Michael T. Abrams, M.P.H., Ph.D.
Michael A. Carome, M.D.
Sydney M. Wolfe, M.D.
Public Citizen
1600 20th Street N.W.
Washington, DC 20009

January 18, 2023

Re: Docket No. FDA-2022-P-0149

Dear Dr. Abrams, Dr. Carome, and Dr. Wolfe:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA, the Agency, or we) on February 8, 2022 (Petition). In the Petition, you request that:

> the [U.S. Drug Enforcement Administration (DEA)] Administrator and the Commissioner of Food and Drugs initiate the proceedings to place (a) gabapentin (2-[1-(aminomethyl) cyclohexyl] acetic acid), including its salts, (including the brand name products Gralise and Neurontin) and (b) gabapentin enacarbil (1-{[({(1RS)-1-[(2-methylpropanoyl)oxy] ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid), including its salts, (including the brand name product Horizant) into schedule V of the [Controlled Substances Act] because the drugs have a marked potential for abuse with serious consequences that include psychological effects, physical dependence, seizures, suicide, and overdose death.

(Petition at 1).

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

I. BACKGROUND

A. Gabapentin and Gabapentin Enacarbil

On December 30, 1993, FDA approved an immediate-release gabapentin formulation as adjunctive therapy in the treatment of partial onset seizures.[1] FDA subsequently approved gabapentin for the management of postherpetic neuralgia in adults, which is associated with damage to nerve fibers during shingles infection.[2]

[1] Neurontin (gabapentin), new drug application (NDA) 20235.
[2] See Neurontin labeling dated February 2005, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/20235s029,20882s015,21129s016lbl.pdf; see also Gralise (gabapentin) labeling dated April 2, 2020, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf.

Gabapentin enacarbil is a prodrug of gabapentin, first approved by FDA in 2011 (NDA 22399). Like gabapentin, it is indicated for the management of postherpetic neuralgia in adults. Gabapentin enacarbil is also indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome.[3] Gabapentin enacarbil is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles. The same daily dose of gabapentin and gabapentin enacarbil results in different plasma concentrations of gabapentin.

The mechanism of action by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury models, acute herpes zoster infection models). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.[4]

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 Controlled Substances Act (CSA) creates a system by which drugs are categorized based on their currently accepted medical use, potential for abuse, and physical or psychological dependence potential. Under the CSA, each category, known as a "schedule," is associated with several 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.[6] Practitioners, dispensers, drug manufacturers, and distributors of controlled substances are required to register with the DEA.[7]

- Drugs and substances in schedule I have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.[8]
- Drugs and 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 substance may lead to severe psychological or physical dependence.[9]

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[3] See Horizant (gabapentin enacarbil) labeling dated April 2020, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf.
[4] See Neurontin (gabapentin) labeling dated April 2020, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf
[5] The DEA implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act. Titles II and III are referred to in this petition response as the Controlled Substances Act (CSA).
[6] See generally, 21 U.S.C. 821–831; 21 CFR 1300–1317.
[7] Id.
[8] 21 U.S.C. 812(b)(1).
[9] 21 U.S.C. 812(b)(2).

- Drugs and substances in schedule III have a potential for abuse less than the drugs or 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 substance may lead to moderate or low physical dependence or high psychological dependence.[10]
- Drugs and substances in schedule IV have a low potential for abuse relative to drugs or substances in schedule II and have a currently accepted medical use in treatment in the United States, and abuse of the drug may lead to limited physical dependence or psychological dependence relative to drugs or substances in schedule III.[11]
- Drugs and substances in schedule V have a low potential for abuse relative to drugs or substances in schedule IV and have a currently accepted medical use in treatment in the United States, and abuse of the drug or substance may lead to limited physical dependence or psychological dependence relative to the drugs or substances in schedule IV.[12]

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.[13] Under DEA regulations, any interested person may petition the agency to initiate rulemaking proceedings to schedule a controlled substance.[14] Before initiating such proceedings, DEA must gather the necessary data and request from the HHS Secretary a scientific and medical evaluation and the Secretary's recommendation as to whether such drug or substance should be controlled.[15] FDA performs the medical and scientific evaluation of a substance for control under the CSA, with concurrence of the National Institute on Drug Abuse (NIDA), as described in a Memorandum of Understanding between FDA and NIDA dated March 8, 1985.[16]

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 substance

Factor 4: The drug's history and its 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

[10] 21 U.S.C. 812(b)(3).
[11] 21 U.S.C. 812(b)(4).
[12] 21 U.S.C. 812(b)(5).
[13] 21 U.S.C. 811.
[14] 21 U.S.C. 811(a); 21 CFR 1308.43(a).
[15] 21 U.S.C. 811(b); 21 CFR 1308.43(d).
[16] "Memorandum of Understanding With the National Institute on Drug Abuse" (50 FR 9518, March 8, 1985).

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

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

After consideration of the eight factors, the HHS Secretary must make a recommendation with respect to the appropriate schedule, if any, under which a 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 the DEA and FDA initiate proceedings to place gabapentin and gabapentin enacarbil, including their salts, in schedule V 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 makes the scheduling decisions under the CSA.[17] DEA has established processes for evaluating petitions related to scheduling actions. As stated above, we will communicate with DEA as appropriate regarding gabapentin, gabapentin enacarbil, and their salts.

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

On December 19, 2019, FDA issued a drug safety communication warning that serious breathing difficulties may occur in patients using gabapentin or pregabalin who have respiratory risk factors.[18] These warnings include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease that reduce lung function. The elderly are also at higher risk of breathing difficulties associated with gabapentin and pregabalin.

Our evaluation shows that the use of these medicines, often referred to as gabapentinoids, has been growing for prescribed medical use, as well as misuse and abuse. Gabapentinoids are often taken in combination with central nervous system (CNS) depressants, which increases the risk of respiratory depression. CNS depressants include opioids, anti-anxiety medicines, antidepressants, and antihistamines. There is less evidence supporting the risk of serious breathing difficulties in healthy individuals taking gabapentinoids alone.

As a result of these findings, we required that new warnings about the risk of respiratory depression be added to the prescribing information of the gabapentinoids. On April 2, 2020, FDA approved labeling to include respiratory depression in the WARNINGS AND

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

[18] "FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) When used with CNS depressants or in patients with lung problems" (Dec. 19, 2019), available at https://www.fda.gov/media/133681/download.

PRECAUTIONS section of the labeling for these products.[19] We have also required the drug manufacturers to conduct clinical trials to further evaluate their abuse potential, particularly in combination with opioids, because misuse and abuse of these products together is increasing, and co-use may increase the risk of respiratory depression.[20] Special attention will be paid to the respiratory depressant effects during this abuse potential evaluation.

On January 19, 2022, we issued an FDA Drug Safety Podcast for health care professionals to reemphasize the messaging from the December 19, 2019, drug safety communication on gabapentinoid use and respiratory depression.[21]

We will continue to monitor the safety of gabapentin, gabapentin enacarbil, and their salts and may take additional action, if necessary.

III. CONCLUSION

In sum, for the reasons stated above, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[19] Neurontin labeling (4/2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s068,020882s049,021129s049lbl.pdf.
[20] You may search the Postmarket Requirements and Commitments database, available at https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.
[21] FDA Drug Safety Podcast, "FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)" (Jan. 19, 2022), available at https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin.