Airmen. The effective date and time will thereafter be continuously published in the Airport/Facility Directory.

Paragraph 6002 Class E airspace Designated as Surface Areas.

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AWP CA E2 Salinas, CA [Removed]

Paragraph 6004 Class E airspace areas designated as an extension to Class D surface area.

* * * * *

AWP CA E4 Salinas, CA [Modified]

Salinas Municipal Airport, CA
(Lat. 36°39′46″ N., long. 121°36′23″ W.)

That airspace extending upward from the surface within 1.8 miles each side of the 150° bearing of Salinas Municipal Airport extending from the 4.3-mile radius of the airport to 8 miles southeast of the airport. This Class E airspace area is effective during the specific dates and times established in advance by a Notice to Airmen. The effective date and time will thereafter be continuously published in the Airport/Facility Directory.

Paragraph 6005 Class E airspace areas extending upward from 700 feet or more above the surface of the earth.

* * * * *

AWP CA E5 Salinas, CA [New]

Salinas Municipal Airport, CA
(Lat. 36°39′46″ N., long. 121°36′23″ W.)

That airspace extending upward from 700 feet above the surface within a 13.1-mile radius of Salinas Municipal Airport.

Issued in Seattle, Washington, on September 26, 2013.

Johanna Forkner,

Acting Manager, Operations Support Group, Western Service Center.

[FR Doc. 2013–24744 Filed 10–21–13; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–374]

Schedules of Controlled Substances: Placement of Perampanel into Schedule III

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes to place the substance perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate], including its salts, isomers, and salts of isomers, into Schedule III of the Controlled Substances Act (CSA). This proposed action is based on a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (HHS) and on an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions of Schedule III controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, and possess) or propose to handle perampanel.

DATES: Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). Comments must be submitted electronically or postmarked on or before November 21, 2013. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

Interested persons, defined as those ''adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811),'' 21 CFR 1300.01, may file a request for hearing or waiver of participation pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and 1316.47. Requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before November 21, 2013.

ADDRESSES: To ensure proper handling of comments, please reference ''Docket No. DEA–374'' on all electronic and written correspondence. The DEA encourages that all comments be submitted 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. Go to *http://www.regulations.gov* and follow the on-line instructions at that site for submitting comments. An electronic copy of this document and supplemental information to this proposed rule are also available at *http://www.regulations.gov* for easy reference. Paper comments that duplicate electronic submissions are not necessary. All comments submitted to *http://www.regulations.gov* will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments, in lieu of electronic comments, they should be sent via regular or express mail to: Drug Enforcement Administration, Attention: DEA **Federal Register** Representative/ODW, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Ruth A. Carter, Chief, Policy Evaluation and Analysis Section, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that comments received in response to this docket are considered part of the public record and will be made available for public inspection and posted at *http://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made public, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all 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 it to be made publicly available, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available.

Comments containing personally identifying information or confidential business information identified as directed above will be made publicly available in redacted form. The Freedom of Information Act (FOIA) applies to all comments received. If you wish to personally inspect the comments and materials received or the supporting documentation the DEA used in preparing the proposed action, these materials will be available for public inspection by appointment. To arrange

a viewing, please see the **FOR FURTHER INFORMATION CONTACT** paragraph, above.

Requests for Hearing, Notice of Appearance at Hearing, or Waiver of Participation in Hearing

Pursuant to the provisions of the CSA (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, and 21 CFR part 1316 subpart D. In accordance with 21 CFR 1308.44(a)–(c), requests for a hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing may be submitted only by interested persons, defined as those ''adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811).'' 21 CFR 1300.01. Such requests or notices must conform to the requirements of 21 CFR 1308.44(a) or (b) and 1316.47 or 1316.48, as applicable, and include a statement of the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and 1316.49, including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

Please note that pursuant to 21 U.S.C. 811(a), the purpose and subject matter of a hearing held in relation to this rulemaking is restricted to ''(A) find[ing] that such drug or other substance has a potential for abuse, and (B) mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of [Title 21] for the schedule in which such drug is to be placed. . . .'' Requests for hearing, notices of appearance at the hearing, and waivers of an opportunity for a hearing or to participate in a hearing must be submitted to the DEA using the address information provided above.

