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**DEPARTMENT OF JUSTICE**

**Drug Enforcement Administration**

**21 CFR Part 1308**

**[Docket No. DEA-468]**

**Schedules of Controlled Substances: Removal of Naldemedine from Control**

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

**ACTION:** Final rule.

**SUMMARY:** With the issuance of this final rule, the Drug Enforcement Administration removes the substance naldemedine (4*R*,4*aS*,7*aR*,12*bS*)-3-(cyclopropylmethyl)-4*a*,7,9-trihydroxy-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl)-2,3,4,4*a*,5,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-6-carboxamide) including its salts from the schedules of the Controlled Substances Act. Prior to the effective date of this rule, naldemedine was a schedule II controlled substance because it can be derived from opium alkaloids. This action removes the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule II controlled substances, on persons who handle (manufacture, distribute, reverse distribute, dispense, conduct research, import, export, or conduct chemical analysis) or propose to handle naldemedine.

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

**FOR FURTHER INFORMATION CONTACT:** Michael J. Lewis, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

**SUPPLEMENTARY INFORMATION:**

**Legal Authority**

Pursuant to 21 U.S.C. 811(a)(2), the Attorney General may, by rule, “remove any drug or other substance from the schedules if he finds that the drug or other substance does not meet the requirements for inclusion in any schedule.” The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the Drug Enforcement Administration (DEA). 28 CFR 0.100.

The Controlled Substances Act (CSA) provides that proceedings for the issuance, amendment, or repeal of the 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)<sup>1</sup>, or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated at the request of the Acting Assistant Secretary for Health of the HHS and by a petition by the drug sponsor to DEA to remove naldemedine from the list of scheduled controlled substances of the CSA, and is supported by, *inter alia*, a recommendation from the Assistant Secretary of the HHS and an evaluation of all relevant data by the DEA. This action removes the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled

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<sup>1</sup> As set forth in a memorandum of understanding entered into by the HHS, the Food and Drug Administration (FDA), and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary’s scheduling responsibilities under the CSA, with the concurrence of the NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

substances, including those specific to schedule II controlled substances, on persons who handle or propose to handle naldemedine.

## **Background**

Naldemedine, known chemically as (4*R*,4*aS*,7*aR*,12*bS*)-3-(cyclopropylmethyl)-4*a*,7,9-trihydroxy-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl)-2,3,4,4*a*,5,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-6-carboxamide, is an opium alkaloid derivative. Naldemedine is a high-affinity antagonist at the mu, kappa, and delta opioid receptors. On March 23, 2016, a new drug application (NDA) was submitted by Shionogi Inc. (Sponsor) to the Food and Drug Administration (FDA) for approval of naldemedine for the treatment of opioid induced constipation in patients with chronic non-cancer pain. The FDA approved naldemedine for marketing on March 23, 2017, under the trade name Symproic® (0.2 mg tablets).<sup>2</sup> Naldemedine is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Opioid-induced constipation is caused by an activation of mu-opioid receptors in the gastrointestinal tract. Naldemedine, a peripheral acting mu-opioid antagonist, can prevent OIC.

## **DEA and HHS Eight Factor Analyses**

On June 8, 2016, the DEA received a petition from the drug sponsor requesting that the DEA amend 21 CFR 1308.12(b)(1) to exclude naldemedine as a schedule II substance from the Controlled Substances Act (CSA). The petitioner stated that naldemedine is a

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<sup>2</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2017/208854Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/208854Orig1s000ltr.pdf) (last accessed 04/13/2017).

potent peripherally acting mu-opioid receptor antagonist. In accordance with 21 CFR 1308.43(c), the DEA accepted the petition for filing on August 5, 2016.

On March 22, 2017, the HHS provided the DEA with a scientific and medical evaluation document prepared by the FDA entitled “Basis for the Recommendation to Decontrol Naldemedine and its Salts from the Controlled Substances Act.” After considering the eight factors in 21 U.S.C. 811(c), including consideration of the substance’s abuse potential, legitimate medical use, and dependence liability, the Assistant Secretary of the HHS recommended that naldemedine and its salts be removed from schedule II of the CSA. In response, the DEA conducted its own eight factor analysis of naldemedine pursuant to 21 U.S.C. 811(c). Both the DEA and HHS analyses are available in their entirety in the public docket of this rule (Docket Number DEA-468) at <http://www.regulations.gov> under “Supporting and Related Material.”

#### **Determination to Decontrol Naldemedine**

After a review of the available data, including the scientific and medical evaluation and the recommendation to decontrol naldemedine from HHS, the DEA published in the *Federal Register* a notice of proposed rulemaking (NPRM) entitled “Schedules of Controlled Substances: Removal of Naldemedine from Control” which proposed removal of naldemedine including its salts from the schedules of the CSA. 82 FR 32153, July 12, 2017. The proposed rule provided an opportunity for interested persons to file a request for a hearing in accordance with DEA regulations by August 11, 2017. No requests for such a hearing were received by the DEA. The NPRM also provided an opportunity for interested persons to submit written comments on the proposal on or before August 11, 2017.

## **Comments Received**

The DEA received six comments on the proposed rule to remove naldemedine from control. Five commenters supported the decontrol of naldemedine. One commenter submitted a comment not related to the proposed decontrol action.

### *Support*

One commenter stated that naldemedine does not induce euphoria therefore limiting its potential for abuse. Another commenter stated that naldemedine can help alleviate constipation which will reduce the amount of time a patient is absent from work or the need for placement on disability. Further, another commenter stated that since naldemedine is a naltrexone derivative, it should be unscheduled.

