DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–949]

Schedules of Controlled Substances: Placement of Daridorexant in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: On January 7, 2022, the United States Food and Drug Administration approved a new drug application for QUIVIVIQ (daridorexant) tablets for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place daridorexant and its salts in schedule IV of the Controlled Substances Act (CSA). In accordance with the CSA, as amended by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing daridorexant in schedule IV, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of such isomers is possible within the specific chemical designation, thereby facilitating the commercial distribution of QUIVIVIQ as a lawful controlled substance.

DATES: The effective date of this rule is April 7, 2022. Comments must be submitted electronically or postmarked on or before May 9, 2022. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before May 9, 2022.

ADDRESSES: Interested persons may file written comments on this rulemaking in accordance with 21 U.S.C. 811(j)(3) and 21 CFR 1308.43(g). To ensure proper handling of comments, please reference ''Docket No. DEA–949'' on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to *http://www.regulations.gov and follow the online instructions at that site for submitting comments.* Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, VA 22152.
- *Hearing requests:* All requests for hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

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

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. The Drug Enforcement Administration (DEA) will make comments available, unless reasonable cause is given, for public inspection online at *http://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want DEA to make it publicly available, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want DEA to make it publicly available, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

DEA will generally make available in publicly redacted form comments containing personal identifying information and confidential business information identified, as directed above. If a comment has so much confidential business information or personal identifying information that DEA cannot effectively redact it, DEA may not make available publicly all or part of that comment. Comments posted to *http://www.regulations.gov* may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as confidential as directed above.

An electronic copy of this document and supplemental information to this interim final rule (IFR) are available at *http://www.regulations.gov* for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking ''on the record after opportunity for a hearing''. Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and such requests must include a statement of the person's interests in the proceeding and the

objections or issues, if any, concerning which the person desires to be heard. 21 CFR 1316.47(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for hearings and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above.

Background and Legal Authority

Under the Controlled Substances Act (CSA), as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (section 2(b) of Pub. L. 114–89), DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the Food and Drug Administration (FDA). As provided in 21 U.S.C. 811(j), this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of the Department of Health and Human Services (HHS) has advised DEA that an NDA has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS), and that it appears that such drug has an abuse potential; and (2) the Secretary recommends that DEA control the drug in schedule II, III, IV, or V pursuant to 21 U.S.C. 811(a) and (b). In these circumstances, DEA is required to issue an IFR controlling the drug within 90 days.

Subsection (j)(2) states that the 90-day timeframe starts the later of (1) the date DEA receives HHS' scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Subsection (j)(3) specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause therefore. Thus, the purpose of subsection (j) is to speed the process by which DEA schedules newly approved drugs that are currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.[1]

[1] Given the parameters of subsection (j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

Subsection (j)(3) further provides that the IFR shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of 21 U.S.C. 811(b) through (d) and 812(b).

Daridorexant, chemically known as [(S)-2-(5-chloro-4-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-methylpyrrolidin-1-yl](5-methoxy-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone, is a new molecular entity (NME) with CNS activity. Daridorexant is a dual orexin receptor antagonist that inhibits the orexin neuropeptide-induced activation of the orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R) subtypes. Daridorexant shares chemical structure and pharmacological mechanism of action with certain schedule IV CNS depressants such as suvorexant and lemborexant.

On January 8, 2021, Idorsia Pharmaceuticals, Ltd (Sponsor) submitted an NDA to FDA for QUIVIVIQ (daridorexant) tablets for use as a treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. On January 7, 2022, DEA received notification that FDA, on the same date, approved this NDA. The recommended dosage is 25–50 mg once per night, taken orally within 30 minutes before going to bed, with at least seven hours remaining prior to planned awakening.

Determination To Schedule Daridorexant

On December 22, 2021, DEA received from HHS a scientific and medical evaluation entitled ''Basis for the Recommendation to Control Daridorexant and its Salts in schedule IV of the Controlled Substances Act'' and a scheduling recommendation. Pursuant to 21 U.S.C. 811(b) and (c), this document contained an eight-factor analysis of the abuse potential, legitimate medical use, and dependence liability of daridorexant, along with HHS's recommendation to control daridorexant and its salts under schedule IV of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review pursuant to 21 U.S.C. 811(c). DEA concluded that daridorexant meets the 21 U.S.C. 812(b)(4) criteria for placement in schedule IV of the CSA.