Legal Authority

The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970 and the Controlled Substances Import and Export Act, as amended, and collectively referred to as the Controlled Substances Act (CSA) (21 U.S.C. 801–971). The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), parts 1300 to 1321. The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, controlled substances are classified into one of five schedules based upon their potential for abuse, their currently accepted medical use, and the degree of dependence the substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c), and the current list of all scheduled substances is published at 21 CFR part 1308. Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, ''add to such a schedule or transfer between such schedules any drug or other substance if he (A) finds that such drug or other substance has a potential for abuse, and (B) makes with respect to such drug or other substance the findings prescribed by [21 U.S.C. 812(b)] for the schedule in which such drug is to be placed . . . .'' Pursuant to 28 CFR 0.100(b), the Attorney General has delegated this scheduling authority to the Administrator of the DEA who has further delegated this authority to the Deputy Administrator of the DEA under 28 CFR 0.104.

The CSA provides that 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); or (3) on the petition of any interested party. 21 U.S.C. 811(a). If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions of Schedule III on the manufacture, distribution, dispensing, importation, exportation, research, instructional activities, and possession of perampanel.

Background

Perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate] is a new chemical entity with central nervous system (CNS) depressant and hallucinogenic properties. The HHS states that on October 22, 2012, the Food and Drug Administration (FDA) approved a new drug application for perampanel as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel will initially be marketed in the United States under the trade name FYCOMPA®. Perampanel is a non-competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptor antagonist. Perampanel was approved in Europe in May 2012 and has been marketed there since July 2012.

Proposed Determination to Schedule Perampanel

Pursuant to 21 U.S.C. 811(a), proceedings to add a drug or substance to those controlled under the CSA may be initiated by request of the Secretary of the Department of Health and Human Services (HHS). On January 22, 2013, the HHS recommended that the DEA add perampanel to Schedule III of the CSA and provided the DEA with the scientific and medical evaluation document, ''Basis for the Recommendation for Control of Perampanel and Its Salts in Schedule III of the Controlled Substances Act.'' Following consideration of the eight factors determinative of control under the CSA, with findings related to the substance's abuse potential, legitimate medical use, and dependence liability, the HHS recommended that perampanel be controlled in Schedule III of the CSA. In response, the DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS, and all other relevant data, and completed an eight factor review document pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in its proposed scheduling decision. Please note that the DEA and HHS analyses are available in their entirety under ''Supporting and Related Material'' in the public docket for this proposed rule, at *http://www.regulations.gov*, under Docket Number ''DEA–374.'' Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. *The Drug's Actual or Relative Potential for Abuse:* Perampanel is a new chemical entity that has been marketed in Europe since July 2012. According to the HHS, since perampanel has been marketed in Europe only since July 2012, there is a lack of information regarding perampanel's actual or relative potential for abuse. However, the legislative history of the CSA offers the following criterion for assessing a new drug or substance's potential for abuse:

The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as

having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.[1]

According to the HHS, perampanel is a non-competitive AMPA-type glutamate receptor antagonist, which has been demonstrated by various groups. Antagonism of the AMPA receptors has been shown to produce a broad-spectrum anti-convulsant activity of focal and generalized epilepsy in animal models.

The HHS states that monkeys self-administered perampanel at rates similar to or greater than those for pentobarbital (Schedule II). These data indicate that perampanel may have a high psychological dependence liability. It was demonstrated in rats that cessation of administration of perampanel produced withdrawal symptoms similar to those produced after cessation of diazepam (Schedule IV) administration.

