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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-1775]

Schedules of Controlled Substances: Placement of Oveporexton in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule; request for comments.

SUMMARY: On August 5, 2026, the United States Food and Drug Administration (FDA) approved a new drug application for Orzeyful (oveporexton) for the treatment of narcolepsy type 1 in adults. The Department of Health and Human Services (HHS) provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place oveporexton, chemically known as *N*-[(2*S*,3*R*)-2-[[3-(3,5-difluorophenyl)-2-fluorophenyl]methyl]-4,4-difluoro-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]ethanesulfonamide, 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 oveporexton, including its salts, isomers and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the CSA.

DATES: This rule is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. 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, together with a written statement of position on the matters of fact and law asserted in

the hearing, must be received on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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-1775" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages commenters to submit comments 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 *https://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. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment. 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.

- *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 filed with the DEA Administrator, who will make the determination of whether a hearing will be needed to address such matters of fact and law in the rulemaking. Such requests must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. For informational purposes, a courtesy copy of requests for hearing and waivers

of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

- *Paperwork Reduction Act Comments:* All comments concerning collections of information under the Paperwork Reduction Act must be submitted to the Office of Information and Regulatory Affairs, OMB, Attention: Desk Officer for DOJ, Washington, DC 20503. Please state that your comment refers to Docket No. DEA-1775.

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

SUPPLEMENTARY INFORMATION: In this interim final rule (IFR), Drug Enforcement Administration (DEA) is adding oveporexton to schedule IV of the Controlled Substances Act (CSA).

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. DEA will make comments available for public inspection online at *https://www.regulations.gov*, unless reasonable cause is given. Such information includes personal or business identifying information (such as name, address, State or Federal identifiers, etc.) voluntarily submitted by the commenter.

Commenters submitting comments which include personal identifying information (PII), confidential, or proprietary business information that the commenter does not want made publicly available should submit two copies of the comment. One copy must be marked "CONTAINS CONFIDENTIAL INFORMATION" and should clearly identify all PII or business information the commenter does not want to be made publicly available, including any supplemental materials. DEA will review this copy, including the claimed PII and confidential

business information, in its consideration of comments. The second copy should be marked "TO BE PUBLICLY POSTED" and must have all claimed confidential PII and business information already redacted. DEA will post only the redacted comment on *https://www.regulations.gov* for public inspection. DEA generally will not redact additional information contained in the comment marked "TO BE PUBLICLY POSTED." The Freedom of Information Act applies to all comments received.

For easy reference, an electronic copy of this document and supplemental information to this IFR are available at *http://www.regulations.gov*.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(j)(3), an interested person may "request a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551–559.[1] Interested persons, as defined in 21 CFR 1300.01(b), may file requests for a hearing in conformity with the requirements of 21 CFR 1308.44(a) and 1316.47(a), and such requests must:

(1) state with particularity the interest of the person in the proceeding;

(2) state with particularity the objections or issues concerning which the person desires to be heard; and

(3) state briefly the position of the person with regard to the objections or issues. Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(c), together with a written statement of position on the matters of fact and law involved in any hearing.[2]

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. The decision whether a hearing will be needed to

[1] 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D.
[2] 21 CFR 1316.49.

address such matters of fact and law in the rulemaking will be made by the Administrator. If a hearing is needed, DEA will publish a notice of hearing on the interim final rule in the *Federal Register*.[3] Further, once the Administrator determines a hearing is needed to address such matters of fact and law in rulemaking, he will then designate an Administrative Law Judge (ALJ) to preside over the hearing. The ALJ's functions shall commence upon designation, as provided in 21 CFR 1316.52.

In accordance with 21 U.S.C. 811 and 812, the purpose of a hearing would be to determine whether oveporexton meets the statutory criteria for placement in schedule IV.

Legal Authority

Under the CSA, as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (section 2(b) of Pub. Law 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 a New Drug Application (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 of HHS 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 811(j)(2) states that the 90-day timeframe starts 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. Subsection 811(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 811(j) is to speed the process by which

[3] 21 CFR 1308.44(b), 1316.53.

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.[4]

Subsection 811(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).

Background

Oveporexton (also known as TAK-861) is a new molecular entity with CNS activity as an orexin type 2 receptor (OX2R) agonist. Selective OX2R agonism is a distinct pharmacological mechanism of action from other substances currently listed in the CSA.

