DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–837]

Schedules of Controlled Substances: Removal of [18F]FP–CIT From Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Drug Enforcement Administration removes [18F]FP–CIT (chemical names: [18F]N-ω-fluoropropyl-β-CIT; fluorine-18-N-3-fluoropropyl-2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane; [18F]fluoropropylcarbomethoxy nortropane) from the schedules of the Controlled Substances Act. Prior to the effective date of this rule, [18F]FP–CIT was a schedule II controlled substance because it can be derived from cocaine, a schedule II substance, via ecgonine, also a schedule II substance. This action removes the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule II controlled substances, on persons who handle (manufacture, distribute, reverse distribute, dispense, engage in research, import, export, conduct instructional activities or chemical analysis with, or possess) or propose to handle [18F]FP–CIT.

DATES: Effective December 21, 2022.

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

SUPPLEMENTARY INFORMATION:

Legal Authority

Under the Controlled Substances Act (CSA), each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause.[1] The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c) and the current list of scheduled substances is published at 21 CFR part 1308.

Pursuant to 21 U.S.C. 811(a)(2), the Attorney General may, by rule, ''remove any drug or other substance from the schedules if he finds that the drug or other substance does not meet the requirements for inclusion in any schedule.'' The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the Drug Enforcement Administration (DEA).[2]

The CSA provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated by the Attorney General on the petition of any interested party.[3] This action was initiated by a petition to remove [18F]FP–CIT from the list of scheduled controlled substances of the CSA, and is supported by, *inter alia,* a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (HHS) and an evaluation of all relevant data by DEA. This action removes the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule II controlled substances, on persons who handle or propose to handle [18F]FP–CIT.

Background

[18F]FP–CIT (chemical names: [18F]N-ω-fluoropropyl-β-CIT; fluorine-18-N-3-fluoropropyl-2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane; [18F]fluoropropylcarbomethoxy nortropane) is described as a diagnostic substance that is used in assisting the evaluation of adult patients with suspected Parkinsonian syndromes. It is an entity used in the visualization of striatal dopamine transporters (DAT) using positron emission tomography (PET) imaging. [18F]FP–CIT is not yet approved by the United States Food and Drug Administration (FDA) and no New Drug Application (NDA) for [18F]FP–CIT or any [18F]FP–CIT-containing drug has been submitted to FDA.

[18F]FP–CIT is structurally similar to [123I]ioflupane, known as DaTscan or [123I]FP–CIT. Both [18F]FP–CIT and [123I]ioflupane were developed as clinical diagnostic substances to visualize DAT and contain the same tracer amount of the precursor, ecgonine. The only difference between these two compounds is the radiotracer (^{123}I versus ^{18}F). On January 14, 2011, FDA approved the NDA for [123I]ioflupane-containing drug product, DaTscan, for use to visualize striatal DAT in the brains of adult patients with suspected Parkinsonian syndromes using single photon emission computed tomography (SPECT) imaging. DEA removed [123I]ioflupane from schedule II of the CSA on September 11, 2015.[4]

The starting material for the synthesis of [18F]FP–CIT and [123I]ioflupane is *N*-nor-β-CIT (2β-carbomethoxy-3β -(4-iodophenyl) nortropane), which is derived from cocaine, a schedule II substance, via ecgonine (a schedule II substance). Thus, by definition[5] [18F]FP–CIT is currently controlled in schedule II of the CSA. On June 28, 2018, DEA received a petition from Advanced Imaging Projects to initiate proceedings to amend 21 CFR 1308.12(b)(4) so as to decontrol [18F]FP–CIT (proposed tradename Fluoroseek) from schedule II of the CSA. On October 6, 2018 and November 6, 2018, DEA received supplemental information from the Petitioner; DEA accepted the petition for filing on November 28, 2018.