According to the HHS, a clinical study of recreational drug abusers (with histories of abuse of sedative hypnotic and psychoactive drugs such as ketamine (Schedule III) and alprazolam (Schedule IV)) using ketamine (Schedule III), alprazolam (Schedule IV), and perampanel produced subjective effects indicative of abuse potential. The subjective effects reported were ''euphoria,'' ''high,'' and ''drug-liking.'' For the measures of ''floating,'' ''spaced out,'' and ''detached,'' perampanel produced similar responses to those of ketamine (Schedule III) and greater responses than those of alprazolam (Schedule IV). The study used 8, 24, and 36 mg doses of perampanel, 100 mg doses of ketamine (Schedule III), 1.5 and 3mg doses of alprazolam (Schedule IV), or a placebo. Those that received 24 and 36 mg doses of perampanel reported measures of ''sedation,'' ''slowed down,'' ''confused,'' ''clear crisp vision,'' and ''attention span'' at levels similar to or greater than alprazolam (Schedule IV) and greater than ketamine (Schedule III). Forty-six percent of the subjects reported euphoria-type adverse events (AEs) with the 24 and 36 mg perampanel doses, which was higher than the rate reported for 3 mg alprazolam (Schedule IV) (13 percent), and lower than that reported for 100 mg ketamine (Schedule III) (89 percent). The data from the study indicated that perampanel produces behavioral and subjective effects in humans similar to or greater than alprazolam (Schedule IV) and similar to ketamine (Schedule III).

According to the HHS, based on results from the clinical study with recreational drug users, it is reasonable to assume that perampanel will appeal to individuals who prefer to abuse drugs that elicit the subjective and behavioral effects of alprazolam (Schedule IV) and ketamine (Schedule III). The HHS anticipates that abuse will result in: diversions of perampanel from legitimate pharmaceutical distribution channels; significant use of perampanel contrary to or without medical advice; and a substantial capability to create hazards to the abuser's health and to the safety of the community.

2. *Scientific Evidence of the Drug's Pharmacological Effects, If Known:* Perampanel is a non-competitive antagonist of the AMPA glutamate receptor. According to the HHS, perampanel is also a direct and indirect antagonist of the NMDA receptor. The HHS states that perampanel is pharmacologically similar to ketamine (Schedule III), a NMDA receptor antagonist and a recreational drug known for its euphorigenic, dissociative, and hallucinogenic properties. Binding studies revealed that perampanel did not inhibit binding at any receptor site by more than 50 percent.

According to the HHS, based on electrophysiological assays performed on ion channels of $GABA_A$ receptors, perampanel would be expected to cause sedation, muscle relaxation, impairment of motor coordination and memory, development of dependency, and occurrence of benzodiazepine-like withdrawal symptoms after discontinuation.

The DEA further adds that perampanel has inhibited AMPA-induced increases in $[Ca^{2+}]_i$ in rat cortical neurons in a concentration-dependent manner, with an IC_{50} of 93 nM. Perampanel (300 nM) inhibited AMPA receptor-mediated excitatory postsynaptic field potentials (f-EPSPs) in rat hippocampal slices by 50 percent. Perampanel inhibited AMPA receptor-mediated f-EPSPs in a dose-dependent manner, with 10 μM causing complete inhibition; the IC_{50} was 230 nM.

According to the HHS, animal studies indicate that perampanel is a depressant. The Irwin test is an observational procedure that assesses and scores the effects of drugs on rodents' behavior and physiology. Perampanel (5 mg/kg), administered orally by gavage, decreased alertness, touch response, body position, limb tone, grip strength, body tone, spontaneous activity, and abdominal tone, and caused staggering and inhibition of palpebral opening (eyelid) in male rats.

The HHS reported on two human abuse potential studies that were performed in healthy, adult, recreational poly-drug users. In the first study, eight doses of perampanel (8, 12, 16, 20, 24, 28, 32, and 36 mg) were administered to the subjects. It was determined that 36 mg was the maximum tolerated dose (MTD). The most commonly reported AEs were psychiatric, in particular euphoria, which occurred at a rate of 22.6 percent in the higher dose group which received 24, 28, 32, and 36 mg doses of perampanel.

In the second human abuse potential study, perampanel produced subjective responses similar to or greater than those produced by alprazolam (Schedule IV) and ketamine (Schedule III). Perampanel (8, 24, and 36 mg), ketamine (Schedule III) (100 mg), alprazolam (Schedule IV) (1.5 and 3 mg), and placebo were administered to 34 subjects who were current recreational poly-drug users with histories of CNS depressant and psychedelic drug use. The effects of perampanel (24 and 36 mg) on the drug-liking Visual Analogue Scale (VAS) were higher than that of alprazolam (Schedule IV) (1.5 and 3 mg) and similar to ketamine (Schedule III) (100 mg). For the Addiction Research Center Inventory Morphine-Benzedrine Group (ARCI MBG) (euphoria) measure, the responses produced by perampanel (24 and 36 mg) were comparable to those produced by alprazolam (Schedule IV) (3 mg) and ketamine (Schedule III) (100 mg), indicating that perampanel produces euphoria comparable to that produced by alprazolam (Schedule IV) and ketamine (Schedule III). The rates reported for euphoria AEs were 37 percent for the 8 mg dose and 46 percent for the 24 and 36 mg doses of perampanel. The rates reported for euphoria AEs for 3 mg alprazolam (Schedule IV) and 100 mg ketamine (Schedule III), were 13 percent and 89 percent, respectively.