Pursuant to subsection 811(j), and based on HHS' scheduling recommendation, the approval of the NDA by HHS/FDA, and DEA's determination, DEA is issuing this IFR to schedule daridorexant as a schedule IV controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both DEA and HHS analyses are available in their entirety under ''Supporting Documents'' in the public docket for this interim final rule at *http://www.regulations.gov,* under Docket Number ''DEA–949.'' Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. Its Actual or Relative Potential for Abuse

Daridorexant is an NME that has not been marketed in the United States or any country; evidence regarding its diversion, illicit manufacturing, or deliberate ingestion is lacking. There are no reports of law enforcement encounters of daridorexant in the National Forensic Laboratory Information System (NFLIS) database.[2] However, daridorexant is related in action to schedule IV depressants such as suvorexant and lemborexant. It is thus reasonable to assume that daridorexant may be diverted from legitimate channels, used contrary to or without medical advice, and otherwise abused so as to create hazards to the users and to the safety of the community to an extent similar to that of schedule IV CNS depressants. In clinical studies, daridorexant produced abuse-related effects in humans similar to suvorexant and zolpidem (schedule IV sedatives) and shares pharmacological mechanism of action similar to suvorexant and lemborexant; thus, it is likely to be abused for its sedative effects contrary to medical advice.

2. Scientific Evidence of Its Pharmacological Effects, if Known

Daridorexant shares pharmacological profiles with other dual orexin receptor antagonists such as suvorexant and lemborexant, schedule IV CNS depressants. Data from the orexin binding studies demonstrated that daridorexant behaved as an insurmountable antagonist at the dual orexin receptors (OXIR and OX2R).

[2] NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. It systematically collects results from drug chemistry analyses conducted by State and local forensic laboratories. NFLIS data were queried on January 18, 2022.

Daridorexant is similar to suvorexant in its potency and duration of action at OX1R; however, it is more potent and has double the occupancy time as suvorexant at OX2R.

In animal studies, oral doses of daridorexant (100, 300, and 1000 mg/kg) produced transient decrease in rectally measured body temperature and increased incidence of whole-body tremors. Dose-dependent decline in activity was observed in unstimulated rats. In a study conducted to measure locomotor activity following daridorexant administration, rats given single oral dose of 300 mg/kg showed decline in locomotor activity when compared to the vehicle control group. Daridorexant's reinforcing properties were assessed by determining whether self-administration behavior was maintained when the drug was substituted for cocaine. Data from this study showed that rats self-administered cocaine (0.8 mg/kg/infusion), but doses of 0.1, 0.3, and 1 mg/kg/infusion of daridorexant produced a significantly lower mean number of active lever presses.

A randomized, double-blind, double-dummy, active-and placebo-controlled, 6-way cross-over study was conducted to determine the abuse potential of single oral doses of daridorexant. Suvorexant (150 mg) and Zolpidem (30 mg) served as the positive controls. Subjects received daridorexant at therapeutic (50 mg) and supratherapeutic (100 and 150 mg) doses. Bipolar visual analog scale (VAS) for Drug-Liking (0–100) served as the primary end. A score of 0 described a drug-disliking response; a score of 50 represented a neutral response, while a score of 100 described a strong drug liking. Drug liking scores following supratherapeutic doses (100 and 150 mg) of daridorexant showed statistically significant increases as compared to placebo on positive subjective measures (VAS measures for Drug Liking, Take Drug Again, Overall Drug Liking, High, and Good Drug Effects) and were statistically similar to those following suvorexant and zolpidem. Further, using a Drowsiness/Alertness VAS and an observer assessment of alertness/sedation, daridorexant's sedative properties were assessed. Both measures demonstrate that similar to suvorexant and zolpidem, daridorexant elicits drowsiness and sedation.

Data from Phase 1 clinical safety studies showed that daridorexant (5–200 mg) administered to 478 subjects produced somnolence in 52.7 percent (252), fatigue in 10.9 percent (52), and disturbances in attention in 3.8 percent (18) of subjects, respectively. Daridorexant at every dose produced somnolence at a rate that is 2- to 3-fold higher than that reported in the placebo-treated group. In two Phase 2 studies conducted to evaluate the efficacy and safety of daridorexant in subjects with insomnia disorder (one with adults (aged 18–64 years) at doses of 5–50 mg and the other with the elderly (≥65 years) at doses of 10–50 mg), daridorexant treatment led to reports of somnolence that exceeded reports of other effects that may be associated with abuse potential, including fatigue (5 (2.1 percent)) and dizziness (3 (1.3 percent). In three Phase 3 studies, which were conducted as confirmatory studies in adults and elderly subjects with insomnia disorder and were similarly designed to the two Phase 2 studies, the treatment-emergent adverse effects with the highest number of reports were somnolence (38 (2.14 percent)), fatigue (34 (1.91 percent)), and dizziness (26 (1.46 percent)). These types of reports were similar to those reported in the Phase 1 and 2 studies. The reported adverse events from the Phase 1, 2, and 3 studies demonstrate there were no significant abuse-related signals in these studies.

