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January 31, 2020

Stephen M. Hahn, M.D.  
Commissioner  
Food and Drug Administration  
U.S. Department of Health and Human Services  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research  
Food and Drug Administration  
U.S. Department of Health and Human Services  
10903 New Hampshire Avenue  
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Rigoberto A. Roca, M.D.  
Acting Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
U.S. Department of Health and Human Services  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**RE: New drug application for tramadol-celecoxib combination tablet for management of acute pain**

Dear Commissioner Hahn, Dr. Woodcock, and Dr. Roca:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) not to approve the new drug application (NDA) submitted by Esteve Pharmaceuticals for a tramadol 44 milligrams (mg) and celecoxib 56 mg fixed-dose combination product for management of acute pain in adults. This NDA was the subject of the January 15, 2020, joint meeting of the FDA's Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

Public Citizen strongly opposes approval of the tramadol-celecoxib combination product because evidence from recent studies strongly counters the dangerously false assumption that tramadol, which was placed in schedule IV under the Controlled Substances Act (CSA) (21 U.S.C. § 811)

in 2014, is safer; less likely to cause misuse, dependence, and addiction; and has a better safety profile than schedule II and schedule III opioids.

In its briefing document for the January 15 advisory committee meeting, the FDA stated that as a schedule IV drug, tramadol is considered to have a lower potential for abuse relative to the drugs in schedule III of the CSA, and abuse of tramadol may lead to limited physical dependence or psychological dependence relative to drugs in schedule III. But, in an accompanying footnote, the agency pointed out that “Re-evaluation of the scheduling status was not considered as part of the review of this NDA.”<sup>1</sup>

As you are aware, on November 6, 2019, Public Citizen petitioned the Drug Enforcement Administration and FDA to initiate the proceedings for rescheduling tramadol from schedule IV to schedule II of the CSA.<sup>2</sup> We do not expect the FDA or DEA to have responded to our petition already. However, we had included in our petition several important new studies relevant to the misuse and dangers of tramadol that were published before the FDA had completed its internal evaluation of the NDA for the tramadol-celecoxib combination product and prepared the agency’s briefing document for the advisory committees. Disappointingly, none of these studies were discussed in the FDA’s briefing document or presented by the FDA at the January 15 advisory committee meeting.

For the FDA not to incorporate the results of these newer studies as part of its evaluation of the tramadol-celecoxib combination product ignores the following 2017 recommendation to the FDA from the National Academies of Sciences, Engineering, and Medicine (National Academies):

An integrated framework for opioid regulation would include all relevant outcomes with an impact on public health... [A]pplication of this step to an opioid would involve consideration of its impact on such outcomes as users’ short- and long-term pain relief and functional improvements (the potential benefits); hyperalgesia, misuse, OUD, overdose, and death (the potential risks) ...<sup>3</sup>

This National Academies recommendation clearly argues for a thorough, up-to-date review of all new evidence, including data from systematic epidemiologic studies, regarding the risk of misuse for tramadol compared with schedule II drugs such as hydrocodone and oxycodone.

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<sup>1</sup> Food and Drug Administration. FDA briefing document: Joint meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. January 15, 2020 (AM session). <https://www.fda.gov/media/134128/download>. Accessed January 30, 2020. Page 10.

<sup>2</sup>Public Citizen. Petition to the Drug Enforcement Administration and Food and Drug Administration to reschedule the opioid tramadol from schedule IV to schedule II. November 6, 2019. <https://www.citizen.org/wp-content/uploads/2497.pdf>. Accessed January 30, 2020.

<sup>3</sup> National Academies of Science, Engineering and Medicine. Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>. Pages 388-389.

However, findings from two particularly relevant recent studies concerning tramadol that were cited and discussed in our petition were not presented at the recent advisory committee meeting.

The first study, published in May 2019 by Thiels et al, sought to “determine the risk of transitioning from acute to prolonged opioid use in opioid-naïve patients treated with tramadol for postoperative pain.”<sup>4</sup> The study involved a retrospective analysis of de-identified claims data from OptumLabs Data Warehouse, which includes data for commercial and Medicare Advantage enrollees in a large, private U.S. health plan, from January 1, 2009, to June 30, 2018, with last surgery on December 31, 2017, for opioid-naïve patients undergoing one of 20 commonly performed elective surgical procedures spanning multiple specialties, including general surgery, orthopedic surgery, colorectal surgery, urologic surgery, thoracic surgery, and gynecological surgery. The authors classified all postoperative discharge prescriptions into one of five mutually exclusive categories: (1) no opioid prescription; (2) any long-acting opioid (with or without any short-acting opioid, including tramadol); (3) tramadol only; (4) a short-acting opioid other than tramadol (served as the reference group); and (5) tramadol with another short-acting opioid.

