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July 29, 2024

Re: Docket No. FDA-2019-P-5268

Dear Dr. Carome and Dr. Taghipour:

This letter responds to your citizen petition, received by the Food and Drug Administration (FDA, the Agency, or we) on November 6, 2019 (Petition), and supplement dated May 28, 2020. In the Petition, you request the following:

> that the [Drug Enforcement Administration (DEA)] Administrator and the Commissioner of Food and Drugs immediately initiate the proceedings for rescheduling 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, its salts, its optical and geometric isomers, and salts of these isomers (including tramadol) [hereinafter "tramadol"] from schedule IV to schedule II of the [Controlled Substances Act (CSA)] because the drug has a high potential for abuse – with use potentially leading to severe psychological or physical dependence – and is considered dangerous.

(Petition at 1).

We have carefully considered your Petition, your supplement and other information available to the Agency. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Tramadol

FDA first approved a new drug application (NDA) for a tramadol product in 1995.[2] Since that time, the Agency has approved NDAs for other tramadol products and approved numerous generic tramadol products.[3] Tramadol is an opioid agonist generally indicated in adults for the

[1] We note that Dr. Wolfe, Public Citizen's Health Research Group, was a signatory on this Citizen Petition and has since passed away.
[2] Ultram (tramadol hydrochloride (HCl)), new drug application (NDA) 020281.
[3] For the current list of approved products visit FDA's Web site at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Tramadol is a centrally acting synthetic opioid analgesic that produces its primary opioid-like action through the parent compound and an active metabolite (O-desmethyltramadol). In the United States, tramadol is available as an oral, single-active ingredient product in both immediate-release and extended-release formulations. Tramadol is also available in combination with acetaminophen or celecoxib. Tramadol, including FDA-approved drug product formulations containing tramadol, is currently controlled in schedule IV under the CSA, as described by regulation[4] and below.

B. Scheduling of Drugs

Congress enacted the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended (21 U.S.C. 801-971), to control drugs and other substances that have a potential for abuse.[5] The CSA creates a system by which drugs are categorized based on their "currently accepted medical use in treatment in the United States," "potential for abuse," and physical or psychological dependence potential.[6] Under the CSA, each category, known as a "schedule," is associated with various different requirements and restrictions. Depending on the schedule, controls may include manufacturing and production quotas, site security requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export requirements.[7] Practitioners, dispensers, drug manufacturers, and distributors of controlled substances are required to register with the DEA.[8]

The different schedules under the CSA are defined as follows:

- Drugs and other substances in schedule I have no currently accepted medical use in treatment in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.[9]
- Drugs and other substances placed in schedule II have a high potential for abuse and have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and abuse of the drug or other substance may lead to severe psychological or physical dependence.[10]
- Drugs and other substances in schedule III have a potential for abuse less than the drugs or other substances in schedules I and II and have a currently accepted medical use in treatment in the United States, and abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.[11]
- Drugs and other substances in schedule IV have a low potential for abuse relative to drugs or other substances in schedule III and have a currently accepted medical use in treatment in the United States, and abuse of the drug or other substance may lead to

[4] 21 CFR 1308.14(b)(3)
[5] The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970. Titles II and III are referred to in this petition response as the CSA.
[6] See 21 U.S.C. 812(b).
[7] See generally, 21 U.S.C. 821–831; 21 CFR 1300–1317.
[8] Id.
[9] 21 U.S.C. 812(b)(1).
[10] 21 U.S.C. 812(b)(2).
[11] 21 U.S.C. 812(b)(3).

limited physical dependence or psychological dependence relative to drugs or other substances in schedule III.[12]

- Drugs and other substances in schedule V have a low potential for abuse relative to drugs or other substances in schedule IV and have a currently accepted medical use in treatment in the United States, and abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.[13]

Under the CSA, drug scheduling is an effort coordinated between DEA and the Department of Health and Human Services (HHS), where a final scheduling action is taken by DEA.[14] Under DEA regulations, any interested person may petition the Agency to initiate rulemaking proceedings to schedule a controlled substance.[15] Before initiating such proceedings, DEA must gather the necessary data and other information, including the HHS Secretary's scientific and medical evaluation of the drug or other substance and the HHS Secretary's recommendation as to whether such drug or other substance should be controlled, and, if so, the schedule in which it should be controlled.[16] HHS's scientific and medical determinations "must be binding [on DEA] until issuance of a notice of proposed rulemaking"; once formal rulemaking has commenced, DEA must continue to accord "significant deference" to those determinations.[17]

Generally, FDA, on behalf of the HHS Secretary, performs the medical and scientific evaluation of a substance for control under the CSA. Under 21 U.S.C. 811(b) of the CSA, the medical and scientific analysis considers the following eight factors determinative of control of the drug under the CSA:

Factor 1: The drug's actual or relative potential for abuse

Factor 2: Scientific evidence of the drug's pharmacological effects, if known

Factor 3: The state of current scientific knowledge regarding the drug or other substance

Factor 4: The drug's history and current pattern of abuse

Factor 5: The scope, duration, and significance of abuse

Factor 6: What, if any, risk there is to the public health

Factor 7: The drug's psychic or physiological dependence liability

[12] 21 U.S.C. 812(b)(4).
[13] 21 U.S.C. 812(b)(5).
[14] 21 U.S.C. 811.
[15] 21 U.S.C. 811(a); 21 CFR 1308.43(a).
[16] 21 U.S.C. 811(b); 21 CFR 1308.43(d).
[17] *Questions Related to the Potential Rescheduling of Marijuana*, 45 Op. O.L.C. ___, at *25-26 (Apr. 11, 2024); *see also* 21 U.S.C. 811(b).

