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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–1743]

Schedules of Controlled Substances: Placement of Centanafadine in Schedule III

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule; request for comments.

SUMMARY: On July 24, 2026, the United States Food and Drug Administration (FDA) approved a new drug application for Simtriyo (centanafadine) for the treatment of attention-deficit/hyperactivity disorder in adults and pediatric patients aged 6 years and older, weighing at least 20 kg. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place centanafadine, chemically known as (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in schedule III 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 centanafadine, including its salts, isomers (whether optical, positional, or geometric), and salts of such isomers whenever the existence of such salts, isomers, and salts of isomers is possible in schedule III 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-1743" 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-1743.

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), the Drug Enforcement Administration (DEA) is adding centanafadine, including its salts, to schedule III 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

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

the address information provided above. The decision whether a hearing will be needed to 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 IFR 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 centanafadine meets the statutory criteria for placement in schedule III.

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 and 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

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

good cause therefore. Thus, the purpose of subsection 811(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.[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

Centanafadine is a new molecular entity with CNS activity, acting as a novel triple reuptake inhibitor that targets norepinephrine, dopamine, and serotonin. Its mechanism of action has some similarities to schedule II stimulants like cocaine.

On November 24, 2025, Otsuka Pharmaceutical Development and Commercialization, Inc. (Sponsor) submitted an NDA for centanafadine to FDA. On July 24, 2026, FDA approved the NDA for centanafadine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients aged 6 years and older, weighing at least 20 kg. Centanafadine will be formulated as extended-release capsules for once-daily oral administration.

Determination to Schedule Centanafadine

On July 18, 2026, DEA received from HHS a scientific and medical evaluation entitled "Basis for the Recommendation to Control Centanafadine and Its Salts in Schedule III 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 centanafadine, along with HHS's recommendation to control centanafadine under schedule III 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 centanafadine meets the 21 U.S.C. 812(b)(3) criteria for placement in schedule III 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 centanafadine as a schedule III 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-1743." 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

According to HHS, because centanafadine has not been legally marketed in the United States or any other country, the legitimate drug channels for centanafadine are limited to the research conducted with the drug, and to manufacturing facilities and the supply chain to produce centanafadine for legitimate drug research. HHS further notes that, because centanafadine has not been legally marketed in the United States or any other country, abuse of centanafadine would be limited to incidents during the conduct of clinical studies or following diversion of supplies from research or manufacturing activities of centanafadine. According to HHS, suspected diversion of centanafadine occurred in one of the thirty-seven clinical studies conducted during the development of centanafadine. Three subjects in the study were suspected of abusing or diverting centanafadine based on medication handling irregularities. DEA's

National Forensic Laboratory Information System (NFLIS)-Drug[5] data show that there is no report of law enforcement encounters of centanafadine in the United States. Centanafadine is a triple reuptake inhibitor that targets the specific transporters of norepinephrine (NET), dopamine (DAT), and serotonin (SERT), and it is a CNS stimulant. HHS states that centanafadine produces self-administration in rats and full generalization to amphetamine in a rat drug discrimination study (*see* Factor 2). In two human abuse potential studies, centanafadine produced subjective responses that indicate the drug has rewarding properties (see Factor 2). Accordingly, its mechanism of action and reinforcing properties share similarities with schedule II stimulants, like cocaine and methylphenidate, with known abuse potential. Both FDA and DEA concluded that centanafadine has an abuse potential lower than those of schedule II stimulants.

2. Scientific Evidence of Its Pharmacological Effects, if Known

In Vitro Studies

Based on *in vitro* binding and functional reports, HHS noted that centanafadine acts as a triple reuptake inhibitor that targets norepinephrine, dopamine, and serotonin to achieve its CNS stimulant effects.

Binding Affinity and Functional Study: Centanafadine binds with high affinity to NET, SERT, and DAT, and inhibits the reuptake of these neurotransmitters. Conversely, its major metabolite, EB-10601, showed weak-to-no affinity for these three transporters, suggesting that it likely does not contribute to centanafadine's therapeutic efficacy. Neither compound showed significant activity at other CNS receptors measured.[6]

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[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 were queried on July 20, 2026.