DEA and HHS Eight-Factor Analyses

Pursuant to 21 U.S.C. 811(b), on May 2, 2019, DEA provided the necessary data on [18F]FP–CIT, along with the petition, to HHS with a request for a scientific and medical evaluation and scheduling recommendation for [18F]FP–CIT. On April 16, 2021, DEA received from HHS a scientific and medical evaluation, conducted by FDA[6], and a recommendation to remove [18F]FP–CIT from all schedules of the CSA. Following consideration of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, HHS recommended that [18F]FP–CIT be removed from all schedules of control of the CSA. In response, DEA conducted its own eight-factor analysis of [18F]FP–CIT pursuant to 21 U.S.C. 811(c). Both DEA and HHS analyses are available in their entirety in the public docket for this rule (Docket Number DEA–837) at *https://www.regulations.gov* under ''Supporting and Related Material''.

Determination To Decontrol [18F]FP–CIT

On November 4, 2021, DEA published a notice of proposed rulemaking (NPRM) to remove [18F]FP–CIT from the schedules of the CSA. 86 FR 60785. The NPRM provided an opportunity for interested persons to file a request for a

[1] 21 U.S.C. 812.

[2] 28 CFR 0.100.

[3] 21 U.S.C. 811(a).

[4] 80 FR 54715.

[5] 21 CFR 1308.12(b)(4).

[6] As discussed in a memorandum of understanding entered into by FDA and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. 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.

hearing in accordance with DEA regulations by December 6, 2021. No requests for such a hearing were received by DEA. The NPRM also provided an opportunity for interested persons to submit comments on the proposal on or before December 6, 2021.

Comments Received

DEA received six comments on the NPRM to remove [18F]FP–CIT from control.

Support for rulemaking: Five commenters supported decontrol of [18F]FP–CIT. Four of these commenters noted the potential therapeutic benefit of this radiolabeled substance related to diagnosing Parkinson's disease.

DEA Response: DEA appreciates these comments in support of this rulemaking.

Opposition to rulemaking: One commenter opposed decontrol of [18F]FP–CIT, suggesting rescheduling cocaine, or any cocaine derivative, is a safety concern and such rescheduling would wrongly signal that cocaine is less harmful than cannabis.

DEA Response: DEA does not agree with the commenter's concern about harm. [18F]FP–CIT is derived from cocaine, a schedule II substance, via ecgonine, a schedule II substance. As described below [18F]FP–CIT is manufactured as a radiopharmaceutical containing minute amounts of this radiolabeled substance in limited and specified places (*e.g.,* nuclear pharmacies) and distributed and handled under a highly regulatory environment.

As stated by FDA in its scientific and medical evaluation, radioligands in general are used in very dilute, or low dose formulations, and are unlikely to produce pharmacological effect and be abused, which is the case for the [123I]ioflupane-containing drug product, DaTscan. Similar to [123I]ioflupane, [18F]FP–CIT is expected to be present in low concentration in the final drug product, thus it is unlikely that [18F]FP–CIT will produce stimulant effects or be abused. Further, due to its radioactive nature and similar to the handling of [123I]ioflupane, [18F]FP–CIT will be restricted to nuclear medicine departments and radiopharmacies authorized to handle radioactive substances. Both nuclear medicine departments and radiopharmacies are highly regulated by multiple federal, state and local regulating agencies.

Based on the totality of the available scientific data, FDA stated that [18F]FP–CIT does not conform with the findings for schedule II in 21 U.S.C. 812(b)(2) or in any other schedule as set forth in 21 U.S.C. 812(b). Based on FDA's scientific and medical review of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, HHS recommended that [18F]FP–CIT be removed from all schedules of the CSA. Pursuant to 21 U.S.C. 811(b), the recommendations of HHS shall be binding on DEA as to such scientific and medical matters and if the Secretary recommends that a drug or other substance not be controlled, DEA shall not control the drug or other substances. As stated in the NPRM, after careful review of all relevant data including HHS's scientific and medical evaluation and scheduling recommendation, DEA concurred with HHS's assessment that there is no evidence that [18F]FP–CIT has a comparable potential for abuse relative to schedule V substances. DEA is therefore promulgating this final rule to remove [18F]FP–CIT from control under the CSA and notes that non-radiolabeled FP–CIT remains a schedule II substance.

