additional 90 days.[8] On May 10, 2022, the court issued another order to postpone the effective date of the final rule by an additional 90 days.[9] The court ordered that the new effective date of the final rule is July 8, 2023. Pursuant to the court order, any obligation to comply with a deadline tied to the effective date is similarly postponed, and those obligations and deadlines are now tied to the postponed effective date.

To the extent that 5 U.S.C. 553 applies to this action, the Agency's implementation of this action without opportunity for public comment, effective immediately upon publication today in the **Federal Register**, is based on the good cause exception in 5 U.S.C. 553(b)(B). Seeking public comment is impracticable, unnecessary, and contrary to the public interest. The 90-day postponement of the effective date, until July 8, 2023, is required by court order in accordance with the court's authority to postpone a rule's effective date pending judicial review (5 U.S.C. 705). Seeking prior public comment on this postponement would have been impracticable, as well as contrary to the public interest in the orderly issuance and implementation of regulations.

Dated: May 24, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–11568 Filed 5–31–22; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–990]

Schedules of Controlled Substances: Placement of Ganaxolone in Schedule V

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule; request for comments.

SUMMARY: On March 18, 2022, the United States Food and Drug Administration approved a new drug application for ZTALMY, an oral suspension of ganaxolone, for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder in patients two years of age and older. The Department of Health and Human Services provided the Drug Enforcement Administration with a scheduling recommendation to place ganaxolone and its salts in schedule V of the Controlled Substances Act. In accordance with the Controlled Substances Act, as amended by the Improving Regulatory Transparency for New Medical Therapies Act, Drug Enforcement Administration is hereby issuing an interim final rule placing ganaxolone, including its salts in schedule V of the Controlled Substances Act.

DATES: This rule is effective June 1, 2022. Comments must be submitted electronically or postmarked on or before July 1, 2022. 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). 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.

Interested persons may file a request for a hearing or waiver of a hearing in accordance with 21 U.S.C. 811(j)(3) and 21 CFR 1308.44. Requests for a hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before July 1, 2022.

ADDRESSES: To ensure proper handling of comments, please reference ''Docket No. DEA–990'' 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 a 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

Please note, 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

[8] *R.J. Reynolds Tobacco Co.,* No. 6:20–cv–00176 (E.D. Tex. February 10, 2022) (order postponing effective date), Doc. No. 94.

[9] *R.J. Reynolds Tobacco Co.,* No. 6:20–cv–00176 (E.D. Tex. May 10, 2022) (order postponing effective date), Doc. No. 96.

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 Publ. 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 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 interim final rule (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]

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).

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a new molecular entity (NME) with CNS activity. Ganaxolone is a neuroactive positive allosteric modulator of gamma-aminobutyric acid type-A (GABA-A) receptors and an inhibitory neurosteroidal substance that shares structural features and a pharmacological mechanism of action with progesterone and schedule IV depressants alfaxalone and brexanolone.

On July 20, 2021, Marinus Pharmaceuticals, Inc. (Sponsor) submitted an NDA for ganaxolone to FDA. On March 18, 2022, DEA received notification that FDA, on the same date, approved the NDA for ZTALMY (ganaxolone oral suspension), under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients two years of age and older. Pursuant to its FDA-approved prescription drug labeling, ZTALMY is to be administered orally three times daily (TID) with food on a titration schedule through a dose-escalation protocol over the first 3 weeks of drug administration. Patients weighing 28 kg or less receive a final dose of 21 mg/kg TID (63 mg/kg/day) and patients weighing more than 28 kg receive a final dose of 600 mg TID (1800 mg/day).[2]

Determination To Schedule Ganaxolone

On March 14, 2022, DEA received from HHS a scientific and medical evaluation entitled ''Basis for the Recommendation to Control Ganaxolone and its Salts in Schedule V 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 ganaxolone, along with HHS's recommendation to control ganaxolone and its salts under schedule V 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 ganaxolone meets the 21 U.S.C. 812(b)(5) criteria for placement in schedule V 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 ganaxolone as a schedule V 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 *http://www.regulations.gov,* under Docket Number ''DEA–990.'' 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

Ganaxolone is an NME that has not been marketed in the United States or

[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.

[2] *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215904s000lbl.pdf.* Date accessed March 28, 2022.

any country. Thus, evidence regarding its diversion, illicit manufacturing, or deliberate ingestion is currently lacking. DEA notes that there are no reports of law enforcement encounters of ganaxolone in the National Forensic Laboratory Information System (NFLIS) database,[3] which collects drug cases submitted to and analyzed by state and local forensic laboratories. Ganaxolone has sedative effects and is likely to have abuse potential, although less than that of schedule IV sedatives such as lorazepam. Thus, it is reasonable to assume that ganaxolone may be diverted from legitimate channels, used contrary to or without medical advice, and capable of creating hazards to the users and to the safety of the community. In preclinical and clinical studies, ganaxolone produced effects that are less than that of schedule IV sedative drugs such as methohexital and lorazepam. Ganaxolone produced positive subjective responses and euphoria-related adverse events (AEs) that were significantly greater than placebo, but statistically less than that of lorazepam (schedule IV) in healthy humans, nondependent with a history of recreational use of CNS depressants; thus, it is likely to be abused for its sedative effects contrary to medical advice.