[6] Department of Health and Human Services. (2026). Basis for the recommendation to control centanafadine and its salts in schedule III of the Controlled Substances Act. U.S. Department of Health and Human Services, July 17, 2026. Page 4.

Intracerebral Microdialysis Study: Oral administration of centanafadine (3–30 mg/kg) in rats dose-dependently increased extracellular norepinephrine, dopamine, and serotonin in the prefrontal cortex, as well as dopamine and serotonin in the ventral striatum. These microdialysis findings support the mechanism of action for centanafadine as a triple reuptake inhibitor at NET, DAT, and SERT.

Preclinical Behavioral Studies

Drug Discrimination: An HHS-reviewed drug discrimination study demonstrated that oral centanafadine fully generalizes to an amphetamine cue, indicating substantial potential for human abuse. In female rats trained to distinguish schedule II stimulant, amphetamine (0.3 mg/kg, intraperitoneal) from saline under a fixed-ratio (FR) 5 schedule, centanafadine achieved full generalization (76 percent) at the 10 mg/kg oral dose, producing a mean plasma concentration of 718 ng/mL, which is roughly half the human highest concentration (C_{max}) (1460 ng/mL) achieved at a dose of 200 mg twice daily. Similar to schedule II stimulant methylphenidate (83 percent generalization at 5 mg/kg oral dose) and schedule IV stimulant phentermine (93 percent generalization at 3 mg/kg oral dose), centanafadine mimics the interoceptive stimulus effects of amphetamine, strongly indicating an inherent abuse liability.[7]

Self-Administration: An HHS-reviewed intravenous self-administration study demonstrated that centanafadine possesses rewarding properties that sustain reinforcement, signaling an inherent risk of human abuse. In rats trained on a FR5 schedule to self-administer cocaine (0.36 mg/kg/injection, maintained at 19 injections per session) or undergo saline extinction (not greater than 5 injections per session), centanafadine sustained self-administration above saline levels across all doses tested. The two highest doses produced a degree of self-administration of 13 injections per session at the 0.03 mg/kg/injection dose and 15 injections/session from the 0.10 mg/kg/injection dose ($p < 0.001$ for both compared to saline).

[7] Department of Health and Human Services. (2026). Basis for the recommendation to control centanafadine and its salts in schedule III of the Controlled Substances Act. U.S. Department of Health and Human Services, July 17, 2026. Page 5.

Schedule II methylphenidate and unscheduled bupropion similarly sustained cocaine-like self-administration at their highest doses, though bupropion data was excluded from the final assessment due to its uncontrolled regulatory status. While the rate of centanafadine self-administration remained statistically lower than cocaine (maintained at 19 injections per session) across all doses ($p < 0.001$), centanafadine's capacity to maintain active reinforcement mimics the profiles of schedule II stimulants, confirming its potential for abuse.[8]

Pharmacological and Behavioral Studies in Human

Human Abuse Potential (HAP) studies assess a drug's abuse liability by comparing a test drug to active controls and placebos. As described in HHS's scientific and medical evaluation, two HAP studies were conducted by the drug sponsor to assess the abuse potential of centanafadine in participants who were non-dependent, recreational drug users.

The first HAP study was a randomized, double-blind, placebo- and active-controlled, crossover trial that evaluated the oral abuse potential of immediate-release centanafadine (400 mg and 800 mg, representing 2 and 4 times the therapeutic levels) against placebo and active positive controls: immediate-release amphetamine (40 mg) and lisdexamfetamine (150 mg) in 36 healthy male, nondependent recreational stimulant users. Data from the study demonstrated that supratherapeutic doses of centanafadine produced positive subjective effects that were significantly greater than those by placebo and comparable to those by schedule II stimulants (amphetamine and lisdexamfetamine).