On December 10, 2025, Takeda Pharmaceuticals U.S.A., Inc. (Sponsor) submitted an NDA for oveporexton to FDA. On August 5, 2026, FDA approved the NDA for oveporexton (Orzeyful) for the treatment of narcolepsy type 1 (NT1) in adults. The approved formulation consists of tablets in 0.5 mg, 1 mg, and 2 mg strengths, with a recommended dosage of either 1 mg or 2 mg taken orally twice daily.

Determination to Schedule Oveporexton

On July 31, 2026, DEA received from HHS a scientific and medical evaluation titled "Basis for the Recommendation to Control Oveporexton 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 oveporexton, along with HHS's recommendation to control oveporexton under schedule IV of the CSA.

[4] Given the parameters of subsection 811(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.

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 oveporexton 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's scheduling recommendation, the approval of the NDA by HHS/FDA, and DEA's determination, DEA is issuing this IFR to schedule oveporexton 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 IFR at *https://www.regulations.gov*, under Docket Number "DEA-1775." 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

Oveporexton is new molecular entity that has not been marketed legally or illegally in the United States and was recently approved for treatment of NT1 in China and Japan. Given that oveporexton is new to the global market, evidence regarding its diversion, illicit manufacturing, or abuse is currently lacking. FDA is not aware of any diversion from research activities or manufacturing facilities for oveporexton, and DEA's National Forensic Laboratory Information System (NFLIS)-Drug[5] database reflects that oveporexton has not been encountered by law enforcement in the United States.

[5] NFLIS-Drug represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by Federal, State and local forensic laboratories in the United States. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. *See Schedules of Controlled Substances: Placement of Carisoprodol Into Schedule IV*, 76 FR 77330, 77332 (Dec. 12, 2011). NFLIS-Drug data was queried on August 20, 2026.

Oveporexton is an OX2R-selective agonist with demonstrated CNS activity. There are currently no OX2R-selective agonists listed in the CSA. In nonclinical studies, oveporexton produces stimulant-like behavioral alterations in rodents and has weak reinforcing effects, as demonstrated by a rat self-administration study. In humans, some potential abuse-related treatment-emergent adverse events involving oveporexton occurred across clinical trials with higher incidence at supratherapeutic doses. Also, a human abuse potential study showed that supratherapeutic doses of oveporexton produced abuse-related subjective effect ratings that were not statistically significantly different from phentermine (schedule IV) (*see* Factor 2). Based on these data, oveporexton has a potential for abuse similar to the schedule IV stimulant phentermine, making it reasonable to assume its potential for diversion, misuse, and creating a hazard to the health of individuals or the community will be similar to that of substances in schedule IV of the CSA.

2. Scientific Evidence of Its Pharmacological Effects, if Known

The pharmacological effects of oveporexton were assessed using available nonclinical and clinical data. *In vitro* binding and functional studies demonstrate that oveporexton is a potent and selective OX2R agonist which lacks off-target effects at other receptor targets associated with abuse potential. Animal behavioral studies show that oveporexton has some stimulant-like and reinforcing properties. Oveporexton produced transient stimulant-like behavior in rats, with the most frequent behavioral observation in the modified Irwin's multiple observation method being slight restlessness 1–2 hours after administration of ≥20 mg/kg oral oveporexton. In a drug discrimination study in rats, oveporexton at doses up to 5 mg/kg (orally) did not substitute for the discriminative stimulus of the schedule II stimulant, *d*-amphetamine (0.3 mg/kg, subcutaneously). A second drug discrimination study revealed that rats could not be trained to discriminate oveporexton from placebo under the conditions tested. Additionally, in an intravenous self-administration study in rats, oveporexton at 0.03 mg/kg/0.2 mL infusion was self-administered more than vehicle control in cocaine-trained rats, but the other three tested

oveporexton doses (0.01, 0.1, and 0.3 mg/kg/0.2 mL infusion) were not self-administered more than vehicle. From this result, HHS concluded that oveporexton produces weak reinforcing effects in male cocaine-maintained rats.

The human clinical trial data described by HHS further demonstrate oveporexton's abuse potential. In a human abuse potential study, healthy adult non-dependent, recreational drug users with CNS stimulant experience rated all evaluated doses of oveporexton (6 mg, 18 mg, and 30 mg, taken orally) more favorably than placebo across primary and secondary endpoints associated with abuse potential. In this study, the maximal subjective Drug Liking scores (primary endpoint) were not statistically significantly different between the positive control (phentermine 75 mg; schedule IV) and oveporexton (18 mg and 30 mg). In addition, HHS's review of adverse events across clinical safety and efficacy studies indicated that oveporexton produced dose-dependent increases in potential abuse-related treatment-emergent adverse events. The most common oveporexton potential abuse-related adverse event in clinical trial participants without narcolepsy was "euphoric mood." Such adverse events were infrequent in the intended treatment population (persons with NT1) at recommended therapeutic doses of oveporexton (≤4 mg/day).

