July 2020. In seven post-mortem toxicology reports in June 2020 and July 2020, bromphine was found in combination with fentanyl, flualprazolam, and heroin. Evidence suggests that individuals are using bromphine as a replacement to heroin or other opioids, either knowingly or unknowingly.

Factor 5. Scope, Duration, and Significance of Abuse

Bromphine has been described as a potent synthetic opioid and evidence suggests it is being abused for its opioidergic effects (see Factor 6). According to a recent publication by CFSRE - NPS Discovery, bromphine has been positively identified in seven death investigation cases spanning between June 2020 and July 2020. These cases correspond to three states—Illinois (3), Minnesota (3), and Arizona (1). Most (n = 6) of the decedents were male. The decedents' ages ranged between 40's and 60's with an average age of 52 years. Other substances identified in postmortem blood specimens obtained from these decedents include flualprazolam, a nonscheduled benzodiazepine (n = 5), fentanyl, a schedule II substance (n = 7), and heroin, a schedule I substance (n = 4).

⁵ Email communications with Northeastern Illinois Regional Crime Laboratory, dated 7/1/2020 and 6/11/2020.

⁶ NMS Labs, in collaboration with the Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation and the Organized Crime Drug Enforcement Task Force at the United States Department of Justice, has received funding from the Centers for Disease Control and Prevention to develop systems for the early identification and notification of novel psychoactive substances in the drug supply within the United States.

The appearance of benzodiazepines and other opioids is common with polysubstance abuse.

NFLIS registered 20 reports of bromphine from Ohio (4), Pennsylvania (1), and Wisconsin (15) in 2019 and 2020. NFLIS was queried on August 18, 2020, for bromphine. Due to the rapid appearance of the drug, bromphine is most likely under reported as forensic laboratories secure reference standards for the confirmative identification and reporting of this substance.

The population likely to abuse bromphine appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, fentanyl, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in samples obtained from bromphine seizures and post-mortem toxicology reports. Because abusers of bromphine are likely to obtain it through unregulated sources, the identity, purity, and quantity of bromphine are uncertain and inconsistent, thus posing significant adverse health risks to the end user. The misuse and abuse of opioids have been demonstrated and are well-characterized. According to the most recent data from the National Survey on Drug Use and Health (NSDUH),⁷ as of 2018, an estimated 10.3 million people aged 12 years or older misused opioids in the past year, including 9.9 million prescription pain reliever misusers and 808,000 heroin users. In 2018, an estimated 2 million people had an opioid use disorder which included 1.7 million people with a prescription pain reliever use disorder and 500,000 people with heroin use disorder. This population abusing opioids is likely to be at risk of abusing bromphine. Individuals who initiate use

⁷ The National Survey on Drug Use and Health (NSDUH), formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of nonmedical use of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The NSDUH provides yearly national and state level estimates of drug abuse, and includes prevalence estimates by lifetime (*i.e.*, ever used), past year, and past month abuse or dependence.

(*i.e.*, use a drug for the first time) of brophine are likely to be at risk of developing substance use disorder, overdose, and death similar to that of other opioid analgesics (*e.g.*, fentanyl, morphine, etc.). Law enforcement reports demonstrate that brophine is being illicitly distributed and abused.

Factor 6. What, if Any, Risk There Is to the Public Health

The increase in opioid overdose deaths in the United States has been exacerbated recently by the availability of potent synthetic opioids on the illicit drug market. Data obtained from pre-clinical studies demonstrate that brophine exhibits a pharmacological profile similar to that of other mu (μ)-opioid receptor agonists. Data from *in vitro* studies completed in 2020 showed that brophine binds to and activates the μ -opioid receptors. In the [³⁵S]GTP γ S cell-based receptor assay, brophine, similar to fentanyl, acted as a μ -opioid receptor agonist. Brophine's activation of μ -opioid receptor was also shown to involve recruitment of beta-arrestin-2, a regulatory protein whose interaction with the μ -opioid receptor has been implicated in the adverse effects of μ -opioid receptor activation. Brophine binds to and activates the μ -opioid receptor and has efficacy on scale with fentanyl. It is well established that substances that act as μ -opioid receptor agonists have a high potential for addiction and can induce dose-dependent respiratory depression.

As with any μ -opioid receptor agonist, the potential health and safety risks for users of brophine are high. The public health risks associated to the abuse of heroin and other μ -opioid receptor agonists are well established and have resulted in large numbers of drug treatment admissions, emergency department visits, and fatal overdoses. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids other than methadone, are predominantly responsible for drug overdose deaths in recent years. A CDC report shows that, from 2013 to 2018, opioid-related overdose deaths in the United States increased from 25,052 to 46,802.

Of the drug overdose deaths for 2018, opioids were involved in about 69.5 percent of all drug-involved overdose deaths.

In the United States, the abuse of opioid analgesics has resulted in large numbers of treatment admissions, emergency department visits, and fatal overdoses. The introduction of potent synthetic opioids such as brophine into the illicit market may serve as a portal to problematic opioid use for those seeking these powerful opioids.

Brophine has been co-identified with other substances in seven post-mortem toxicology cases in June and July of 2020. These substances include other opioids such as fentanyl and heroin, and other substance classes such as benzodiazepines. These deaths occurred in three states: Illinois, Arizona, and Minnesota. Information gathered from case history findings shows that brophine use is similar to that of classic opioid agonists. As documented by toxicology reports, poly-substance abuse remains common in fatalities associated with the abuse of brophine.