The second HAP study was a randomized, double-blind, placebo- and active-controlled, single-dose crossover trial evaluating the oral abuse potential of immediate-release centanafadine (200, 400, and 800 mg) against a schedule II positive control (15 and 30 mg immediate-release amphetamine) and placebo in 61 healthy, nondependent recreational stimulant users. Unlike the first study, which focused exclusively on supratherapeutic doses, this second trial evaluated both

[8] Department of Health and Human Services. (2026). Basis for the recommendation to control centanafadine and its salts in schedule III of the Controlled Substances Act. U.S. Department of Health and Human Services, July 17, 2026. Page 7.

therapeutic and supratherapeutic ranges by testing doses roughly equivalent to the final marketing therapeutic strengths (210 and 280 mg) alongside doses that were approximately 2 and 4 times higher than the therapeutic doses. Throughout each session, subjective responses were tracked using Visual Analogue Scales (VAS) and the Addiction Research Center Inventory (ARCI) scales, which measured stimulant-specific effects on the Amphetamine subscale (0–11 range) and the Benzedrine subscale (0–13 range).

Subjective Visual Analog Scale Outcomes

Primary Liking and Reinforcement: Centanafadine produced responses just outside the placebo range that were statistically significantly lower than amphetamine, except when comparing 800 mg centanafadine to 15 mg amphetamine. For Overall Drug Liking, amphetamine demonstrated high scores that differed significantly from all centanafadine doses; meanwhile, centanafadine produced a dose-dependent shift toward drug disliking, with the 400-mg and 800-mg doses differing significantly from placebo. Similarly, on the "Take Drug Again" scale, amphetamine elicited a strong desire to take the drug again that was statistically significantly different than all centanafadine treatments.

Stimulant Profiles and Identification

ARCI-Amphetamine and ARCI-Benzedrine scales: Centanafadine and amphetamine generated stimulant-like responses above placebo, with 30 mg amphetamine producing the highest scores across both measures. ARCI-Amphetamine scores reached 5.9 and 7.7 for the 15 and 30-mg doses of amphetamine, respectively, compared to scores of 5.1, 4.8, and 4.9 from the 200-, 400-, and 800-mg doses of centanafadine, respectively, and score of 2.8 from placebo. On the ARCI-Benzedrine scale, the 15- and 30- mg doses of amphetamine produced scores of 8.3 and 9.6, respectively, which were slightly higher than the scores of 7.3, 6.8, and 6.5 from the 200-, 400-, and 800-mg doses of centanafadine, respectively, and score of 5.6 from placebo.

Drug Similarity: On the drug similarity question, centanafadine was categorized as a stimulant generally (either as amphetamine or cocaine), but it was more frequently identified as amphetamine than as cocaine; placebo was identified as any of the stimulants less than 10% of the time.

Adverse Events (AEs)

Euphoria and Stimulant Signs: As described in detail in HHS's review,[9] oral administration of centanafadine exhibited classic stimulant-associated AEs. Both centanafadine and amphetamine produced comparable rates of euphoric mood, decreased appetite, anxiety, agitation, and bruxism (i.e., teeth grinding or jaw clenching). However, amphetamine produced higher rates of hypervigilance, whereas centanafadine was uniquely associated with disorientation at higher doses, dose-dependent tremor, and somnolence (i.e., drowsiness), as well as certain other negative AEs, including nausea and vomiting.

Centanafadine demonstrated a clinical abuse potential profile distinct from schedule II stimulants (amphetamine and lisdexamfetamine), as its detectable stimulant-like activity at supratherapeutic doses (2 and 4 times the therapeutic dose) produced drug liking that was statistically greater than placebo but less than the positive control drug, amphetamine. Furthermore, centanafadine elicited a clear lack of willingness to take the drug again, contrasting sharply with the robust liking and desire for repeat self-administration of amphetamine. Ultimately, the reinforcing properties of centanafadine at high exposure levels are effectively restricted by negative user experiences, limiting its relative abuse liability. Overall data from the two HAP studies demonstrated that supratherapeutic doses of centanafadine produced negative subjective responses and AEs, which are likely to limit the abuse potential of the drug relative to the schedule II drugs, amphetamine and lisdexamfetamine.