In conclusion, the pharmacological effects of oveporexton support that oveporexton has a potential for abuse that is similar to that of the schedule IV stimulant phentermine.

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

Oveporexton, chemically known as *N*-[(2*S*,3*R*)-2-[[3-(3,5-difluorophenyl)-2-fluorophenyl]methyl]-4,4-difluoro-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]ethanesulfonamide, is a new molecular entity that was recently FDA-approved for the treatment of NT1 in adults. This approval indicates that oveporexton has an accepted medical use in treatment in the United States. The recommended dosage of oveporexton for the treatment of NT1 is either 1 mg or 2 mg orally, taken after awakening and then three to five hours later.

Following oral administration, oveporexton is rapidly absorbed, highly distributed (including to the CNS), and shows approximately dose-proportional increases in systemic exposure. The mean terminal elimination half-life of oveporexton is 23.2 hours. Oveporexton is primarily excreted in the feces following cytochrome P450 3A4-predominant hepatic metabolism, with unchanged oveporexton identified as the major circulating species in plasma.

4. Its History and Current Pattern of Abuse

Consistent with the fact that oveporexton is new to the global market, both FDA and DEA are not aware of any diversion or abuse related to oveporexton. Since real-world data on history and patterns of abuse are lacking, there is no data to assess oveporexton's history and current patterns of abuse. However, nonclinical and clinical studies (*see* Factors 1 and 2) support that oveporexton has a potential for abuse similar to that of phentermine (schedule IV).

5. The Scope, Duration, and Significance of Abuse

FDA is not aware of any diversion or abuse of oveporexton from its manufacture and distribution associated with legitimate drug research, and oveporexton has not been previously marketed (legally or illegally) in the United States. DEA's NFLIS-Drug database confirms that oveporexton is absent from the United States illicit drug market. Since this is a new molecular entity, evidence of the scope, duration, and significance of abuse of oveporexton is limited. However, the available data (*see* Factors 1 and 2) indicate that oveporexton has a potential for abuse similar to that of phentermine (schedule IV), and because of this, it is likely to be abused upon its availability in the market.

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

HHS reviewed clinical trial adverse event data to evaluate oveporexton's potential public health risk. Oveporexton produces dose-dependent increases in the incidence of adverse events, including potential abuse-related treatment-emergent adverse events. Potential abuse-related treatment-emergent adverse events occurred in 19.4 percent of participants without narcolepsy taking 30–75 mg/day oveporexton. Adverse Events of Special Interest, such as insomnia and

frequent urination, occurred in up to 16.7 percent of participants without narcolepsy after a 30 mg single dose of oveporexton. DEA adds that transient insomnia and increased urinary frequency occurred in a majority of participants with NT1 taking recommended therapeutic doses of oveporexton (≤4 mg/day) in the Phase 3 trials.

DEA adds that Lammers et al. (2026)[6] performed a secondary analysis of a Phase 2 trial in participants with NT1 (N=112) and determined that oveporexton improved attention, memory, and executive function at 8 weeks. The authors postulated that their findings may be because oveporexton is addressing the pathophysiology of NT1 (i.e., impaired orexigenic neurotransmission) or may be secondary to improved NT1 symptomatology. DEA notes that studies are needed to confirm if cognitive performance benefits extend outside the NT1 population and if the effects are acute or only present after continual use. Nonetheless, DEA considers oveporexton's potential for cognitive enhancement and performance benefits may increase the attractiveness of the drug for diversion and abuse, thereby contributing to oveporexton's overall risk to public health because cognitive enhancement is a major motivation for prescription stimulant diversion and abuse.

Furthermore, a drug's abuse potential is a key indicator of its public health risk. Data presented in Factors 1–3 suggest that oveporexton possesses an abuse potential similar to that of phentermine—a schedule IV stimulant. Therefore, all things considered, as oveporexton becomes available for marketing, it is anticipated that it will present a similar public health risk to that of phentermine.