Factor 8: Whether the substance is an immediate precursor of a substance already controlled

Following consideration of the eight factors, FDA seeks the concurrence of the National Institute on Drug Abuse (NIDA) on its scientific and medical findings and drafted recommendation, as described in a Memorandum of Understanding between FDA and NIDA dated March 8, 1985.[18] The scientific and medical evaluation and the drafted recommendation are then transmitted from FDA to the Office of the Assistant Secretary for Health. The Assistant Secretary for Health is designated to act on behalf of the HHS Secretary to make a recommendation to DEA with respect to the appropriate schedule, if any, under which the drug or other substance should be listed in the CSA. HHS's scheduling recommendation is based on its evaluation of the eight factors and the findings that are required for scheduling under 21 U.S.C. 812(b).

II. DISCUSSION

The Petition requests that DEA and FDA initiate proceedings to transfer tramadol from schedule IV to schedule II of the CSA (Petition at 1).

As stated above in section I.B., although HHS evaluates drugs for abuse potential and makes recommendations for scheduling, DEA is the Federal agency that takes the scheduling actions under the CSA.[19] DEA has established processes for evaluating petitions relating to scheduling actions. As stated above, we will communicate with DEA, as appropriate, regarding tramadol.

As referenced in the Petition (Petition at 9-10), DEA has conducted its evaluation and scheduling process once before with respect to tramadol. On April 25, 2007, DEA, through the Department of Justice, requested that HHS conduct a scientific and medical evaluation and provide a recommendation to DEA for scheduling tramadol.[20] By letter dated September 16, 2010, HHS provided its evaluation and recommendation regarding tramadol, to DEA.[21] On November 4, 2013, DEA published its Notice of Proposed Rulemaking in the *Federal Register* proposing to place tramadol in schedule IV of the CSA.[22] After a public comment period, on July 2, 2014, DEA placed tramadol in schedule IV of the CSA, effective August 18, 2014.[23]

Although we deny the Petition's request to initiate proceedings to reschedule this substance, we are aware of some of the concerns raised in the Petition and have taken action to address such concerns.

Since 2019 when your Petition was submitted, FDA has required a number of safety labeling changes to the prescribing information for tramadol-containing drug products. These specific changes can be seen by date on FDA's web page on Safety-related Labeling Changes,

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[18] "Memorandum of Understanding with the National Institute on Drug Abuse" (50 FR 9518, March 8, 1985). Other HHS components, such as the Office of the Assistant Secretary for Health, may be consulted on a case-by-case basis.

[19] See generally 21 U.S.C. 811, 21 CFR § 1308.43.

[20] HHS Recommendation at 2, available at www.regulations.gov Docket DEA-2013-10-0005.

[21] Id.; see HHS letter to DEA enclosing the HHS Recommendation.

[22] 78 FR 65923 (November 4, 2013).

[23] 79 FR 37623 (July 2, 2014).

https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. For example, the numerous changes include updates to the BOXED WARNING and WARNINGS AND PRECAUTIONS sections, specifically regarding Addiction, Abuse and Misuse, Life-threatening Respiratory Depression, and new subsections on Hyponatremia and Hypoglycemia.

On April 13, 2023, FDA published on its web page an 18-page Drug Safety Communication (DSC) that summarizes Agency updates on prescribing information for all opioid pain medicines to provide additional guidance to prescribers and patients for the safe use of these drug products. The information provided in this DSC includes updates to help reduce unnecessary prescribing. (See https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-prescribing-information-all-opioid-pain-medicines-provide-additional-guidance-safe-use.) Although the DSC is not specific to tramadol, the topics addressed all apply to tramadol products. The materials are written for both consumers and prescribers.

Additionally, FDA has held two Joint Meetings of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee on tramadol drug products in order to receive advice and recommendations on tramadol drug approval issues. On January 15, 2020, FDA held a Joint Meeting, in part, to discuss new drug application (NDA) 213426 for a combined tramadol and celecoxib tablet.[24] The committees were also asked to discuss the safety and efficacy data as well as the overall risk-benefit profile for the product. FDA's presentation included a Review of Recent Data on Use, Misuse, Abuse and Overdose of Tramadol and Comparator Opioid Analgesics. The second Advisory Committee meeting occurred on February 15, 2022; the committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile for NDA 213231, tramadol hydrochloride injection.[25] These meetings also provided an opportunity for the public to hear and present data, information or views on the tramadol drug product issues pending before the committees.

We will continue to monitor the safety of tramadol and may take additional action, if necessary.

[24] *Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments*, 84 FR 66918 (December 6, 2019). Other meeting information is available at: https://public4.pagefreezer.com/browse/FDA/01-01-2023T07:57/https://www.fda.gov/advisory-committees/advisory-committee-calendar/january-15-2020-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-and-drug.

[25] Meeting information is available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/february-15-2022-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-and-drug#event-materials.

III. CONCLUSION

For the reasons stated above, your Petition is denied.

Sincerely,

Marta A. Sokolowska -S Digitally signed by Marta A. Sokolowska -S Date: 2024.07.29 10:47:35 -04'00' On behalf of Dr. Cavazzoni

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research