Adverse Events in Clinical Safety and Efficacy Studies with Centanafadine

[9] Department of Health and Human Services. (2026). Basis for the recommendation to control centanafadine and its salts in schedule III of the Controlled Substances Act. U.S. Department of Health and Human Services, July 17, 2026. Pages 16–17.

Combined safety data from 19 Phase 1 studies (872 centanafadine-treated and 66 placebo-treated healthy subjects) revealed a very low incidence of abuse-related and psychiatric AEs, with most incidents occurring in under 2 percent of participants across all formulation groups. Stimulant-associated AEs exceeding a 2 percent incidence were concentrated primarily in the highest-exposure group (> 400 mg sustained release [SR]) or with specific formulations.

Psychiatric and Mood Effects: Euphoric mood occurred in only one subject (2.0 percent) receiving > 400 mg SR (0.2–0.9 percent in lower doses; 0 percent in placebo). Altered mood appeared exclusively with other formulations (2.1 percent). Insomnia (4.1 percent) and hypervigilance (2.0 percent) were also highest in the > 400 mg SR group.

Cardiovascular Effects: Tachycardia occurred in 4.1 percent of subjects receiving > 400 mg SR (0–1.3 percent in lower doses; 0 percent in placebo).

Gastrointestinal and Appetite Effects: Decreased appetite was most prevalent in the > 400 mg SR cohort (10.2 percent), followed by other formulations (2.1 percent) and < 329 mg extended-release (2.0 percent). Gastrointestinal symptoms peaked in the > 400 mg SR group, led by nausea (14.3 percent), abdominal discomfort (8.2 percent), and diarrhea (10.2 percent).

Human Accidental Overdose and Diversion

Across 37 clinical trials evaluating centanafadine, HHS reported zero instances of drug overdose and suspected cases of drug diversion from one clinical site. In a multicenter, 52-week, open-label Phase 3 trial evaluating the long-term safety of centanafadine SR (400 mg total dose daily) in 662 adults with ADHD, three participants exhibited medication handling irregularities involving suspected or documented abuse or diversion, leading to their removal. Specifically, one participant was disqualified at Week 8 for suspected diversion after a second occurrence of lost or stolen medication, a second participant was removed after accelerating their intake to consume an entire 30-tablet supply within 9 days, and a third participant was discharged after failing a urine drug screen and subsequently claiming to have lost 10 tablets down a drain upon learning of their termination.

In summary, centanafadine is a new molecular entity that exhibits a pharmacological profile similar to that of cocaine (schedule II), functioning as a triple reuptake inhibitor of NET, DAT, and SERT. Preclinical drug discrimination studies in rats demonstrate that centanafadine produces interoceptive effects similarly to amphetamine (schedule II), matching the profiles of established stimulants like methylphenidate (schedule II) and phentermine (schedule IV). HAP studies indicate that centanafadine's subjective stimulant effects are generally less intense than those of amphetamine or lisdexamfetamine, leading to an overall clinical assessment of low misuse potential; however, the drug's administration remains associated with classic stimulant-type AEs. Consequently, based on a comprehensive review of *in vitro* testing, animal self-administration, drug discrimination, HAP studies, and clinical safety profiles, both HHS and DEA concluded that centanafadine possesses abuse potential and requires control under the CSA.