Scheduling Conclusion

Based on consideration of all comments, the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, the Administrator finds that these facts and all relevant data demonstrate that [18F]FP–CIT does not meet the requirements for inclusion in any schedule. As such, DEA is removing [18F]FP–CIT form control under the CSA.

Regulatory Analyses

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

In accordance with 21 U.S.C. 811(a), this scheduling action is subject to formal rulemaking procedures done ''on the record after opportunity for a hearing,'' which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for removing a drug or other substance from the list of controlled substances. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

Executive Order 12988, Civil Justice Reform

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

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. This rule 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.

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612), has reviewed this rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove [18F]FP–CIT from the list of schedules of the CSA. This action will remove regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances for handlers and proposed handlers of [18F]FP–CIT. Accordingly, it has the potential for some economic impact in the form of cost savings.

This rule will affect all persons who handle, or propose to handle, [18F]FP–CIT. [18F]FP–CIT is not currently available or marketed in any country. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the distribution and dispensing rates, if any, of [18F]FP–CIT, DEA is unable to determine the number of entities and small entities which might handle [18F]FP–CIT. In some instances where a controlled pharmaceutical drug is removed from the schedules of the CSA, DEA is able to quantify the estimated number of affected entities and small entities because the handling of the drug is expected to be limited to DEA registrants even after removal from the schedules. In such instances, DEA's knowledge of its registrant population forms the basis for estimating the number of affected entities and small entities. However, DEA does not have a basis to estimate whether [18F]FP–CIT is

expected to be handled by persons who hold DEA registrations, by persons who are not currently registered with DEA to handle controlled substances, or both. Therefore, DEA is unable to estimate the number of entities and small entities who plan to handle [18F]FP–CIT.

Although DEA does not have a reliable basis to estimate the number of affected entities and quantify the economic impact of this final rule, a qualitative analysis indicates that this rule is likely to result in some cost savings. Any person planning to handle [18F]FP–CIT will realize cost savings in the form of saved DEA registration fees, and the elimination of physical security, recordkeeping, and reporting requirements.

Because of these factors, DEA projects that this rule will not result in a significant economic impact on a substantial number of small entities.

Administrative Procedure Act

DEA finds that good cause exists for adopting this rule as a final rule with an immediate effective date under 5 U.S.C. 553(d) because this final rule relieves a restriction.

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 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.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995.[7]

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. However, pursuant to the CRA, DEA is submitting a copy of the final rule to both Houses of Congress and to the Comptroller General.

Signing Authority

This document of the Drug Enforcement Administration was signed on November 14, 2022, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the **Federal Register**.

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, 21 CFR part 1308 is amended to read as follows:

PART 1308— SCHEDULES OF CONTROLLED SUBSTANCES

■ 1. The authority citation for 21 CFR part 1308 continues to read as follows:

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

■ 2. In § 1308.12, revise paragraphs (b)(4)(i) and (ii) and add paragraph (b)(4)(iii) to read as follows:

§ 1308.12 Schedule II.

* * * * *

(b) * * *

(4) * * *

(i) Decocainized coca leaves or extraction of coca leaves, which extractions do not contain cocaine or ecgonine;

(ii) [123I]ioflupane; or

(iii) [18F]FP–CIT.

* * * * *

Scott Brinks,

Federal Register Liaison Officer, Drug Enforcement Administration.

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–477]

Schedules of Controlled Substances: Placement of Zipeprol in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Drug Enforcement Administration places zipeprol (chemical name: 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol), 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 action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. This action imposes 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, conduct instructional activities or chemical analysis with, or possess), or propose to handle zipeprol.

DATES: Effective December 21, 2022.

FOR FURTHER INFORMATION CONTACT: Dr. 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 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543, 1019 U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by 21 U.S.C. 811(d)(2)–(4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention adding a drug or other substance to a specific schedule, the Secretary of the Department of Health and Human Services (HHS),[1] after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance.[2] Based on those

[7] 44 U.S.C. 3501–3521.

[1] As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518 (March 8, 1985). 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).

[2] 21 U.S.C. 811(d)(3).