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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-400]

Schedules of Controlled Substances: Removal of Naloxegol from Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Administrator of the Drug Enforcement Administration removes naloxegol ((5α,6α)-17-allyl-6-((20-hydroxy-3,6,9,12,15,18-hexaoxaicos-1-yl)oxy)-4,5-epoxymorphinon-3,14-diol) and its salts from the schedules of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. Prior to the effective date of this rule, naloxegol 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 naloxegol.

DATES: *Effective Date:* [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

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

Under the CSA, each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c) and the current list of scheduled substances is published at 21 CFR part 1308. 21 U.S.C. 812(a).

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 DEA. 28 CFR 0.100.

The 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),[1] or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by a petition from the drug sponsor to remove naloxegol 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 substances, including those specific to schedule II controlled substances, on persons who handle or propose to handle naloxegol.

Background

Naloxegol, or PEG-naloxol, is a new molecular entity and is a polyethylene glycolyated (PEGylated) derivative of naloxone. Its chemical names are (5α,6α)-17-allyl-6-((20-hydroxy-3,6,9,12,15,18-hexaoxaicos-1-yl)oxy)-4,5-epoxymorphinon-3,14-diol or alpha-6mPEG7-O-naloxol. Naloxegol is an antagonist predominantly of

[1] As discussed in a memorandum of understanding entered into by 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 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.

peripheral mu opioid receptors. The Food and Drug Administration (FDA) approved naloxegol for marketing on September 16, 2014, under the brand name Movantik™.[2] It is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Gastrointestinal adverse events (AEs) effects are commonly experienced by chronic users of opioid analgesics. Opioids delay gastric emptying and intestinal transport, which over time leads to debilitating constipation. OIC is caused by activation of the mu opioid receptor in the GI tract.

DEA and HHS Eight Factor Analyses

The DEA received a petition from the drug sponsor dated March 22, 2012, requesting that the DEA amend 21 CFR 1308.12(b)(1) to exclude naloxegol as a schedule II controlled substance. The petitioner stated that naloxegol is a mu opioid receptor antagonist without mu opioid agonist or partial agonist properties. The DEA accepted the petition for filing on October 1, 2012.

On February 7, 2013 the DEA forwarded to the HHS the data with the sponsor's petition along with a request for a scientific and medical evaluation and the HHS's recommendation as to whether or not naloxegol should be removed from the list of controlled substances. According to the HHS, the sponsor submitted a New Drug Application (NDA) for naloxegol on September 16, 2013. Based on the NDA, the HHS summarized that naloxegol is an antagonist of peripheral opioid receptors for the treatment of OIC.

On August 8, 2014, the HHS provided to the DEA a scientific and medical evaluation

[2] *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails* (last accessed Sept. 26, 2014).

document prepared by the FDA entitled "Basis for the Recommendation to Decontrol Naloxegol and its Salts from Schedule II of 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 naloxegol and its salts be removed from schedule II of the CSA. In response, the DEA conducted its own eight factor analysis of naloxegol 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-400) at *http:www.regulations.gov* under "Supporting and Related Material."

Determination to Decontrol Naloxegol

After a review of the available data, including the scientific and medical evaluation and the recommendation to decontrol naloxegol from HHS, the Deputy Administrator of the DEA published in the *Federal Register* a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Removal of Naloxegol from Control" which proposed removal of naloxegol and its salts from the schedules of the CSA. 79 FR 64349, Oct. 29, 2014. The proposed rule provided an opportunity for interested persons to file a request for a hearing in accordance with DEA regulations by November 28, 2014. 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 November 28, 2014.

Comments Received

The DEA received seven comments on the proposed rule to decontrol naloxegol. Five commenters supported decontrol of naloxegol. Two commenters submitted comments not related to the proposed action.

Support

Commenters in support of decontrolling naloxegol included two members of industry, a former intensive care unit (ICU) nurse, and two patient advocacy groups, all of whom expressed agreement with the DEA's findings that naloxegol does not possess abuse or dependence potential.

DEA Response: The DEA appreciates the comments in support of this rulemaking.

Request for Immediate Effective Date

Four of the commenters specifically requested that a rule decontrolling naloxegol be issued with an immediate effective date. Commenters stated that an immediate effective date was warranted because naloxegol does not have an abuse potential and is a new therapeutic option for opioid-induced constipation with no alternatives currently on the market. Additionally, a commenter distinguished this particular instance of decontrolling a substance that is not yet commercially available and thus would not result in burdens on the healthcare system or law enforcement from other DEA actions to control a substance which necessitated lead time for registrants to make necessary preparations for compliance.

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 absence of comparative effective therapeutic treatments for OIC with similar or less adverse effects

than naloxegol, coupled with the fact that this is an action for decontrol, support 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, the side effects of naloxegol have been shown to be generally mild and reversible. The addition of the polyethylene glycol group decreases the capacity of naloxegol from crossing the blood-brain barrier as compared to naloxone and is therefore expected to limit the potential for interference with centrally mediated opioid analgesia.

In making the determination to make this rule immediately effective, 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 immediately effective 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)(3).

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 naloxegol 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 13563

In accordance with 21 U.S.C. 811(a), this scheduling action is subject to formal rulemaking procedures done "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 Civil Justice Reform to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132

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

Naloxegol is a new molecular entity and is not currently available or marketed in any country. According to publicly available information reviewed by the DEA, naloxegol is anticipated to enjoy patent protection for an extended period of time before generic equivalents may be manufactured and marketed in the United States. Although the number of manufacturers of naloxegol may initially be limited, there is potential for numerous handlers in various business activities, e.g., distributors, hospitals/clinics, pharmacies, practitioners, etc.

This rule will affect all persons who would handle, or propose to handle, naloxegol. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the distribution and dispensing rates of new molecular entities, the DEA is unable to determine the number of entities and small entities which might handle naloxegol. However, the DEA estimates that all persons who would handle, or propose to handle, naloxegol are currently registered with the DEA to handle schedule II

controlled substances. Therefore, the 1.5 million (1,469,418 as of September 2014) controlled substance registrations, representing approximately 426,714 entities, would be the maximum number of entities affected by this rule. The DEA estimates that 417,302 (97.8%) of 426,714 affected entities are "small entities" in accordance with the RFA and Small Business Administration size standards.

The DEA estimates all controlled substances registrants handle both controlled and non-controlled substances and these registrants are expected to handle naloxegol. Additionally, since prospective naloxegol handlers are likely to handle other schedule II controlled substances, the cost savings they would receive as a result of the de-control of naloxegol would be nominal. As naloxegol handlers are likely to handle other schedule II controlled substances, they will need to maintain their DEA registration and keep the same security, reporting, and recordkeeping processes, equipment, and facilities in place and would experience only a nominal reduction in security, reporting, inventory, recordkeeping, and labeling costs.

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 426,714 of which 417,302 are estimated to be small entities. Since the affected entities are expected to handle other schedule II controlled substances and maintain security, reporting, and recordkeeping facilities and processes consistent with schedule II controlled substances handling requirements, the DEA estimates any economic impact (cost savings) will be nominal. Because of these facts, this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, the DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act of 1995 (UMRA), 2 U.S.C. 1501 *et seq.*, that this action would not result in any federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA.

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 companies to compete with foreign-based companies 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 to read as follows:

PART 1308— SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

2. 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, nalmefene, naloxegol, naloxone, and naltrexone, and their respective salts, but including the following:

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Dated: January 16, 2015.

Michele M. Leonhart,
Administrator.

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