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

Centanafadine, chemically known as (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, is a new molecular entity. Centanafadine drug products are formulated as proportionally similar, extended-release capsules in 140 mg, 210 mg, and 280 mg free base strengths (equivalent to 164.4 mg, 246.6 mg, and 328.8 mg hydrochloride salt, respectively). Each capsule utilizes a multi-bead delivery system distributed as 12.2 percent immediate-release, 43.9 percent delayed-release, and 43.9 percent sustained-release beads. According to HHS, chronic once-daily administration of centanafadine (140 mg to 280 mg) results in a slightly greater than dose-proportional increase in C_{max} and Area Under the Curve, with peak plasma concentrations occurring approximately 5 hours post-dose. Steady state is achieved by day 2 with minimal drug accumulation and a mean elimination half-life of 5.2 hours. The drug is primarily metabolized by monoamine oxidase A into an inactive primary lactam metabolite, with excretion occurring via urine (88 percent) and feces (7 percent). Notably, *in vitro* dissolution testing demonstrates a risk of alcohol-induced dose-dumping.

As discussed in the background section, centanafadine has a currently accepted medical use in treatment in the United States because it has been approved by FDA.

4. Its History and Current Pattern of Abuse

Centanafadine has no history of legal or illegal marketing globally, and current data do not reflect an actual real-world pattern of abuse. While distributed for clinical trials and research, evidence of diversion from legitimate channels remains minimal. For instance, a Phase 3 study evaluating centanafadine SR (400 mg daily) in 662 adults with ADHD reported only three subjects with medication handling irregularities involving suspected or known abuse or diversion (*see* Factor 2). Consequently, the assessment of abuse liability of centanafadine relies entirely on nonclinical and clinical studies, which collectively indicate a lower potential for abuse than schedule II stimulants, such as amphetamine, lisdexamfetamine, and methylphenidate. Consistent with the status of centanafadine as a new molecular entity, DEA's parallel search of NFLIS-Drug yielded zero records of law enforcement encounters.

In summary, pharmacological data on centanafadine show that it produces abuse-related effects and has an abuse potential lower than those of schedule II stimulants.

5. The Scope, Duration, and Significance of Abuse

Centanafadine has been not marketed in any country and remains unavailable in the United States, resulting in limited abuse data. Because nonclinical and clinical evaluations indicate that centanafadine possesses an abuse liability profile that overlaps with known schedule II stimulants, there is a risk of post-marketing diversion and abuse. DEA's comprehensive search of law enforcement data yielded zero domestic law enforcement encounters involving centanafadine. However, based on cumulative pharmacology data, centanafadine is anticipated to possess a post-marketing abuse potential that is less than those of schedule II stimulants, such as amphetamine, lisdexamfetamine, and methylphenidate.

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

A drug's abuse potential is a key indicator of its overall risk to public health risk. HHS stated that, while centanafadine possesses an abuse potential comparable to those of schedule II stimulants (e.g., cocaine, amphetamine, and methylphenidate), it is likely that centanafadine will exhibit a lesser abuse profile and present fewer public health risks than those of schedule II stimulants based on dependency data and negative AEs reported in studies. To evaluate public health risk associated with centanafadine, HHS analyzed clinical trial AEs, overdose data, and abuse potential studies and confirmed moderate signals that centanafadine poses some public health risks but to a lesser degree than those posed by schedule II stimulants.

In summary, data from nonclinical and clinical studies indicate that centanafadine's abuse potential and public health risks are comparable, but to a lesser degree, than to those of schedule II stimulants.

7. Its Psychic or Physiological Dependence Liability

Psychic (or psychological) dependence is a state similar to addiction and can be informed by animal self-administration studies, HAP studies and AE reports.

HHS cited investigations that demonstrate that while centanafadine generates clear rewarding properties in both preclinical and clinical studies, centanafadine concurrently elicits dose-dependent negative subjective effects in humans. Collectively, these findings show that it is likely that centanafadine can produce psychological dependence, but likely to a lesser degree than with schedule II stimulants, such as amphetamine and cocaine.

Physical dependence develops from physiological adaptation to repeated drug use and manifests as withdrawal symptoms after abrupt drug discontinuation or reduction of a drug. According to HHS, experimental animal data evaluating chronic administration profiles for centanafadine are currently limited. Although the NDA applicant submitted two physical dependence studies in rats, HHS concluded that these evaluations were invalid for characterizing withdrawal potential, because the utilized dosing regimens failed to achieve systemic plasma concentrations matching therapeutic exposures in humans.