For the measure of feeling ''high'' on a VAS, perampanel (24 and 36 mg) produced responses that were comparable to those for ketamine (Schedule III) (100 mg) and alprazolam (Schedule IV) (1.5 and 3 mg). Perampanel (36 mg) was long-acting for the sedation and ''high'' effects. They lasted at least 22 hours. It was demonstrated that perampanel caused

[1] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., Sess. 1 (1970); *as reprinted in* 1970 U.S.C.C.A.N. 4566, 4601.

NMDA-antagonist specific effects, such as ''floating,'' ''spaced out,'' ''detached,'' and ''feeling happy,'' that were similar to those of ketamine (Schedule III) and greater than those of alprazolam (Schedule IV) (1.5 and 3 mg). The duration of these effects was longer for perampanel (24 and 36 mg) than for ketamine (Schedule III) (100 mg): 24 to 48 hours compared to 3 hours, respectively. The measures of ''sedation,'' ''confused,'' ''slowed down,'' ''attention span,'' and ''clear crisp vision'' following doses of 24 and 36 mg perampanel were similar to, or greater than, alprazolam (Schedule IV), and greater than ketamine (Schedule III). The duration of effects of higher doses of perampanel on the majority of measures was longer than for 3 mg alprazolam (Schedule IV) and 100 mg ketamine (Schedule III).

According to the HHS, in clinical trials that were conducted to study the effect of perampanel on certain chronic diseases, e.g., epilepsy, Parkinson's disease, migraines, multiple sclerosis (MS), and peripheral neuropathy, perampanel caused CNS depressant effects including somnolence/sedation, dizziness, ataxia, confusion, amnesia and memory impairment, euphoria, depression, and suicidality. The AEs that are related to NMDA receptor antagonists were also associated with perampanel. These included psychotic disorder/psychosis, hallucinations, dissociation, delusional behavior, delirium, paranoia, euphoria, agitation, amnesia, confusion, and catatonia.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* Perampanel (2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3) is a white-to-yellowish powder. The molecular formula is $C_{23}H_{15}N_3O \bullet 3/4H_2O$. It is freely soluble in N-methylpyrrolidone, sparingly soluble in acetonitrile and acetone, slightly soluble in methanol, ethanol, and ethyl acetate, very slightly soluble in 1-octanol and diethyl ether, and practically insoluble in heptanes and water.

Perampanel is rapidly and almost completely absorbed, slowly metabolized, and slowly eliminated after oral administration. In humans, the median T_{max} ranged from 0.5–2.5 hours under fasted conditions; the T_{max} increased by 2–3 hours under fed conditions. T_{max} is the amount of time for a substance to reach maximal plasma concentrations after administration. According to the HHS, the mean half-life of perampanel (1 mg) in the fasted state was 84.5 and 129.5 hours for men and women, respectively. The steady state is reached in about 2–3 weeks. Perampanel is slowly metabolized and the metabolites are eliminated rapidly via urine or feces. Three metabolites of perampanel have been identified as HU1, HU2, and HU3. HU1 and HU2 are oxygen glucuronide conjugates and HU3 is a dihydrodiol analog. Oxidative metabolism is mediated by CYP3A4 and/or CYP3A5.

4. *Its History and Current Pattern of Abuse:* An assessment of the history and current pattern of perampanel abuse is not available because it has only been marketed in Europe since July 2012. As stated in HHS's review, the results of a human abuse potential study indicate that perampanel has an abuse potential comparable to or greater than the abuse potential of alprazolam (Schedule IV) and similar to that of ketamine (Schedule III). In addition, higher doses of perampanel produced a high rate of euphoria-type AEs (up to 46 percent). The HHS asserts that the positive subjective effects reported from supratherapeutic doses of perampanel administration are predictive of its potential to be abused. Alprazolam (Schedule IV) and ketamine (Schedule III) have histories of diversion and abuse. Based on perampanel's subjective AE profile and its similarity to ketamine (Schedule III) and alprazolam (Schedule IV), it is reasonable to assume that perampanel will produce an abuse pattern that will have features of both ketamine (Schedule III) and alprazolam (Schedule IV) abuse.