2. Scientific Evidence of Its Pharmacological Effects, if Known

Ganaxolone shares a pharmacological profile with other inhibitory neurosteroids such as alfaxalone and brexanolone, both schedule IV drugs. Ganaxolone acts on GABA-A receptors to enhance the effects of GABA, a major inhibitory neurotransmitter in the CNS. Data from *in vitro* binding studies showed that ganaxolone had significant affinity (greater than 96 percent) for the GABA-chloride channels. Ganaxolone did not show significant affinity (less than 50 percent) for 47 other receptor sites, ion channels, steroid sites, and enzymes. The sites tested included abuse-related sites such as dopamine (D_1 and D_2), serotonin (1a, 2a, and 2c), cannabinoid (CB_1 and CB_2), opioid (mu, kappa, delta), glutamate (NMDA/AMPA, phencyclidine, glycine, kainite), and monoamine transporters (dopamine, serotonin, or norepinephrine). Functional activity studies showed that ganaxolone potentiated GABA-evoked chloride currents in *Xenopus* oocytes expressing human GABA-A receptor subunits.

In animal studies, orally-administered ganaxolone's effect on general behavioral profile showed that it did not produce behavioral activity that differed significantly from the saline-treated group. However, ganaxolone elicited time-dependent (6-hour post treatment) behavior changes such as abnormal gait, grasping loss, abnormal righting reflex, and low carriage indicative of the sedative and muscle relaxation properties of the drug. Ganaxolone's effect on motor coordination was evaluated in three rotarod studies in rats. The studies showed that ganaxolone produced a dose-dependent increase in the number of rats that failed to maintain themselves on the rotarod, indicative of its interference on motor coordination. Ganaxolone produced a dose-dependent decrease in locomotor activity and loss of righting reflex.

In a drug discrimination study using rats trained to discriminate midazolam (schedule IV) and saline, oral doses of ganaxolone (10 and 30 mg/kg) produced full generalization to midazolam stimuli. Ganaxolone's reinforcing properties were assessed by determining whether self-administration behavior was maintained when the drug was substituted for heroin. Data from this study showed that ganaxolone self-administration was much less than that of methohexital (schedule IV) and heroin (schedule I) and was numerically similar to saline. However, ganaxolone at 0.10 mg/kg/injection dose produced self-administration that was statistically significantly greater than saline.

A randomized, double-blind, active- and placebo-controlled, cross-over study was conducted to determine the abuse potential for ganaxolone in healthy, nondependent, recreational CNS depressant users. Oral doses of ganaxolone were compared to an oral dose of lorazepam (schedule IV, served as the positive control). The lower and middle doses of ganaxolone (400 mg and 800 mg, respectively) produced responses within or just outside the acceptable placebo range and were statistically similar to placebo. However, the highest dose of ganaxolone (2000 mg) produced a drug liking score that was significantly different from placebo. The three doses of ganaxolone tested produced drug liking scores that were significantly lower than that of lorazepam. In addition, all three oral doses of ganaxolone (400, 800, and 2000 mg) produced responses on all other positive subjective measures (bipolar visual analog scale for Overall Drug Liking, High, Good Effects, and Take Drug Again) that were statistically less than those produced by 6 mg oral dose of lorazepam.

In 23 Phase 1 clinical safety studies that were conducted using healthy individuals, eight of the studies showed that ganaxolone produced euphoria-related AEs at all doses tested. Of the eight studies, three were repeat-dose studies and five were acute-dose studies. From the three repeat-dose studies, 24 of 64 subjects who received ganaxolone reported euphoria-related AEs at any dose tested, compared to 0 of 17 subjects who received placebo. Of the five acute-dose studies, euphoria-related AEs were reported by 8 of the 101 subjects who received ganaxolone at any dose tested, compared to 1 of 12 subjects who received placebo. Most of the euphoria-related AEs following ganaxolone administration were mild in severity. In Phase 2/3 clinical studies conducted with ganaxolone in either epilepsy patients or post-traumatic stress disorder patients, the degree of euphoria-related AEs could not be determined because all subjects in these studies were concurrently taking antiepileptic drugs (epilepsy patients) or benzodiazepines (post-traumatic stress disorder patients). Because many antiepileptic drugs and benzodiazepines are known to produce euphoria and sedation, and are often controlled in schedule IV of the CSA, their use in human subjects confounds interpreting any ganaxolone euphoria-related AEs that may be reported during these clinical studies. However, in one of the three clinical studies conducted in patients with migraine, euphoria was reported in 3 of the 163 subjects who received a single 750 mg oral dose of ganaxolone (1.8 percent, 2 moderate, 1 severe), compared to 1 of 164 subjects who received placebo (0.6 percent, 1 mild).