Daridorexant, similar to schedule IV drugs such as suvorexant and zolpidem, has sedative effects. In a human abuse potential (HAP) study, daridorexant produced abuse-related effects in humans similar to those of suvorexant and zolpidem. The abuse-related neuropharmacology profile of daridorexant is similar to that of schedule IV CNS depressants, such as suvorexant and lemborexant, and is consistent with its mechanism of action as a dual orexin receptors antagonist.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Daridorexant, chemically known as [(S)-2-(5-chloro-4-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-methylpyrrolidin-1-yl](5-methoxy-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone, is an NME. It is soluble in acidic water and slightly soluble in ethanol. It has one stereoisomer with one chiral center. The drug product is manufactured in tablet dose strengths that contain 25 mg and 50 mg of the active ingredient (*i.e.,* daridorexant) and a series of excipients to aid in taste and tablet disintegration. The excipients in the tablet have no known abuse liability. Daridorexant plasma exposure is dose proportional from 25 mg to 50 mg with an absolute bioavailability of 62 percent, and has consistent pharmacokinetic profile following multiple-dose and single-dose administration with no accumulation.

As discussed in the background section, daridorexant has an accepted medical use in the United States.

4. Its History and Current Pattern of Abuse

There is no information on the history and current pattern of abuse for daridorexant, since it has not been marketed, legally or illegally, in the United States or any country. There is no evidence of diversion of daridorexant that has been distributed for research, such as for clinical trials. Data from preclinical and clinical studies indicate that the abuse potential of daridorexant is similar to that of schedule IV CNS depressants such as suvorexant and lemborexant. Consistent with the fact that daridorexant is an NME; NFLIS database had no records of encounters by the law enforcement.

The pharmacological mechanism of action of daridorexant as a dual orexin receptor antagonist suggests that its pattern of abuse would be similar to schedule IV depressants with a similar mechanism of action, such as suvorexant and lemborexant.

5. The Scope, Duration, and Significance of Abuse

Data from preclinical and clinical studies showed that daridorexant has an abuse potential similar to that of the schedule IV depressants such as suvorexant and zolpidem. Thus, daridorexant, similar to these schedule IV substances, will have low potential for abuse relative to drugs and substances in schedule III. A search by DEA of the NFLIS database found no evidence of law enforcement encounters of daridorexant in the United States. Because daridorexant has a mechanism of action similar to schedule IV drugs suvorexant and lemborexant, it is likely that upon availability of daridorexant in the market, it will be abused similar to these schedule IV depressants.

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

The public health risk associated with daridorexant is largely due to its abuse potential. Data from preclinical and clinical studies showed that daridorexant has abuse potential similar to that of schedule IV depressants zolpidem and suvorexant. Therefore, upon availability for marketing, it is likely to pose a public health risk to a degree similar to these schedule IV depressants. Data from clinical trials showed that daridorexant has rewarding and depressant effects. The abuse of daridorexant may present risks to the

public health at a level similar to those associated with the abuse of schedule IV CNS depressants.

7. Its Psychic or Physiological Dependence Liability

Data obtained from a HAP study demonstrate that similar to suvorexant and zolpidem, daridorexant produced subjective responses to measures such as Drug Liking, Overall Drug Liking, Good Drug Effects, High, and Take Drug Again; indicative of psychological effects. HHS states that the data suggest daridorexant can produce psychic dependence similar to zolpidem and suvorexant, schedule IV depressants.

Results from a physiologic dependence study conducted in rats demonstrate that oral doses (0, 20, or 200 mg/kg/day) of daridorexant administered for 28-days followed by a 14-days discontinuation period did not produce alterations in physiological, neurobehavioral, or locomotor parameters during the discontinuation Phase of the study. Physical dependence signs were not observed in clinical studies after discontinuation of treatment in Phase 3 studies.

Data from animal studies and clinical trials demonstrate that chronic administration of daridorexant did not produce withdrawal signs or symptoms upon discontinuation. Daridorexant does not produce physical dependence.

8. Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA

Daridorexant is not an immediate precursor of any controlled substance, as defined by 21 U.S.C. 802(23).

