



## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

#### 21 CFR Part 1308

[Docket No. DEA-558]

#### Schedules of Controlled Substances: Placement of Lasmiditan in Schedule V.

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Final rule.

**SUMMARY:** This final rule adopts an interim final rule with request for comments published in the *Federal Register* on January 31, 2020, placing lasmiditan (2,4,6-trifluoro-N-(6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl)-benzamide), including its salts, in schedule V of the Controlled Substances Act without change, apart from a minor amendment to the placement ordering of lasmiditan already made by intervening rules. With the issuance of this final rule, the Drug Enforcement Administration maintains lasmiditan, including its salts, in schedule V of the Controlled Substances Act.

**DATES:** The effective date of this final rulemaking is [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

**FOR FURTHER INFORMATION CONTACT:** Terrence L. Boos, Drug and Chemical Evaluation Section, Drug Enforcement Administration; Telephone: (571) 362-3249.

#### SUPPLEMENTARY INFORMATION:

##### Background and Legal Authority

On January 31, 2020, the Drug Enforcement Administration (DEA), pursuant to 21 U.S.C. 811(j), published an interim final rule placing lasmiditan, a recently Food and Drug Administration (FDA)-approved medication for the acute treatment of patients with

migraine, in schedule V of the Controlled Substances Act (CSA).<sup>1</sup> 85 FR 5557. Specifically, this interim final rule placed lasmiditan in 21 CFR 1308.15(e)(4). As provided in paragraph (e), the placement of a substance in this depressant's category includes its salts. However, DEA incorrectly stated in the preamble of the interim final rule that lasmiditan (including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible) was placed in schedule V. The preamble of this final rule now correctly refers solely to lasmiditan and its salts. It bears emphasis that the regulatory text used in this final rule remains unchanged from that used in the interim final rule, apart from the change in placement ordering of lasmiditan due to intervening rules. DEA's issuance of the interim and final rules for placement of cenobamate in schedule V changed the placement order of lasmiditan from §1308.15(e)(4) to 1308.15(e)(5). 85 FR 13741, March 10, 2020; and 85 FR 51340, August 20, 2020.

The interim final rule referenced two supporting documents and stated they were available for viewing on the electronic docket. Specifically, the two documents cited are as follows: (1) The Department of Health and Human Services (HHS) October 2019 scientific and medical evaluation and scheduling recommendation (HHS Eight-Factor analysis), and (2) DEA's January 2020 Eight-Factor analysis. DEA has discovered that these documents were not posted to the electronic docket. However, they were available for viewing at DEA headquarters. Upon publication of this final rule, DEA will post to the docket the DEA January 2020 and HHS Eight-Factor analyses that should have accompanied the interim final rule, as well as DEA's August 2020 Eight-Factor analysis.

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<sup>1</sup> The interim final rule stated that FDA, in October 2019, approved the new drug application for Reyvow (lasmiditan) 50 and 100 mg oral tablets for the acute treatment of migraine with or without aura in adults.

The interim final rule provided an opportunity for interested persons to submit comments as well as file a request for hearing or waiver of hearing, on or before March 2, 2020. DEA did not receive any requests for hearing or waiver of hearing.

### **Comments Received**

In response to the interim final rule, DEA received five comments, four from individuals and one from a pharmaceutical manufacturer (the Sponsor of the new drug application (NDA) for Reyvow (lasmiditan)). One individual supported schedule V placement; two other individuals instead suggested schedule IV placement with the option to reclassify to schedule V after a provisional period; the manufacturer did not provide a position on the scheduling action but requested that the half-life information for lasmiditan be corrected; and the remaining individual expressed views on a non-DEA rulemaking. DEA will not summarize or respond to this last comment as it was outside the scope of this rulemaking.

### **Schedule V Placement**

An individual commenter briefly discussed the background and abuse liability of lasmiditan, and stated that lasmiditan at doses greater than 200 mg has shown potential for abuse. In light of the current opioid epidemic, the commenter believes it is important that DEA appropriately regulate prescription medications with abuse potential. The commenter agreed that the schedule V classification for lasmiditan provides adequate oversight, without being overly regulatory, and will ensure the safety of the public.

DEA Response: DEA determined in the interim final rule, and re-affirms in this final rule, that lasmiditan meets the criteria under 21 U.S.C. 812(b)(5) for schedule V control. As described by HHS, testing of lasmiditan at supratherapeutic dosages (400 mg) did show that it has abuse potential, however these effects of all doses of lasmiditan (100, 200 and 400 mg) were significantly lower than alprazolam (see Factor 2 of 8 factor analysis). DEA appreciates the support for this rulemaking.