In summary, ganaxolone produced incidence of euphoria-related AEs supportive of its abuse potential. In animal studies, ganaxolone produced interoceptive cues that were similar to those of midazolam, a schedule IV depressant, and these data are consistent with the fact that both drugs share a common mechanism of action involving positive allosteric modulation of the GABA-A receptors. In self-administration studies conducted in animals, ganaxolone produced rewarding effects, but its self-administration was lower than methohexital (schedule IV) and heroin (schedule I) injections. As mentioned by HHS, in clinical studies, ganaxolone produced an 8.8 percent incidence of

[3] NFLIS is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS data were queried on January 18, 2022.

euphoria-like AEs, including euphoria, thinking abnormal, feeling drunk, and depersonalization, across acute doses of 300 to 1,500 mg/day and repeat doses of 400 to 2,250 mg/day, as compared to that of placebo (2.3 percent) in healthy individuals.

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

Ganaxolone, chemically known as 3α-hydroxy-3β-methyl-5α-pregnan-20-one, is an NME. It is a structural derivative of allopregnanolone (also known as brexanolone, schedule IV). Ganaxolone is structurally different from brexanolone by the presence of an extra methyl group at the 3β-position. It is insoluble in water, slightly soluble in methanol, ethanol, isopropanol, ethyl acetate, and toluene (5 to 25 mg/mL at 20 degrees Celsius), and soluble in *N,N*-dimethylacetamide. Ganaxolone is a drug product formulated as a 50 mg/mL white to off-white immediate release oral suspension in water and is administered by mouth TID with food. Ganaxolone is absorbed with a time to peak plasma concentration of 2.0 to 3.0 hours following oral administration. It undergoes first pass metabolism following oral administration with 10 percent bioavailability. It is approximately 99 percent protein bound in serum and has a terminal half-life at steady state of about 8–10 hours.

As discussed in the background section, ganaxolone 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 ganaxolone, since it has not been marketed, legally or illegally, in the United States or any other country. There is no evidence of diversion of ganaxolone that has been distributed for research, such as for clinical trials. Data from preclinical and clinical studies indicate that the abuse potential of ganaxolone is less than that of schedule IV CNS depressants such as methohexital and lorazepam. Consistent with the fact that ganaxolone is an NME, the NFLIS database had no records of encounters by law enforcement.

In summary, pharmacological data on ganaxolone show that it produces abuse-related AEs and has an abuse potential less than that of schedule IV CNS depressants.

5. The Scope, Duration, and Significance of Abuse

Data from preclinical and clinical studies showed that ganaxolone has an abuse potential that is less than that of schedule IV depressants. Thus, ganaxolone has a low potential for abuse relative to substances in schedule IV. A search by DEA of the NFLIS database found no evidence of law enforcement encounters of ganaxolone in the United States. Because ganaxolone is a positive allosteric modulator of GABA-A receptors and has abuse potential, upon availability of ganaxolone in the market, it is likely to be abused.

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

Ganaxolone's abuse potential, although less than that of schedule IV depressants, is an indication of its public health risk. As such, upon availability for marketing, it is likely to pose risk to public health comparable to drugs in schedule V. According to information mentioned in the prescription product label for ZTALMY (ganaxolone), concomitant use of opioids, antidepressants, or other CNS depressants such as alcohol may potentiate incidence of somnolence and sedation in patients receiving ganaxolone. The abuse of ganaxolone may present risks to the public health at a level similar to those associated with the abuse of CNS depressants.

7. Its Psychic or Physiological Dependence Liability

Ganaxolone's psychic and physiological dependence liability was assessed using data from a rat physical dependence study and human data. A physical dependence study was not conducted in clinical studies because abrupt discontinuation of an antiepileptic drug in epileptic patients presents serious safety concerns. As described by HHS, data from a physiologic dependence study conducted in rats demonstrated that chronic administration of ganaxolone produced a decrease in body weight and changes in behavior that included ataxia, rearing, escape attempts from the cage, increased body tone, increased locomotor activity, increased reaction to sound, explosive movements, and piloerection. Decreases in body weight, food and water intake, and increased body temperature were observed upon discontinuation of ganaxolone. During ganaxolone discontinuation, 5 of 10 rats showed behaviors that included increased locomotor activity, increased reaction to sound, hunched posture, and piloerection. Further, since ganaxolone produced positive subjective responses and euphoria-related AEs in human subjects, it is likely that it may produce psychic dependence.