5. *The Scope, Duration, and Significance of Abuse:* According to the HHS review, the scope, duration, and significance of abuse of perampanel are unknown because it has only been marketed in Europe since July 2012. However, the scope, duration, and significance of abuse of perampanel can be predicted from the data obtained in pre-market clinical studies such as abuse potential studies and other clinical studies. In its analysis, the HHS concluded that:

> [I]f perampanel were marketed in the United States, the scope and significance of abuse of perampanel would be similar to or greater than alprazolam [Schedule IV] and similar to or greater than ketamine [Schedule III]. If perampanel were marketed as a non-controlled antiepileptic drug, it is reasonable to assume that perampanel would be abused to an even greater extent than it would be when controlled in Schedule III of the CSA. This is because individuals who abuse such drugs, namely ketamine, would likely prefer to use a drug that is non-controlled, or in a lower level of control, rather than drugs that act similarly and are controlled in [Schedule III], or more restrictive schedules of the CSA.

6. *What, if Any, Risk There Is to the Public Health:* According to HHS, perampanel likely poses a risk to public health similar to or greater than that of alprazolam (Schedule IV) and similar to that of ketamine (Schedule III). The HHS asserts that the ability of a drug to have an abuse potential is an indication of the public health risk associated with the drug. As summarized in Factor 2, supratherapeutic doses of perampanel (24 and 36 mg) produced euphoria-type AEs in 46 percent of subjects, which was greater than the rate of euphoria AEs in subjects given 3 mg alprazolam (Schedule IV) (13 percent) and less than that produced by 100 mg ketamine (Schedule III) (89 percent).

Clinical studies have demonstrated that perampanel does affect psychomotor performance. In a study of healthy volunteers, single and multiple doses of 8 and 12 mg perampanel dose-dependently impaired psychomotor performance. In the same study, healthy volunteers were given alcohol until their alcohol blood level reached 80–100 mg/100 ml, in addition to perampanel. The effects of perampanel on complex tasks, such as driving ability, were additive or supra-additive to the impairment effects of alcohol.

According to the HHS, the risk of perampanel to the public health was demonstrated by the AEs of aggression, anger, hostility, suicidal ideation and attempts, and homicidal ideation and threats associated with perampanel during the clinical trials. The FYCOMPA® drug label includes a boxed warning alerting prescribers and ultimate users to these public health risks. Approximately 50 subjects from the clinical trials, without previous relevant psychiatric histories, developed psychotic disorders, such as paranoia, delusion, delirium, schizophrenia, and catatonia while taking perampanel. This indicates that perampanel may cause users to display unpredictable or aggressive behavior towards themselves or others. Based on the AEs of perampanel summarized above, the HHS determined that the public health risks of perampanel are likely to be similar to other CNS drugs, such as ketamine (Schedule III).

7. *Its Psychic or Physiological Dependence Liability:* According to the HHS, low (up to 14.7 mg/kg) and high doses (up to 43.5 mg/kg) of oral perampanel were administered to rats for 4 weeks, followed by a 1-week withdrawal period. During the withdrawal period, the rats displayed withdrawal symptoms indicative of dependence, such as hyper-reactivity and muscle rigidity, along with reduced food consumption.

According to the HHS, the physical dependence of perampanel in humans

has not been fully evaluated, because in Phase 3 clinical trials, symptoms of withdrawal were collected in only a small fraction of patients. Reported withdrawal symptoms included fatigue/lethargy/asthenia, irritability, anxiety/nervousness, worsening of mood/tearfulness, mood swings, sleep disorders, weight changes, changes in appetite, muscle pain/stiffness, diarrhea/nausea/vomiting, rhinorrhea, lacrimation, headache, dizziness, hallucinations, panic, and craving/drug seeking. The HHS asserts that the limited results demonstrate that discontinuation of perampanel administration causes signs and symptoms of withdrawal.