HHS reviewed withdrawal data from two Phase 3 clinical trials in adults with ADHD. Following abrupt discontinuation of centanafadine SR (200 mg or 400 mg daily), patients were monitored for 10 days using the Study Medication Withdrawal Questionnaire (SMWQ). SMWQ scores were indistinguishable between the active treatment and placebo groups at all time points. Based on these data, HHS concluded that centanafadine does not induce a withdrawal syndrome, indicating that chronic therapeutic administration followed by abrupt cessation does not produce physical dependence.

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

Centanafadine 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, 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 centanafadine. As such, DEA hereby schedules centanafadine 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).[10] 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)(3-), finds that:

(1) Centanafadine has a potential for abuse less than the drugs or other substances in schedules I and II.

Centanafadine is a novel triple reuptake inhibitor that targets NET, DAT, and SERT and is a CNS stimulant. While its mechanism of action shares similarities with those of schedule II

[10] 21 U.S.C. 812(b).

stimulants, preclinical and clinical data demonstrate that centanafadine possesses an abuse potential lower than those of substances in schedules I and II. In animal self-administration and drug discrimination models, centanafadine produced reinforcing and interoceptive effects similar to known schedule II stimulants, including cocaine, amphetamine, and methylphenidate. Similarly, in two HAP studies, centanafadine elicited positive subjective responses that were significantly greater than those of placebo, closely approximating or falling slightly below those of amphetamine and lisdexamfetamine. However, centanafadine produced a dose-dependent increase in negative subjective responses and a higher prevalence of AEs like nausea from supratherapeutic doses. Overall, the evidence from nonclinical and clinical evaluations indicates that centanafadine possesses an abuse liability lower than those of schedule II controlled substances.

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

Centanafadine was approved by FDA for the treatment of ADHD in adults and pediatric patients aged 6 years and older weighing at least 20 kg. Thus, centanafadine has a currently accepted medical use in treatment in the United States.

(3) Abuse of centanafadine may lead to moderate or low physical dependence or high psychological dependence.

According to HHS, therapeutic use of centanafadine did not produce a withdrawal syndrome in patients who were abruptly discontinued from the drug following chronic use. However, the ability of centanafadine to produce positive subjective responses at supratherapeutic doses suggests that centanafadine can produce psychic dependence, although this may be mediated by concurrent negative subjective responses and AEs. In contrast, schedule II drugs amphetamine and lisdexamfetamine produced positive responses without comparable negative responses. Overall, these data suggest that centanafadine has a dependence

potential less than that of certain schedule II stimulants and may lead to moderate or low physical dependence or high psychological dependence.

Based on these findings, the Administrator concludes that centanafadine and its salts warrant control in schedule III of the CSA.[11]

Requirements for Handling Centanafadine

Centanafadine is subject to the CSA's schedule III 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) centanafadine 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 centanafadine 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 centanafadine, or may transfer all quantities of currently held centanafadine to a person registered with DEA. Centanafadine 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.* Centanafadine 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 centanafadine 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 centanafadine pursuant to a lawful prescription.

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[11] 21 U.S.C. 812(b)(3).

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

6. *Records and Reports.* DEA registrants must maintain records and submit reports for centanafadine, 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 centanafadine, or products containing centanafadine, 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 III controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of centanafadine 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 centanafadine 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 centanafadine 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 Federal Food Drug and Cosmetic Act, 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 and 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 a "significant regulatory action" under 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 OMB 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 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. 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 § 1308.13:

a. Redesignate paragraphs (b)(3) through (5) as paragraphs (b)(4) through (6); and

b. Add a new paragraph (b)(3).

The addition reads as follows:

§ 1308.13 Schedule III.

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(b) * * *

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(3) Centanafadine	1641
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SIGNING AUTHORITY

This document of the Drug Enforcement Administration was signed on October 28, 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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