In summary, data from animal studies demonstrate that chronic administration of ganaxolone produces signs or symptoms of withdrawal upon discontinuation. Ganaxolone produces physical dependence.

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

Ganaxolone 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 ganaxolone. As such, DEA hereby schedules ganaxolone 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)(5), finds that:

(1) Ganaxolone has a low potential for abuse relative to the drugs or other substances in schedule IV.

Ganaxolone, a neuroactive steroid, is a positive allosteric modulator of GABA-A receptors and produces sedation in general behavioral studies including rotarod and locomotion studies. In a drug discrimination study in animals, ganaxolone generalized to midazolam (schedule IV), demonstrating it has GABA-A receptor agonist properties. In a self-administration study in animals, ganaxolone self-administration was significantly different from saline, but was less than that of methohexital (schedule IV) and heroin (schedule I). Ganaxolone produced positive subjective responses and euphoria-related AEs less than that of lorazepam (schedule IV), but greater than that of placebo in a human abuse potential study. Furthermore, data from pharmacokinetic clinical studies show that ganaxolone produced incidence of euphoria in 8.8 percent of healthy individuals as compared to 2.3 percent incidence following placebo. Therefore, ganaxolone has some potential for abuse, but it is low relative to lorazepam, methohexital and other substances in schedule IV.

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

FDA recently approved the NDA for ZTALMY (ganaxolone) as an oral adjunctive therapy for the treatment of an epilepsy condition, cyclin-dependent, kinase-like 5 deficiency disorder, in patients aged two years and older. Thus, ganaxolone has a currently accepted medical use in treatment in the United States.

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

Ganaxolone shares a similar pharmacology profile with brexanolone (schedule IV). Data from a rat physical dependence study demonstrated that discontinuation of chronic administration of ganaxolone produced withdrawal syndrome. Thus, abuse of ganaxolone may lead to limited physical dependence. Further, because ganaxolone produced positive subjective responses and euphoria-related AEs, it may produce psychic dependence. However, there were fewer reports of euphoria-related AEs associated with ganaxolone than lorazepam (schedule IV). Ganaxolone may lead to limited physical or psychological dependence relative to other substances in schedule IV.

Based on these findings, the Administrator concludes that ganaxolone warrants control in schedule V of the CSA. 21 U.S.C. 812(b)(5).

Requirements for Handling Ganaxolone

Ganaxolone is subject to the CSA's schedule V 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 V 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, ganaxolone 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 ganaxolone and is not registered with DEA must submit an application for registration and may not continue to handle ganaxolone 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 ganaxolone pursuant to a lawful prescription.

2. *Disposal of stocks.* Any person unwilling or unable to obtain a schedule V registration to handle ganaxolone, but who subsequently does not desire or is not able to maintain such registration must surrender all quantities of currently held ganaxolone, or may transfer all quantities of currently held ganaxolone to a person registered with DEA. Ganaxolone 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.* Ganaxolone 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 ganaxolone 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 ganaxolone pursuant to a lawful prescription.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of ganaxolone 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 ganaxolone must take an inventory of ganaxolone 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 ganaxolone must take an initial inventory of all stocks of controlled substances (including ganaxolone) 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 ganaxolone) 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 ganaxolone pursuant to a lawful prescription.

6. *Records and Reports.* DEA registrants must maintain records and submit reports for ganaxolone, 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 ganaxolone, or products containing ganaxolone, 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 V controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of ganaxolone may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the FDCA, as applicable, and the CSA.

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

10. *Liability.* Any activity involving ganaxolone 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 § 1308.15:

■ a. Redesignate paragraphs (e)(4) through (6) as paragraphs (e)(5) through (7); and

■ b. Add new paragraph (e)(4).

The addition reads as follows:

§ 1308.15 Schedule V.

* * * * *

(e) * * *

(4) Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one)	2401

* * * * *

Anne Milgram,

Administrator.

[FR Doc. 2022–11735 Filed 5–31–22; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–495]

Schedules of Controlled Substances: Placement of N-Ethylhexedrone, alpha-Pyrrolidinohexanophenone, 4-Methyl-alpha-ethylaminopentiophenone, 4′-Methyl-alpha-pyrrolidinohexiophenone, alpha-Pyrrolidinoheptaphenone, and 4′-Chloro-alpha-pyrrolidinovalerophenone in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: By this rule, the Drug Enforcement Administration permanently places six synthetic cathinones, as identified in this rule, in schedule I of the Controlled Substances Act. These six 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, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess) or propose to handle these six specified controlled substances will continue to apply.

DATES: Effective June 1, 2022.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362–8207.

SUPPLEMENTARY INFORMATION: In this rule, the Drug Enforcement Administration (DEA) is permanently