Finding of Necessity of Schedule I Placement to Avoid Imminent Hazard to Public Safety

In accordance with 21 U.S.C. 811(h)(3), based on the available data and information summarized above, the uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of brophine pose an imminent hazard to the public safety. DEA is not aware of any currently accepted medical uses for brophine in the United States. A substance meeting the statutory requirements for temporary scheduling, found in 21 U.S.C. 811(h)(1), may only be placed in schedule I. Substances in schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. Available data and information for brophine indicate that this substance has a high potential for abuse, no currently accepted medical use in treatment in the United States,

and a lack of accepted safety for use under medical supervision. As required by 21 U.S.C. 811(h)(4), the Acting Administrator, through a letter dated September 22, 2020, notified the Assistant Secretary of DEA's intention to temporarily place bupropion in schedule I.

Conclusion

This notice of intent provides the 30-day notice pursuant to 21 U.S.C. 811(h)(1) of DEA's intent to issue a temporary scheduling order. In accordance with 21 U.S.C. 811(h)(1) and (3), the Acting Administrator considered available data and information, herein set forth the grounds for his determination that it is necessary to temporarily schedule bupropion in schedule I of the CSA, and finds that placement of this substance in schedule I of the CSA is necessary in order to avoid an imminent hazard to the public's safety.

The temporary placement of bupropion in schedule I of the CSA will take effect pursuant to a temporary scheduling order, which will not be issued before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. Because the Acting Administrator hereby finds that it is necessary to temporarily place bupropion in schedule I to avoid an imminent hazard to the public safety, the temporary order scheduling this substance will be effective on the date the order is published in the *Federal Register*, and will be in effect for a period of two years, with a possible extension of one additional year, pending completion of the regular (permanent) scheduling process. 21 U.S.C. 811(h)(1) and (2). It is the intention of the Acting Administrator to issue a temporary scheduling order as soon as possible after the expiration of 30 days from the date of publication of this document. Upon publication of the temporary order, bupropion will then be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution,

reverse distribution, importation, exportation, research, conduct of instructional activities and chemical analysis, and possession.

The CSA sets forth specific criteria for scheduling a drug or other substance. Regular scheduling actions in accordance with 21 U.S.C. 811(a) are subject to formal rulemaking procedures done “on the record after opportunity for a hearing” conducted pursuant to the provisions of 5 U.S.C. 556 and 557. 21 U.S.C. 811. The regular scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions that conclude the regular scheduling process of formal rulemaking are subject to judicial review. 21 U.S.C. 877. Temporary scheduling orders are not subject to judicial review. 21 U.S.C. 811(h)(6).

Regulatory Analyses

The CSA provides for a temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). As provided in this subsection, the Administrator (as delegated by the Attorney General) may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from: (1) The publication of a notice in the *Federal Register* of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Secretary of HHS.

Inasmuch as 21 U.S.C. 811(h)(1) directs that temporary scheduling actions be issued by order and sets forth the procedures by which such orders are to be issued, including the requirement of a publication in the *Federal Register* of a notice of intent, the notice-and-comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, do not apply to this notice of intent. The APA expressly differentiates between an order and a rule, as it defines an “order” to mean a “final

disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency *in a matter other than rule making.*” 5 U.S.C. 551(6) (emphasis added). The specific language chosen by Congress indicates an intention for DEA to proceed through the issuance of an *order* instead of proceeding by rulemaking. Given that Congress specifically requires the Administrator to follow rulemaking procedures for *other* kinds of scheduling actions, *see* 21 U.S.C. 811(a), it is noteworthy that, in 21 U.S.C. 811(h)(1), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

In the alternative, even assuming that this notice of intent might be subject to section 553 of the APA, the Acting Administrator finds that there is good cause to forgo the notice-and-comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency to avoid an imminent hazard to the public safety.

Although DEA believes this notice of intent to issue a temporary scheduling order is not subject to the notice-and-comment requirements of section 553 of the APA, DEA notes that in accordance with 21 U.S.C. 811(h)(4), the Acting Administrator took into consideration comments submitted by the Assistant Secretary in response to the notice that DEA transmitted to the Assistant Secretary pursuant to such subsection.

Further, DEA believes that this temporary scheduling action is not a “rule” as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, DEA is not required by section 553 of the APA or any other law to publish a general notice of proposed rulemaking.

In accordance with the principles of Executive Orders (E.O.) 12866, 13563, and 13771, this notice of intent is not a significant regulatory action. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866 classifies a “significant regulatory action,” requiring review by the Office of Management and Budget (OMB), as any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of \$100 million or more or adversely affect in a material way the economy; a sector of the economy; productivity; competition; jobs; the environment; public health or safety; or State, local, or tribal governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs, or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President’s priorities, or the principles set forth in the Executive Order. Because this is not a rulemaking action, this is not a significant regulatory action as defined in Section 3(f) of E.O. 12866. In addition, this action does not meet the definition of an E.O. 13771 regulatory action, and the repeal and cost offset requirements of E.O. 13771 have not been triggered.

This action will 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. Therefore, in accordance with E.O. 13132 (Federalism), it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

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 proposes to amend 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, add paragraph (h)(49) to read as follows:

§ 1308.11 Schedule I

* * * * *

(h) * * *

(49) 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, its isomers, esters, ethers, salts and salts of isomers, esters and ethers (Other names: bromphine; 1-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one).....9098

* * * * *

Timothy J. Shea,
Acting Administrator.