7. Its Psychic or Physiological Dependence Liability

Psychic (or psychological) dependence is a state similar to addiction and can be inferred through animal self-administration studies, human abuse potential studies, case reports, and

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[6] Lammers, G. J., Plazzi, G., Mignot, E., Pizza, F., Dauvilliers, Y., Barateau, L., Maruff, P., Scammell, T. E., Latzman, R. D., Naylor, M., Olsson, T., Stukalin, E., Tanaka, S., Volfson, D., Khachadourian, V., & Harel, B. T. (2026). Effects of Oveporexton, an Orexin Receptor 2-Selective Agonist, on Cognition in Narcolepsy Type 1: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Neurology*, *83*(2), 145–152. https://doi.org/10.1001/jamaneurol.2025.4825

epidemiological data. In an intravenous self-administration study in cocaine-trained rats, one (of four) oveporexton doses produced a small, but statistically significant increase in the number of infusions per session compared to vehicle control. In a human abuse potential study conducted in non-dependent, recreational drug users with CNS stimulant experience (N=43), the Take Drug Again scores were similar between phentermine 75 mg and supratherapeutic doses of oveporexton (18 mg and 30 mg). The reinforcing effects of oveporexton in animals and subjective effect scores indicative of reinforcing effects in humans align closely with phentermine rather than stronger stimulants (i.e., schedule II stimulants), suggesting oveporexton's potential to induce drug-seeking behavior is expected to be correspondingly lower than schedule II stimulants. Taken together, these data indicate that oveporexton is unlikely to cause psychic dependence in humans.

Physical dependence develops from physiological adaptation to repeated drug use and manifests as withdrawal symptoms after abrupt drug discontinuation or reduction of a drug. A minority of female rats exhibited some sporadic effects of oveporexton withdrawal (writhing/abdominal spasm, eye closure and jaw chomping) following discontinuation after 28 days of oral oveporexton administration, but there were no robust signals of physical dependence. HHS reviewed drug-discontinuation-emergent adverse events from six repeated-dose oveporexton trials (N=277 participants) to determine if there was clinical evidence for withdrawal demonstrating physical dependence. Oveporexton did not show consistent or dose-related withdrawal effects in these trials. The adverse event data from the clinical trials corroborates the oveporexton preclinical data demonstrating a lack of physical dependence in rats. Thus, overall, data indicate that oveporexton does not appear to produce substantial physical dependence.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA

Oveporexton is not an immediate precursor of any substance already controlled under the CSA, as defined by 21 U.S.C. 802(23).

Conclusion: After considering the scientific and medical evaluation and scheduling recommendation provided by HHS, as well as DEA's own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of oveporexton. As such, DEA hereby schedules oveporexton 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).[7] 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, pursuant to 21 U.S.C. 812(b)(4), finds that:

1) Oveporexton has a low potential for abuse relative to the drugs or other substances in schedule III.

Oveporexton is an OX2R-selective agonist; this mechanism of action is distinct from other substances known to have a potential for abuse and already listed under the CSA. Animal behavioral studies show oveporexton produces some stimulant-like behaviors, does not substitute for the discriminative stimulus of *d*-amphetamine, and maintains self-administration at a significant level in cocaine-trained rats at one (of four) dose levels. Potential abuse-related treatment-emergent adverse events occurred infrequently across clinical studies, but the incidence of such events was consistently higher in participants receiving supratherapeutic doses of oveporexton. A human abuse potential study showed oveporexton produced positive subjective effects in stimulant-experienced, recreational drug users. All evaluated doses of oveporexton (6, 18, and 30 mg) demonstrated statistically significantly higher scores than placebo across primary and secondary endpoint measures indicative of abuse potential. For the

[7] 21 U.S.C. 812(b).

primary endpoint, oveporexton 18 mg and 30 mg produced maximal Drug Liking scores that were comparable to the active comparator (phentermine 75 mg). Since oveporexton produced abuse-related subjective responses similar to phentermine, oveporexton's potential for abuse is also expected to be similar to phentermine (schedule IV). As such, the evidence indicates that oveporexton has a low potential for abuse relative to the drugs or other substances in schedule III.

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

On August 5, 2026, FDA approved the NDA for Orzeyful (oveporexton) for the treatment of NT1 in adults. Thus, oveporexton has a currently accepted medical use in treatment in the United States.

