



## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

#### 21 CFR Part 1308

[Docket No. DEA-658]

#### **Schedules of Controlled Substances: Placement of Remimazolam in Schedule IV**

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

**ACTION:** Final rule.

**SUMMARY:** This final rule adopts, without change, an interim final rule with request for comments published in the *Federal Register* on October 6, 2020, placing the substance remimazolam, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the Controlled Substances Act. With the issuance of this final rule, DEA maintains remimazolam, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the Controlled Substances Act.

**DATES:** The effective date of this rulemaking is [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

**FOR FURTHER INFORMATION CONTACT:** Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: 571-776-2265.

#### **SUPPLEMENTARY INFORMATION:**

##### **Background and Legal Authority**

On October 6, 2020, the Drug Enforcement Administration (DEA), pursuant to 21 U.S.C. 811(j), published an interim final rule (IFR) [85 FR 63014] to make remimazolam (including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible), a schedule IV controlled substance(s). See 21 CFR 1308.14(c)(51) (DEA Controlled Substance Code 2846).

Over time, alternative chemical names have been used to describe this same specific substance. In the preamble to the IFR, DEA provided “4*H*-imidazol[1,2-*a*][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4*S*)-methyl ester, benzenesulfonate (1:1) and also, methyl 3-[(4*S*)-8-bromo-1-methyl-6-pyridin-2-yl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepin-4yl]propanoate benzenesulfonic acid”<sup>1</sup> as the chemical names of remimazolam, which refer to the benzenesulfonic acid salt of remimazolam. Since DEA controlled remimazolam and its salts, isomers, and salts of isomers in schedule IV by publication of the IFR, DEA believes it is more appropriate to include chemical names consistent with the free base of this substance, namely “4*H*-imidazol[1,2-*a*][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4*S*)-methyl ester and methyl 3-[(4*S*)-8-bromo-1-methyl-6-pyridin-2-yl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepin-4yl]propanoate” in the preamble of this final rule. It bears emphasis that the chemical that is the subject of this final rule is the same substance that was the subject of the IFR. DEA simply is using alternative chemical descriptions to refer to that same substance in this preamble.

Remimazolam is a new molecular entity with central nervous system depressant properties, and the Food and Drug Administration (FDA), in July 2020, approved the use of BYFAVO (Remimazolam) as an intravenous medication for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes

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<sup>1</sup> The Department of Health and Human Services also referred to the substance by these chemical names in its April 2020 scientific and medical evaluation and scheduling recommendation.

or less. The IFR to schedule remimazolam provided opportunity for interested persons to submit comments, as well as file a request for hearing or waiver of hearing, on or before November 5, 2020. DEA did not receive any requests for hearing or waiver of hearing.

### **Comments Received**

In response to the IFR, DEA received three comments, from one individual and two anonymous sources. One commenter supported schedule IV placement; the second commenter suggested placement in schedule III instead; and the third commenter 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 IV Placement**

An anonymous commenter briefly expressed that schedule IV was the appropriate schedule for remimazolam based on the data from clinical trials conducted, limited side effects, and its better performance as compared to similar substances such as midazolam.

DEA Response: DEA determined in the IFR, and re-affirms in this final rule, that remimazolam meets the criteria under 21 U.S.C. 812(b)(4) for schedule IV control. As described by the Department of Health and Human Services (HHS),<sup>2</sup> and in DEA's August 2020 eight-factor analysis, remimazolam demonstrated abuse potential similar to midazolam, a schedule IV depressant. DEA appreciates the support for this rulemaking.

### **Schedule III Placement**

One individual commenter expressed concerns with DEA's placement of remimazolam in schedule IV and instead suggested placing remimazolam in schedule III. The commenter briefly discussed the pharmacology of remimazolam and noted that both HHS and DEA stated the abuse potential and public health risk of remimazolam is similar to schedule IV benzodiazepines. However, the commenter stated that remimazolam

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<sup>2</sup> Basis for the Recommendation to Control Remimazolam and Its Salts in Schedule IV of the Controlled Substances Act. Department of Health and Human Services. April 15, 2020. Received by DEA on July 10, 2020.

induced “positive euphoria related responses in [a] human abuse potential study leading to dependence to relative drugs in schedule III” and recommended classifying remimazolam as schedule III “due to FDA placing a black box warning label on benzodiazepines and the numerous studies illustrating [the abuse and misuse of benzodiazepines] within the public communities.” The commenter noted that schedule III provided more restrictions and could protect the public from harm. The individual summarized four reference articles related to the historic medical use and abuse of prescription benzodiazepines, diversion and trafficking of licit and illicit benzodiazepines, and the serious adverse effects that may occur with misuse and abuse of benzodiazepines, including an increase in benzodiazepine-related deaths. Further, the commenter believed that the opioid epidemic has overshadowed the benzodiazepines misuse and abuse, but suggested that benzodiazepines and opioids are working “in tandem wreaking havoc in the lives of many” and that “creating a strong foundation through classification of drugs can place precedent in ensuring the health and safety of American citizens.”