## **Schedule IV Placement with Option to Reclassify After Provisional Period**

Two individual commenters expressed concerns with DEA's placing lasmiditan in schedule V due to the overall lack of data for the drug's abuse and dependence risks. One of these commenters cited a 2019 Phase 1 randomized, placebo- and alprazolam-controlled crossover study, which provided both therapeutic (100 and 200 mg) and supratherapeutic (400 mg) dosages of lasmiditan to the study subjects<sup>2</sup>. This commenter stated that the researchers, after characterizing the subjective-liking drug effects, considered lasmiditan to have a low potential for abuse (compared to schedule IV alprazolam). However, the study authors listed the common adverse events occurring for lasmiditan at the three doses – 100 mg, 200 mg, and 400 mg – and specifically noted that higher doses produced greater events for somnolence (32.7%, 40.0%, and 54.5%, respectively) and euphoric mood (25.5%, 49.1%, and 45.5%, respectively). This same commenter stated that this was the only study of this type conducted, and its small study size of 58 participants could have a large margin for error.

The other commenter also stated, very generally without referring to any specific study findings, that lasmiditan has lower potential for abuse and dependence than alprazolam. This commenter noted though the similar therapeutic effects for lasmiditan at higher doses, and stated this could be problematic for patients with chronic migraine taking lasmiditan. This commenter referenced a 2015 journal article (Weatherall, 2015)<sup>3</sup>, and stated “[s]tudies have shown that those who suffer from chronic migraines also have medication overuse.” In the commenter's opinion, such medication overuse could lead to heightened abuse and dependence risks.

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<sup>2</sup> Wilbraham, D., Berg, P. H., Tsai, M., Liffick, E., Loo, L. S., Doty, E. G., & Sellers, E. (2020). Abuse Potential of Lasmiditan: A Phase 1 Randomized, Placebo- and Alprazolam-Controlled Crossover Study. *Journal of clinical pharmacology*, 60(4), 495–504.

<sup>3</sup> Weatherall, M. W. (2015). The diagnosis and treatment of chronic migraine. *Therapeutic Advances in Chronic Disease*, 6(3), 115-123.

As a result, this commenter believed schedule IV was more appropriate for this nascent drug, as a schedule IV classification provides more oversight by physicians for prescribing this drug to patients. Specifically, this commenter referenced a 2019 publication, updated in 2020, that indicated schedule IV drugs are drugs utilized for pain control as long as the provider deems the drug medically necessary and beneficial to the patient. Both commenters urged DEA to consider placing lasmiditan in schedule IV for a probationary or provisional time period with the option to reclassify lasmiditan as a schedule V substance. This option could be implemented once more rigorous clinical studies are conducted, and the analyzed results accurately demonstrate potential for abuse and dependency, justifying schedule V placement.

DEA Response: DEA notes that FDA approved an NDA for Reyvow (lasmiditan), and HHS provided DEA with an evaluation and a scheduling recommendation for control of lasmiditan in schedule V. As provided in 21 U.S.C. 811(j), the scheduling recommendation by HHS and the FDA approval of the NDA necessitated DEA review and its own determination for the scheduling action (to first issue the interim final rule and subsequently to issue this final rule) pursuant to 21 U.S.C. 811(a) and (b) and 812. As discussed in the interim final rule, DEA's scheduling determination was based on consideration of the eight factors listed in 21 U.S.C. 811(c), HHS' scientific and medical evaluation and scheduling recommendation, and all other relevant data. DEA concurred with HHS' recommendation that lasmiditan has low potential for abuse relative to substances in schedule IV and therefore supported – and continues to support through this final rule – placement of lasmiditan in schedule V. DEA notes that under 21 U.S.C. 811(b), HHS' recommendations shall be binding on the Administrator of DEA (as delegated by the Attorney General) as to any scientific or medical considerations involved in three of the eight factors specified in 21 U.S.C. 811(c) (i.e., factors 1, 4, and 5). Regarding the commenters' issues with lasmiditan's placement

in schedule V, there is still significant oversight for schedule V drugs. For both the interim final rule and this final rule, DEA made the findings required under 21 U.S.C. 812(b)(5) for the placement of lasmiditan in schedule V. None of the commenters requested a hearing on the scheduling of lasmiditan.

DEA would like to further clarify that the commenter who cited Weatherall, 2015 over-generalized the author's statements on the studies' findings pertaining to chronic migraine patients and medication overuse. In actuality, Weatherall (2015) stated that "[m]any patients with chronic migraine also have medication overuse," suggesting that while medication overuse does occur in migraine patients, it does not occur in all patients as stated by the commenter.

### **Half-life Information for Lasmiditan**

The manufacturer commenter (the Sponsor of the NDA for Reyvow (lasmiditan)) stated that the interim final rule, in the factor 3 discussion, inaccurately listed the half-life for lasmiditan as "approximately 31 hours," based on a general reference to rat studies. The commenter contended that DEA used findings from one specific rat study, which was included in the NDA for lasmiditan, to set this long half-life for lasmiditan. The commenter noted that this study determined the half-life by measuring circulating levels of radioactivity, and the reported findings were actually 27-32 hours. In addition, the commenter stated that, similarly to half-life findings for lasmiditan in clinical studies, this rat study's findings of a longer half-life is not a reflection of lasmiditan alone. Rather, this half-life reflects "all drug-related analytes (*i.e.*, pharmacologically inactive metabolites), some of which have longer half-lives than the parent drug, lasmiditan." This commenter provided findings from another rat study included in the NDA for lasmiditan, which used a non-radiolabeled dose of lasmiditan. The commenter stated that this rat study used measures to detect only the half-life of the parent (intact) drug, lasmiditan; the study reported the mean lasmiditan half-life in plasma as 2-3 hours.