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

Nonclinical and clinical study data demonstrate that oveporexton does not appear to produce physical dependence and poses a low risk of psychological dependence. Oveporexton did not produce withdrawal signs and symptoms following abrupt discontinuation, indicating there was no development of physical dependence under the conditions evaluated. This was demonstrated by a lack of robust withdrawal effects in rats when oveporexton was discontinued after four weeks of oral administration and further supported by clinical trial drug-discontinuation-emergent adverse events involving oveporexton, which occurred infrequently and inconsistently across participant populations.

Oveporexton possesses weak reinforcing properties, which suggests that oveporexton poses a low risk of producing psychological dependence in humans. In the rat self-administration study, one dosing condition (oveporexton 0.03 mg/kg/0.2 mL infusion) increased the drug self-administration rate relative to vehicle control, but the effect was not dose-dependent, leading HHS to conclude that oveporexton possesses only weak reinforcing

properties. In a human abuse potential study conducted in stimulant-experienced, non-dependent recreational drug users, Take Drug Again scores were comparable between the two highest doses of oveporexton (18 mg and 30 mg) and the schedule IV comparator (phentermine 75 mg). The data suggest the reinforcing properties of oveporexton align with those of phentermine. Therefore, oveporexton's psychological dependence liability is expected to be similar to that of phentermine (schedule IV). In conclusion, abuse of oveporexton may lead to limited physical or psychological dependence relative to drugs or other substances in schedule III.

Based on these findings, DEA concludes that oveporexton warrants control in schedule IV of the CSA.[8]

Requirements for Handling Oveporexton

Oveporexton is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distributing, dispensing, importing, exporting, research, and conduct of instructional activities, 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) oveporexton 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. These registration requirements, however, are not applicable to patients (end users) who possess oveporexton pursuant to a lawful prescription.

2. *Disposal of Stocks.* Any person unwilling or unable to obtain a DEA registration must surrender all quantities of currently held oveporexton or may transfer all quantities of currently held oveporexton to a person registered with DEA. Oveporexton 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.

[8] 21 U.S.C. 812(b)(4).

3. *Security.* Oveporexton is subject to schedule III-V security requirements for DEA registrants and must be handled and stored in accordance with 21 CFR 1301.71-1301.77, pursuant to 21 U.S.C. 821, 823, and 871(b). Non-practitioners handling oveporexton 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 oveporexton pursuant to a lawful prescription.

4. *Labeling and Packaging.* All labels and packaging for commercial containers of oveporexton 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 oveporexton must have an initial inventory of all stocks of controlled substances (including oveporexton) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Any person who registers with DEA to handle oveporexton must take an initial inventory of all stocks of controlled substances (including oveporexton) 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 inventory of all controlled substances (including oveporexton) on hand every two years, pursuant to 21 U.S.C. 827, 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 oveporexton pursuant to a lawful prescription.

6. *Records and Reports.* DEA registrants must maintain records and submit reports for oveporexton, 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 in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and 1317.

7. *Prescriptions.* All prescriptions for oveporexton, or products containing oveporexton, 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 oveporexton 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, as applicable, and the CSA.

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

10. *Liability.* Any activity involving oveporexton 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

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 811(j) specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause.

Executive Orders 12866 and 14294

The Office of Management and Budget ("OMB") has determined that, although this rule is not economically significant under section (3)(f)(1) of Executive Order 12866, this rule is nonetheless a "significant regulatory action" under section 3(f) of the Order. OMB has therefore reviewed this rule.

DEA scheduling actions are not subject to E.O. 14294, Fighting Overcriminalization in Federal Regulations.

Executive Order 12988, Civil Justice Reform

This rulemaking 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 proposed 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.

Paperwork Reduction Act

This rule would require compliance with the following existing Office of Management and Budget (OMB)-approved collections: 1117-0003, 1117-0004, 1117-0006, 1117-0008, 1117-0009, 1117-0010, 1117-0012, 1117-0014, 1117-0021, and 1117-0056. 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.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA), 5 U.S.C. 601-612, applies to rules that are subject to the notice-and-comment requirements of the APA at 5 U.S.C. 553. The RFA's 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 the APA or any other law to publish a general notice of proposed rulemaking. 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 and certifies that this proposed 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 rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804(2). 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 (f)(8) through (14) as paragraphs (f)(9) through (15); and

b. Add a new paragraph (f)(8).

The addition reads as follows:

§ 1308.14 Schedule IV.

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SIGNING AUTHORITY

This document of the Drug Enforcement Administration was signed on November 6, 2026, by DEA Administrator Terrance C. Cole. 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.

Heather Achbach,
Federal Register Liaison Officer,
Drug Enforcement Administration.

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