DEA Response: DEA considered the commenter’s position; however, does find placement in schedule IV to be appropriate for remimazolam. As discussed briefly in the background and legal authority section above, and in more detail in the IFR [85 FR 63014, 63015-63016], FDA approved the New Drug Application (NDA) for BYFAVO (remimazolam), and HHS provided DEA with a scientific and medical evaluation and a scheduling recommendation for control of remimazolam in schedule IV. Pursuant to 21 U.S.C. 811(j), the scheduling recommendation by HHS and FDA approval of the NDA necessitated DEA’s review and its own determination for the scheduling action (to first issue the IFR and subsequently to issue this final rule) in accordance with 21 U.S.C. 811(b). DEA considered HHS’ scientific and medical evaluation and scheduling recommendation, and all other relevant data and concurred with HHS’ recommendation

that remimazolam has low potential of abuse relative to substances in schedule III and therefore supported – and continues to support through this final rule – placement of remimazolam in schedule IV. DEA notes that under 21 U.S.C. 811(b), HHS’s recommendation 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 pertaining to the substance’s actual or relative potential for abuse, its history and current pattern of abuse, and the scope, duration, and significance of abuse). Regarding the commenter’s public safety concerns with remimazolam’s placement in schedule IV, there is still significant oversight for schedule IV drugs. For both the IFR and this final rule, DEA made the findings required under 21 U.S.C. 812(b)(4) for the placement of remimazolam in schedule IV.

### **Requirements for Handling Remimazolam**

As indicated above, remimazolam has been a schedule IV controlled substance by virtue of an IFR issued by DEA in October 2020. Thus, this final rule does not alter the regulatory requirements applicable to handlers of remimazolam that have been in place since that time. Nonetheless, for informational purposes, we restate here those requirements. Remimazolam is subject to the Controlled Substances Act’s (CSA) schedule IV 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 IV 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) remimazolam, or who desires to handle remimazolam, 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 intends to handle remimazolam, and is not registered with DEA, must submit an application for registration and may not continue to handle remimazolam 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 remimazolam pursuant to a lawful prescription.

2. *Disposal of stocks.* Any person who does not desire or is not able to maintain a schedule IV registration must surrender all quantities of currently held remimazolam or may transfer all quantities of remimazolam 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.* Remimazolam is subject to schedule III-V security requirements for DEA registrants and it must be handled and stored in accordance with 21 CFR 1301.71-1301.77. Non-practitioners handling remimazolam 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 remimazolam must comply with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302.

5. *Inventory.* Since October 6, 2020, every DEA registrant who possesses any quantity of remimazolam must take an inventory of remimazolam on hand, pursuant to 21 U.S.C. 827 and 958, 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 remimazolam, pursuant to 21 U.S.C. 827, 832(a), and 958(e), and in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and 1317.

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

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of remimazolam 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 remimazolam 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 remimazolam 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, without change, affirms the amendment made by the IFR that is already in effect. 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 IFR scheduling the drug within 90 days. Additionally, subsection (j) specifies that the rulemaking shall become

immediately effective as an IFR without requiring DEA to demonstrate good cause. DEA issued an IFR on October 6, 2020, and solicited public comments on that rule. Subsection (j) further provides 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 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 \$100,000,000 or more (adjusted annually for inflation) in any 1 year.” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

*Paperwork Reduction Act of 1995*

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

*Congressional Review Act (CRA)*

This rule is not a major rule as defined by the CRA, 5 U.S.C. 804. However, pursuant to the CRA, DEA is submitting a copy of this final rule 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.

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

Accordingly, the IFR amending 21 CFR part 1308, which published on October 6, 2020 (85 FR 63014), is adopted as final without change.

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

[FR Doc. 2021-11512 Filed: 6/1/2021 8:45 am; Publication Date: 6/2/2021]