Conclusion: After considering the scientific and medical evaluation and scheduling recommendation provided by HHS, and its own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of daridorexant. As such, DEA hereby schedules daridorexant as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA lists the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA (Administrator), pursuant to 21 U.S.C. 812(b)(4), finds that:

(1) Daridorexant has a low potential for abuse relative to the drugs or other substances in Schedule III.

Daridorexant, similar to schedule IV depressants such as suvorexant and lemborexant, is an orexin receptor antagonist. It produced sedation in general behavioral and locomotor studies. In a HAP study, oral administration of therapeutic (50 mg) and supratherapeutic doses (100 and 150 mg) of daridorexant produced increases in positive subjective measures such as Drug Liking, Overall Drug Liking, Good Drug Effects, High, and Take Drug Again that were statistically greater than those produced by placebo. These subjective responses following daridorexant were statistically similar to those produced by the positive control drugs that are schedule IV depressant such as zolpidem and suvorexant. These data show that daridorexant has an abuse potential that is similar to the schedule IV drugs zolpidem and suvorexant. Because daridorexant is similar to suvorexant and zolpidem in its abuse potential, daridorexant has a low potential for abuse relative to the drugs or other substances in schedule III.

(2) Daridorexant has a currently accepted medical use in treatment in the United States.

FDA recently approved the NDA for daridorexant as an oral treatment for adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Thus, daridorexant has a currently accepted medical use in treatment in the United States.

(3) Abuse of daridorexant may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

Data from both preclinical and clinical studies demonstrate that discontinuation of daridorexant was not associated with withdrawal symptoms indicative of physical dependence. Because daridorexant produced positive subjective responses in a HAP study similar to those of zolpidem and suvorexant (both schedule IV drugs), it is likely that daridorexant can produce psychic dependence to an extent that is similar to these schedule IV substances. Thus, abuse of daridorexant may lead to limited physical or psychological dependence relative to the drugs or other substances in schedule III.

Based on these findings, the Administrator concludes that daridorexant warrants control in schedule IV of the CSA. 21 U.S.C. 812(b)(4).

Requirements for Handling Daridorexant

Daridorexant is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule IV substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle, daridorexant 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. Any person who currently handles or intends to handle daridorexant and is not registered with DEA must submit an application for registration and may not continue to handle daridorexant unless DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. These registration requirements, however, are not applicable to patients (end users) who possess daridorexant pursuant to a lawful prescription.

2. *Disposal of stocks.* Any person unwilling or unable to obtain a schedule IV registration must surrender all quantities of currently held daridorexant, or may transfer all quantities of currently held daridorexant to a person registered with DEA. Daridorexant is required to be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, state, local, and tribal laws.

3. *Security.* Daridorexant is subject to schedule III–V security requirements for DEA registrants and it must be handled and stored in accordance with 21 CFR 1301.71–1301.77. Non-practitioners handling daridorexant must also comply with the employee screening requirements of 21 CFR 1301.90–1301.93. These requirements, however, are not applicable to patients (end users) who possess daridorexant pursuant to a lawful prescription.

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

5. *Inventory.* Every DEA registrant who possesses any quantity of

daridorexant must take an inventory of daridorexant on hand, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who registers with DEA to handle daridorexant must take an initial inventory of all stocks of controlled substances (including daridorexant) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b).

After the initial inventory, every DEA registrant must take an inventory of all stocks of controlled substances (including daridorexant) on hand every two years, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11. These requirements, however, are not applicable to patients (end users) who possess daridorexant pursuant to a lawful prescription.

6. *Records and Reports.* DEA registrants must maintain records and submit reports for daridorexant, pursuant to 21 U.S.C. 827, 832(a), and 958(e), and in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and 1317.

7. *Prescriptions.* All prescriptions for daridorexant, or products containing daridorexant, must comply with 21 U.S.C. 829, and be issued in accordance with 21 CFR parts 1306 and 1311, subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of daridorexant may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act (FDCA), as applicable, and the CSA.

9. *Importation and Exportation.* All importation and exportation of daridorexant must comply with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

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

Regulatory Analyses

Administrative Procedure Act

Section 553 of the APA (5 U.S.C. 553) generally requires notice and comment for rulemakings. However, 21 U.S.C. 811(j) provides that in cases where a certain new drug is (1) approved by HHS, under section 505(c) of the FDCA and (2) HHS recommends control in CSA schedule II–V, DEA shall issue an IFR scheduling the drug within 90 days. As stated in the legal authority section, the 90-day time frame is the later of: (1) The date DEA receives HHS's scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Additionally, subsection (j) specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause.