One commenter stated that senators and representatives should support the removal of naldemedine to allow for safe and efficacious use of the drug due to its lack of abuse potential in clinical use. This commenter further suggested that naldemedine be made available to the public without the need for a prescription to treat individuals overdosed on opioids.

*DEA Response:* The DEA appreciates the comments in support of this rulemaking. The comment about making naldemedine available without prescription does not relate to the factors determinative of control of a substance (21 U.S.C. 811(c)) or the criteria for placement of a substance in a particular schedule (21 U.S.C. 812(b)).

### *Unrelated Comment*

A commenter expressed concerns about reports on “opioid epidemic” without consideration of the need for opioids by chronic pain patients. This commenter felt

“patients are being denied, dismissed and overlooked by our drs (sic) due to all the scrutiny associated with treating chronic pain disease.”

*DEA Response:* Because naldemedine is not an opioid analgesic, this comment about the use of opioid analgesic in the management of pain is unrelated to the current decontrol action. Further it does not relate to the factors determinative of control of a substance (21 U.S.C. 811(c)) or the criteria for placement of a substance in a particular schedule (21 U.S.C. 812(b)).

*Request for Immediate Effective Date*

The drug sponsor (Shionogi Inc.) requested that the effective date of this decontrol action correspond to the date of publication of the Final Rule.

*DEA Response:* Generally, DEA scheduling actions are effective 30 days from the date of publication of the final rule in the *Federal Register*. 21 CFR 1308.45; *see also* 5 U.S.C. 553(d). In accordance with 21 CFR 1308.45, the DEA finds that the limited availability of effective therapeutic treatments for opioid induced constipation (OIC), coupled with the fact that this is an action for decontrol, supports the finding that conditions of public health require this action to be effective immediately upon publication in the *Federal Register*. Due to adverse side effects, the majority of treatment alternatives currently available for OIC have restricted clinical application. By comparison, in clinical studies, naldemedine was well tolerated and exhibited a good safety profile in patients with opioid-induced bowel dysfunction.

In making the determination to make this rule effective immediately, the DEA took into consideration the effects of immediate implementation. The DEA agrees that making this rule immediately effective is in the best interest of the public health and will

not burden registrants, the healthcare system or law enforcement. The DEA notes that its decision to make this rule effective immediately aligns with the exceptions to the 30-day effective date requirement of the Administrative Procedure Act (APA). One of the APA's exceptions to the 30-day effective date is for a substantive rule granting or recognizing an exemption or which relieves a restriction. 5 U.S.C. 553(d)(1).

### **Scheduling Conclusion**

Based on the consideration of all comments, the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the Administrator finds that these facts and all relevant data demonstrate that naldemedine does not meet the requirements for inclusion in any schedule, and will be removed from control under the CSA.

### **Regulatory Analyses**

#### *Executive Orders 12866 and 15363*

In accordance with 21 U.S.C. 811(a), 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 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 regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 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*

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The 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 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 Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612) (RFA), has reviewed this 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 rule is to remove naldemedine from the list of schedules of the CSA. This action removes regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances for handlers and proposed handlers of naldemedine.

Accordingly, it has the potential for some economic impact in the form of cost savings.

This rule will affect all persons who handle, or propose to handle, naldemedine. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence handling of naldemedine, the DEA is unable to determine the number of



entities and small entities which might handle naldemedine. However, the DEA estimates that all persons who handle, or propose to handle naldemedine, are currently registered with the DEA to handle controlled substances. Therefore, the 1.7 million (1,683,023 as of April 2017) controlled substance registrations, representing approximately 436,761 entities, would be the maximum number of entities affected by this rule. The DEA estimates that 425,856 (97.5%) of 436,761 affected entities are “small entities” in accordance with the RFA and Small Business Administration size standards.

The DEA estimates all controlled substance registrants handle both controlled and non-controlled substances and these registrants are expected to continue to handle naldemedine. Additionally, since prospective naldemedine handlers are likely to handle other controlled substances, the cost benefits they would receive as a result of the de-control of naldemedine is minimal. As naldemedine handlers continue to handle other controlled substances, they will need to maintain their DEA registration and keep the same security and recordkeeping processes, equipment, and facilities in place and would experience only minimal reduction in security, inventory, recordkeeping, and labeling costs. Physical security control requirements are the same for controlled substances listed in schedules II, III, IV, and V for the vast majority of registrants (practitioners).

While the DEA does not have a basis to estimate the number of affected entities, the DEA estimates that the maximum number of affected entities is 436,761 of which 425,856 are estimated to be small entities. Since the affected entities are expected to handle other controlled substances and maintain security and recordkeeping facilities and processes consistent with controlled substances, the DEA estimates any economic impact

will be minimal. Because of these facts, this rule will not have a 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.*, the DEA has determined and certifies 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 UMRA of 1995.

*Paperwork Reduction Act*

This action does not impose a new collection of information requirement under the Paperwork Reduction Act, 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 section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). This rule will not result in: An annual effect on the economy of \$100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of

United States-based enterprises to compete with foreign based enterprises in domestic and export markets. However, pursuant to the CRA, the DEA has submitted 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.

For the reasons set out above, 21 CFR part 1308 is 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), 956(b), unless otherwise noted.

2. In § 1308.12, revise the introductory text of paragraph (b)(1) to read as follows:

**§ 1308.12 Schedule II.**

\* \* \* \* \*

(b) \* \* \*

(1) Opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate excluding apomorphine, thebaine-derived butorphanol, dextrorphan, nalbuphine, naldemedine, nalmeferone, naloxegol, naloxone, and naltrexone, and their respective salts, but including the following:

\* \* \* \* \*

Dated: September 22, 2017.

Chuck Rosenberg,

*Acting Administrator.*

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