Therefore, the commenter requested that DEA correct the factor 3 discussion regarding the lasmiditan half-life data to state: “Rat studies demonstrate that lasmiditan has a half-life of 2-3 hours.”

DEA Response: The eight-factor analysis described in the interim final rule is an abridged version of DEA’s eight-factor analysis. Regarding the commenter’s request that factor 3 discussion provide half-life findings from an additional rat study, both the DEA (January 2020) and HHS eight-factor analyses conducted as part of the interim final rule process noted the half-life in their respective tables. In DEA’s August 2020 eight-factor analysis, information was added in Factor 3 to describe this additional study and show a shorter half-life (2-3 hours) of lasmiditan as compared to the long half-life obtained from the study measuring radioactivity (see Table 5 and 6 of DEA 8-factor analysis). DEA agrees with the commenter that longer half-lives of pharmacologically inactive metabolites can occur.

Based on the rationale set forth in the interim final rule, DEA adopts the interim final rule without change.

### **Requirements for Handling Lasmiditan**

As indicated above, lasmiditan has been a schedule V controlled substance by virtue of the interim final rule issued by DEA in January 2020. Thus, this final rule does not alter the regulatory requirements applicable to handlers of lasmiditan that have been in place since that time. Nonetheless, for informational purposes, we restate here those requirements. Lasmiditan is subject to the CSA’s schedule V regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule V substances, including, but not limited to, 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) lasmiditan, or who desires to handle lasmiditan, must be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Any person who currently handles or intends to handle lasmiditan, and is not registered with DEA, must submit an application for registration and may not continue to handle lasmiditan unless DEA has approved that application for registration, 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 lasmiditan pursuant to a lawful prescription.

2. *Disposal of stocks.* Any person who obtains a schedule V registration to handle lasmiditan but who subsequently does not desire, or is not able to maintain such registration must surrender all quantities of lasmiditan, or may transfer all quantities of lasmiditan to a person registered with DEA in accordance with 21 CFR part 1317, in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Lasmiditan is subject to schedule III–V security requirements for DEA registrants, and it must be handled and stored in accordance with 21 CFR 1301.71–1301.93. Non-practitioners handling lasmiditan must also comply with the employee screening requirements of 21 CFR 1301.90–1301.93.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of lasmiditan 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 lasmiditan was required to keep an inventory of lasmiditan on hand, as of January 31, 2020, pursuant to



21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

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

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

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule V controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of lasmiditan 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 and the CSA.

9. *Importation and Exportation.* All importation and exportation of lasmiditan 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 lasmiditan 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*

This final rule affirms the amendment made by the interim final rule that is already in effect with a minor change in placement ordering of lasmiditan as discussed above. Section 553 of the Administrative Procedure Act (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 and (2) HHS recommends control in CSA schedule II–V, DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, subsection (j) specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause. DEA issued an interim final rule on January 31, 2020, which provided notice and an opportunity for a hearing on the record and solicited public comments on that rule. Subsection (j) further states that after giving interested persons the opportunity to comment and to request a hearing, the Attorney General, as delegated to the Administrator of DEA, shall issue a final rule in accordance with the scheduling criteria of 21 U.S.C. 811 (b) through (d) and 812(b). DEA is now responding to the comments submitted by the public and issuing the final rule in accordance with subsection (j).

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

In accordance with 21 U.S.C. 811(a) and (j), this scheduling action is subject to formal rulemaking procedures performed “on the record after opportunity for a hearing,” which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

*Executive Order 12988, Civil Justice Reform*

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

*Executive Order 13132, Federalism*

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

*Executive Order 13175, Consultation and Coordination with Indian Tribal Governments*

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

*Regulatory Flexibility Act*

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. As noted in the above discussion regarding the applicability of the APA, DEA was not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply.

*Unfunded Mandates Reform Act of 1995*

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.*, DEA has determined that this action would not result in any Federal mandate that may result “in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation) in any 1 year.” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

*Paperwork Reduction Act of 1995*

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments,

individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

*Congressional Review Act*

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. However, DEA is submitting the required reports to the Government Accountability Office, the House, and the Senate under the CRA.

**List of Subjects in 21 CFR Part 1308**

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

Accordingly, the interim final rule amending 21 CFR part 1308, which was published at 85 FR 5557 on January 31, 2020, and as subsequently amended at 85 FR 13741 and 85 FR 51340, is adopted as a final rule without change.

**D. Christopher Evans,**  
*Acting Administrator*

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