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

In accordance with 21 U.S.C. 811(a) and (j), this scheduling action is subject to formal rulemaking procedures performed ''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 procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) 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. The rule 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 rule does not have tribal implications warranting the application of E.O. 13175. It 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 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. As noted in the above discussion regarding the applicability of the APA, DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply to this IFR.

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. 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. 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.

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 this IFR to both Houses of Congress and to the Comptroller General.

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 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 § 1308.14:
■ a. Redesignate paragraphs (c)(16) through (58) as (c)(17) through (59); and
■ b. Add new paragraph (c)(16).
■ The addition reads as follows:

§ 1308.14 Schedule IV.

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Anne Milgram,

Administrator.

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–491]

Schedules of Controlled Substances: Placement of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA, and FUB-144 in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: By this rule, the Drug Enforcement Administration permanently places five synthetic cannabinoids, as identified in this final rule, in schedule I of the Controlled Substances Act. These five substances are currently listed in schedule I pursuant to a temporary scheduling order. As a result of this rule, 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, or possess), or propose to handle these five specified controlled substances will continue to apply.

DATES: Effective April 7, 2022.

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

SUPPLEMENTARY INFORMATION:

In this final rule, the Drug Enforcement Administration (DEA) is permanently scheduling the following five controlled substances in schedule I of the Controlled Substances Act (CSA), including their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

- Ethyl 2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate (other name: 5F-EDMB-PINACA),
- Methyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate (other names: 5F-MDMB-PICA; 5F-MDMB-2201),
- *N*-(Adamantan-1-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (other names: FUB-AKB48; FUB-APINACA; AKB48 *N*-(4-fluorobenzyl)),
- 1-(5-Fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (other names: 5F-CUMYL-PINACA; SGT-25), and
- (1-(4-Fluorobenzyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (other name: FUB-144).

Legal Authority

The CSA provides that issuing, amending, or repealing of the scheduling of any drug or other substance may be initiated by the Attorney General (1) on his own motion; (2) at the request of the Secretary of the Department of Health and Human Services (HHS); [1] or (3) on the petition of any interested party. 21 U.S.C. 811(a). The then-Acting Administrator of DEA (as delegated by the Attorney General to the Administrator of DEA) initiated this action on his own motion, and is supported by, *inter alia,* a recommendation from the then-Acting Assistant Secretary for Health of HHS and an evaluation of all relevant data by DEA. The regulatory controls and administrative, civil, and criminal sanctions of schedule I controlled substances on any person who handles (manufactures, distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) or proposes to handle 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA, and FUB-144 will continue to apply as a result of this action.

[1] As set forth 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, 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.

Background

On April 16, 2019, DEA published an order in the **Federal Register** amending 21 CFR 1308.11(h) to temporarily place ethyl 2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-EDMB-PINACA); methyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-MDMB-PICA); *N*-(adamantan-1-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (trivial names: FUB-AKB48; FUB-APINACA; AKB48 N-(4-FLUOROBENZYL)); 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide (trivial names: 5F-CUMYL-PINACA; SGT-25); and (1-(4-fluorobenzyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (trivial name: FUB-144) in schedule I of the CSA pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). 84 FR 15505. That temporary scheduling order took effect on the date of publication, and was based on findings by the then-Acting Administrator of DEA that the temporary scheduling of these five synthetic cannabinoids (SCs) was necessary to avoid an imminent hazard to the public safety pursuant to 21 U.S.C. 811(h)(1).

On March 30, 2021, DEA published a notice of proposed rulemaking (NPRM) in the **Federal Register** to permanently control the five SCs in schedule I of the CSA. 86 FR 16553. On March 31, 2021, DEA published an order to extend the temporary scheduling of the five SCs by one year, until April 16, 2022. 86 FR 16669.

DEA and HHS Eight Factor Analyses

On February 26, 2021, HHS provided DEA with a scientific and medical evaluation and scheduling recommendation, prepared by the Food and Drug Administration (FDA), entitled ''Basis for the Recommendation to Place Ethyl 2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate [5F-EDMB-PINACA]; methyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate [5F-MDMB-PICA]; *N*-(adamantan-1-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide [FUB-AKB48;FUB-APINACA; AKB48 *N*-(4-fluorobenzyl)]; 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide [5F-CUMYL-PINACA; SGT-25]; and (1-(4-fluorobenzyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone [FUB-144; FUB-UR-144] and Their Salts, Isomers, and Salts of Isomers in Schedule I of the Controlled Substances Act.''