Thiels et al found that of the 444,764 patients who met the study’s inclusion criteria and had at least 180 days of follow-up, 357,884 [80.5%] had a discharge prescription for one or more opioids. The most common type of discharge prescription was one or more short-acting opioids other than tramadol (n=333,289, 74.9%), whereas 13,519 patients (3%) received tramadol alone and 5,457 (1.2%) received tramadol with another short-acting opioid. Tramadol was the third most frequently prescribed opioid in the study, ranking behind hydrocodone and short-acting oxycodone.

They also found that relative to patients prescribed non-tramadol short-acting opioids at discharge following surgery, patients prescribed tramadol had a 6% increased risk of additional opioid use, defined as at least one opioid fill 90 to 180 days after surgery (p=0.049); a 47% increased risk of persistent opioid use, defined as any span of opioid use starting in the 180 days after surgery and lasting at least 90 days (p<0.001); and a 41% increased adjusted risk of CONSORT-defined chronic opioid use/dependence, defined as an opioid-use episode starting in the 180 days after surgery that spans at least 90 days and includes either 10 or more opioid fills or 120 or more days’ supply of opioids (p=0.013).

In other words, relative to the reference group of patients with non-tramadol short-acting opioids — consisting mainly of hydrocodone and short-acting oxycodone — patients prescribed tramadol after surgery had a statistically significant 47% higher risk of persistent opioid use and a statistically significant 41% higher risk of CONSORT-defined chronic opioid use/dependence.

Thiels et al concluded the following:

We found that tramadol, a drug that is scheduled at a lower risk level than other common short acting opioids (schedule IV versus schedule II for hydrocodone and oxycodone),

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<sup>4</sup> Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. *BMJ*. 2019;365:l1849.

has a similar or somewhat greater risk of prolonged opioid use after surgery. Although all factors related to the safety of a drug must be considered, from the standpoint of opioid dependence, the Drug Enforcement Administration and FDA should consider rescheduling tramadol to a level that better reflects its risks of prolonged use.

The most evident reason for this high risk of tramadol misuse is the striking difference in the refill policies for schedule II drugs (no refills allowed) versus schedule IV drugs (up to five refills allowed in six months).

The second study, published by Harrison and Walsh in February 2019, examined the increase in the rate of tramadol prescribing in four states following the 2014 rescheduling of hydrocodone combination products from schedule III to schedule II.<sup>5</sup> The major finding of this study was that the decline in the rates of hydrocodone product prescribing per 100 residents following the 2014 rescheduling of hydrocodone combination products was largely offset by a dramatic increase in the rates of prescribing of tramadol products per 100 residents in California, Michigan, and New York. For Michigan and New York, the net increase in the rate of tramadol prescribing per 100 residents after the rescheduling of hydrocodone combination products exceeded the net decrement in the rate of hydrocodone product prescribing per 100 residents. Notably, tramadol went from the least frequently prescribed opioid before the scheduling change to the most commonly prescribed non-hydrocodone opioid in California and Michigan, and to the second-most commonly prescribed non-hydrocodone opioid in New York, trailing behind only oxycodone.

This second study highlights the increased, excessive prescribing of tramadol due to the laxity of restrictions under its schedule IV status. The result is a significant increase in persistent and chronic tramadol use compared with oxycodone and hydrocodone use. As mentioned above, chronic use is defined as an opioid use episode starting in the 180 days after surgery that spans at least 90 days and includes either 10 or more opioid fills or 120 or more days' supply of opioids. Such use usually, if not always, leads to opioid dependence.

Whether or not tramadol is eventually rescheduled from schedule IV to schedule II, the FDA should have given careful consideration to newer studies assessing the risks of tramadol, including the two studies discussed above, in its evaluation of the NDA for Esteve's tramadol-celecoxib combination product. By failing to do so, the agency deprived the advisory committees of information that very likely would have caused many more than 13 out of 26 members to vote against approval.

If the FDA decides to approve this drug, it will inevitably lead to a worsening of the opioid epidemic. Further, it will be a reminder that the agency's much-touted opioid regulatory framework is dangerously fragile because the FDA has not seriously heeded the

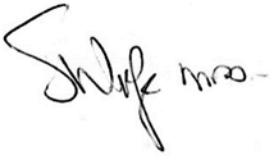
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<sup>5</sup> Harrison ML, Walsh TL. The effect of a more strict 2014 DEA schedule designation for hydrocodone products on opioid prescription rates in the United States. *Clin Toxicol (Phila)*. 57(11):1064-1072.

recommendations for improvement provided more than two and one-half years ago by the National Academies.

Public Citizen therefore urges the FDA to reject the NDA for the tramadol-celecoxib combination product. Thank you for considering our comments on this important matter.

Sincerely,

A handwritten signature in black ink that reads "Sidney M. Wolfe". The signature is written in a cursive style with a horizontal line at the end.

Sidney M. Wolfe, M.D.  
Founder and Senior Adviser  
Public Citizen's Health Research Group

A handwritten signature in black ink that reads "Michael A. Carome". The signature is written in a cursive style with a horizontal line at the end.

Michael A. Carome, M.D.  
Director  
Public Citizen's Health Research Group