8. *Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA:* Perampanel is not an immediate precursor of a substance already controlled under the CSA.

Conclusion: Based on consideration of the scientific and medical evaluation conducted by the HHS and its recommendation, and after considering its own eight-factor analysis, the DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of perampanel. As such, the DEA hereby proposes to schedule perampanel as a controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA outlines 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 by the Assistant Secretary for Health of the HHS, and review of all available data, the Deputy Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(3), finds that:

1. Perampanel has a potential for abuse less than the drugs or other substances in Schedules I and II;

2. Perampanel has a currently accepted medical use in treatment in the United States. Perampanel was approved for marketing by the FDA as an adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older; and

3. Abuse of perampanel may lead to moderate or low physical dependence or high psychological dependence.

Based on these findings, the Deputy Administrator of the DEA concludes that perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate], including its salts, isomers, and salts of isomers, warrants control in Schedule III of the CSA. 21 U.S.C. 812(b)(3).

Requirements for Handling Perampanel

If this rule is finalized as proposed, perampanel would be subject to the CSA's Schedule III regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, research, and conduct of instructional activities, including the following:

Registration. Any person who handles (manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities) perampanel, or who desires to handle perampanel, would be required to be registered with the 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 handles perampanel, and is not registered with the DEA, must be registered with the 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 handles perampanel, and is not registered with the DEA, would need to be registered with the DEA to conduct such activities by the effective date of the final rule.

Security. Perampanel would be subject to Schedule III–V security requirements and would need to be handled and stored in accordance with 21 CFR 1301.71–1301.93, pursuant to 21 U.S.C. 823, 821, 871(b).

Labeling and Packaging. All labels and labeling for commercial containers of perampanel distributed on or after finalization of this rule would need to be in accordance with 21 CFR 1302.03–1302.07, pursuant to 21 U.S.C. 825, 958(e).

Inventory. Every DEA registrant who possesses any quantity of perampanel on the effective date of the final rule would be required to take an inventory of all stocks of perampanel on hand as of the effective date of the rule, pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who becomes registered with the DEA after the effective date of the final rule would be required to take an initial inventory of all stocks of controlled substances (including perampanel) on hand at the time of registration pursuant to 21 U.S.C. 827, 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 would be required to take a biennial inventory of all controlled substances (including perampanel) on hand, on a biennial basis, pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Records. All DEA registrants would be required to maintain records of perampanel pursuant to 21 U.S.C. 827, 958(e) and in accordance with 21 CFR parts 1304 and 1312.

Prescriptions. All prescriptions for perampanel or prescriptions for products containing perampanel would be required to be issued pursuant to 21 U.S.C. 829 and in accordance with 21 CFR part 1306.

Importation and Exportation. All importation and exportation of perampanel would need to be done in accordance with 21 CFR part 1312, pursuant to 21 U.S.C. 952, 953, 957, and 958.

Liability. Any activity with perampanel not authorized by, or in violation of, the CSA, occurring on or after finalization of this proposed rule, would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866 and 13563

In accordance with 21 U.S.C. 811(a), this proposed 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 12866 and the principles reaffirmed in Executive Order 13563.

Executive Order 12988

This proposed regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform 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

This proposed rulemaking does not have federalism implications warranting the application of Executive Order 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175

This proposed rule does not have tribal implications warranting the application of Executive Order 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 Deputy Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601–612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this proposed rule is to place perampanel, including its salts, isomers, and salts of isomers, into Schedule III of the CSA. No less restrictive measures (i.e., non-control) enable the DEA to meet its statutory obligations under the CSA. In preparing this certification, the DEA has assessed economic impact by size category and has considered costs with respect to the various DEA registrant business activity classes.

Perampanel is a new molecular entity, approved by the FDA on October 22, 2012. It was approved in Europe in May 2012, and has been marketed in Europe since July 2012. According to publicly available information reviewed by the DEA, perampanel is currently anticipated to enjoy patent protection for at least a decade before generic equivalents may be manufactured and marketed. Accordingly, the number of currently identifiable manufacturers, importers, and distributors for perampanel is extremely small. The publicly available materials also specify the readily identifiable persons subject to direct regulation by this proposed rule. Based on guidelines utilized by the Small Business Administration, the perampanel manufacturer/distributor/importer was determined not to be a small entity. Once generic equivalents are developed and approved for manufacturing and marketing, there may be additional manufacturers, importers, and distributors of perampanel, but whether they may qualify as small entities cannot be determined at this time.

There are approximately 1.5 million controlled substance registrants, approximately 381,559 of which are estimated to be businesses. The DEA estimates that 371,588 (97 percent) of the affected businesses are considered ''small entities'' in accordance with the RFA and Small Business Administration (SBA) standards. 5 U.S.C. 601(6) and 15 U.S.C. 632. However, due to the wide variety of unidentifiable and unquantifiable variables that could potentially influence the dispensing rates of new chemical entities, the DEA is unable to determine the number of small entities that might dispense (including administer and prescribe) perampanel (e.g., pharmacies and prescribers).

Despite the fact that the number of small businesses potentially impacted by this proposed rule could not be determined at this time, the DEA concludes that they would not experience a significant economic impact as a result of this rule. Currently, 98 percent of DEA registrants (most of which are small businesses) are authorized to handle Schedule III controlled substances. Even if we assume that all of the DEA registrants were to dispense perampanel, (e.g., practitioners prescribe, administer, or dispense the substance, and pharmacies dispense the prescriptions), the costs that they would incur as a result of perampanel scheduling would be minimal. Registrants that dispense (but not prescribe) would incur nominal additional security, inventory, recordkeeping, and labeling costs, as they have already established and implemented the required systems and processes to handle Schedule III controlled substances. For example, pharmacies and institutional practitioners may disperse Schedule II through V controlled substances throughout their stock of non-controlled substances in such a manner as to obstruct theft or diversion of the controlled substances. The inclusion of one additional substance to this system would result in little or no additional burden to such practitioners. In addition, because DEA-registered dispensers must label all Schedule II–V controlled substances dispensed, the requirement to label all controlled substances containing perampanel would not impose a significant economic burden upon DEA-registered dispensers (as the infrastructure and materials for doing so would already be in place). Accordingly, compliance would not require significant manpower, capital investments, or recordkeeping burdens.

Registrants who only prescribe perampanel by oral or written prescription would not incur any additional security, inventory, recordkeeping, or labeling costs as a result of this rule as they would not physically handle perampanel.

Because of these facts, this proposed rule will not result in significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 *et seq.*), on the basis of information contained in the ''Regulatory Flexibility Act'' section above, the DEA has determined and certifies pursuant to UMRA 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 for inflation) in any one year. . . .'' Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of 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.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended 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), unless otherwise noted.

■ 2. Amend § 1308.13 by redesignating paragraphs (c)(11) through (c)(14) as paragraphs (c)(12) through (c)(15) and adding new paragraph (c)(11) to read as follows:

§ 1308.13 Schedule III.

* * * * *

(c) * * *

(11) Perampanel, and its salts, isomers, and salts of isomers 2261

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Dated: October 9, 2013.

Thomas M. Harrigan,

Deputy Administrator.

[FR Doc. 2013–24600 Filed 10–21–13; 8:45 am]

BILLING CODE P

DEPARTMENT OF DEFENSE

Office of the Secretary

32 CFR Part 199

[DOD–2013–HA–0164]

RIN 0720–AB61

TRICARE; Coverage of Care Related to Non-Covered Initial Surgery or Treatment

AGENCY: Office of the Secretary, Department of Defense.

ACTION: Proposed rule.

SUMMARY: The Department of Defense (DoD) is publishing this proposed rule to allow coverage for otherwise covered services and supplies required in the treatment of complications (unfortunate sequelae), as well as medically necessary and appropriate follow-on care, resulting from a non-covered incident of treatment provided pursuant to a properly granted Supplemental Health Care Program waiver. This proposed rule is necessary to protect TRICARE beneficiaries from incurring financial hardships due to the current regulatory restrictions that prohibit TRICARE coverage of the treatment of complications resulting from non-covered medical procedures, even when those procedures were provided while the beneficiary was an active duty member and were authorized by the Director, TRICARE Management Activity (TMA), based on a determination that a waiver authorizing the original non-covered surgery or treatment was necessary to assure adequate availability of health care to the Active Duty member. Additionally, with respect to care that is related to a non-covered initial surgery or treatment, the proposed rule seeks to eliminate any confusion regarding what services and supplies will be covered by TRICARE and under what circumstances they will be covered.

DATES: Comments must be received on or before December 23, 2013. Do not submit comments directly to the point of contact or mail your comments to any address other than what is shown below. Doing so will delay the posting of the submission.

ADDRESSES: You may submit comments, identified by docket number and/or Regulatory Identification Number (RIN) and title, by any of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.
- *Mail:* Federal Docket Management System Office, 4800 Mark Center Drive, East Tower, Suite 02G09, Alexandria, VA 22350–3100.

Instructions: All submissions received must include the agency name and docket number or RIN for this **Federal Register** document. The general policy for comments and other submissions from members of the public is to make these submissions available for public viewing on the Internet at *http://regulations.gov* as they are received without change, including any personal identifiers or contact information.

FOR FURTHER INFORMATION CONTACT: Thomas Doss (703) 681–7512.

SUPPLEMENTARY INFORMATION:

I. Executive Summary

1. Purpose of Regulatory Actions

a. Need for Regulatory Actions

Under the TRICARE private sector health care program, certain conditions and treatments are excluded from coverage. For example, any drug, device, medical treatment, or procedure whose safety and efficacy has not been established by reliable evidence is considered unproven and excluded from coverage. This exclusion includes all services directly related to the unproven drug, device, medical treatment or procedure. Specifically, benefits for otherwise covered services and supplies that are required in the treatment of complications (unfortunate sequelae) resulting from a non-covered incident of treatment, are generally excluded from TRICARE coverage pursuant to title 32 of the Code of Federal Regulation (CFR) section 199.4(e)(9), unless the complication represents a separate medical condition such as a systemic infection, cardiac arrest, and acute drug reaction. TRICARE also excludes any needed follow-on care resulting from a non-covered condition or initial surgery or treatment pursuant to § 199.4(g)(63).

There is currently one exception to this general exclusion, published in the **Federal Register** [76 FR 57642] on September 16, 2011, to allow coverage of otherwise covered services and supplies required in the treatment of complications (unfortunate sequelae) resulting from a non-covered incident of treatment provided in a Military Treatment Facility (MTF), when the initial non-covered service has been authorized by the MTF Commander and the MTF is unable to provide the necessary treatment of the complications. This current exception recognizes that in order to support Graduate Medical Education and maintain provider skill levels, MTF providers are required to perform medical procedures that may be excluded from coverage under the TRICARE private sector program. The final rule at 32 CFR199.4(e)(9)(ii) was viewed as necessary to protect TRICARE beneficiaries from incurring financial hardships in such cases.

Currently, Active Duty Service members (ADSMs) may receive non-covered TRICARE private sector health care services under the Supplemental Health Care Program (SHCP) if a waiver is submitted through the Service and approved by the Director, TMA, or designee, in accordance with § 199.6(f). While the Department wants to ensure that Service members have access to the latest, promising medical technologies and procedures, there must be assurance that the care is safe and effective, and that members are not subjected to undue risk, or rendered unfit for continued service, due to complications suffered as a result of unproven medical care. Consequently, requests for non-covered procedures and treatments, including unproven care, are carefully reviewed in conjunction with other available, proven treatments, if any exist, to determine whether or not approval of the requested care is necessary to assure the adequate availability of health care to the member. Currently, Service members are counseled that the treatment remains a non-covered TRICARE benefit, and that any follow-on care, including care for complications, will not be covered by TRICARE once the member separates or retires. Members are left to make a difficult choice between pursuing a SHCP waiver in an effort to remain fit for full duty while assuming the financial risk of any necessary follow-on care after discharge, or, electing not to receive the care and risk separation from the Service.

Like the existing exception at 32 CFR199.4(e)(9)(ii) for non-covered care provided in a MTF, this proposed exception is narrowly tailored to serve a similar government interest; namely, protecting former active duty members who have received private sector care pursuant to a SHCP waiver in an effort to ensure their fitness for duty and continued service.

Additionally, some confusion has arisen regarding the terms ‘‘complication’’ and ‘‘unfortunate sequelae’’ as these terms are not