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Supplement to Citizen Petition - Docket Number FDA-2019-P-5268

Submitted to:

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Date: May 28, 2020

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and the organization's Health Research Group, the undersigned submit this supplement to our November 6, 2019, citizen petition that was assigned docket number FDA-2019-P-5268. The petition requested that the DEA Administrator and FDA Commissioner 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 (generic name: tramadol) from schedule IV to schedule II of the Controlled Substances Act (CSA). That original petition offered detailed information demonstrating that tramadol should be rescheduled for the following six reasons:

(1) The FDA-approved product labeling for tramadol includes an indication and boxed warnings about the risks of addiction, misuse, and life-threatening respiratory depression that are nearly identical to the indications and boxed warnings found in the labeling for schedule II short-acting opioids, such as oxycodone.

(2) There is now clear recognition that a substantial proportion of the population has the cytochrome P450 2D6 (CYP2D6) genotype, which makes them ultra-rapid metabolizers of tramadol into a form that greatly increases the risk of fatal respiratory depression. This is the case across racial subgroups. The FDA-approved product labeling now warns that individuals who are ultra-rapid metabolizers should not use tramadol. However, few people know whether they are ultra-rapid metabolizers of tramadol because CYP2D6 genotyping generally is not performed prior to prescribing tramadol to patients.

(3) Tramadol has become one of the most prescribed opioids in the U.S., especially since the 2014 rescheduling of hydrocodone combination products from schedule III to schedule II, where other hydrocodone products have long been assigned.

(4) Recent National Survey on Drug Use and Health results have demonstrated that the number of persons who misuse tramadol exceeds those who misuse many schedule II

drugs including morphine, fentanyl, oxymorphone, Demerol (meperidine), and hydromorphone. Moreover, for the interval of 2016 through 2018, the proportion of people using tramadol who misused the drug exceeded the corresponding proportions of those who misused Demerol or morphine and was approximately two-thirds as high as the corresponding proportions of people who misused fentanyl, hydrocodone, or oxycodone.

(5) Research published since tramadol was placed on schedule IV of the CSA in 2014 has established a clear association between tramadol use and increased mortality.

(6) Recently published studies demonstrated that the risk of long-term opioid use following an initial opioid prescription — particularly for the common use of treating pain after surgery — was greater with tramadol than with short-acting schedule II opioids, including short-acting hydrocodone and oxycodone.

Although we believe the above evidence is more than sufficient for your agencies to reschedule tramadol from schedule IV to schedule II, we now offer additional scientific data from another recently published study that supports such action.

For the study, Veronin et al analyzed data from the FDA Adverse Event Reporting System (FAERS) and showed that among 15 common opioids, tramadol is the suspected drug in almost as many adverse events as fentanyl.[1] The researchers reviewed FAERS reports from 2004 to 2016 corresponding to 31,921,755 records. They identified all adverse event reports associated with the use of 15 opioids (see Table 1) selected based on evidence from published studies characterizing them as having high abuse potential. The study demonstrated that of the 784,517 adverse events associated with use of any of the 15 selected opioids, 13% were for tramadol, making it the fourth most common opioid precipitating such reports and as the fifth most common correlate to death.

As you are aware, FAERS data provide only rough signals of adverse events because they are not the result of random (i.e., unbiased) submissions. Still, we present these data because they show that tramadol is a common correlate to adverse drug events, including deaths, associated with opioid use that have been reported to the MedWatch program. Moreover, this is apparent in this real-world signal even in comparison to 14 other commonly used opioids, 11 of which are on schedule II.[2]

[1] Veronin MA, Schumaker RP, Dixit RR, Elath H. Opioids and frequency counts in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database: a quantitative view of the epidemic. *Drug Healthc Patient Saf*. 2019 Aug 19;11:65-70.
[2] Drug Enforcement Administration. Controlled substances – Alphabetical order. May 5, 2020. https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf. Accessed May 18, 2020.

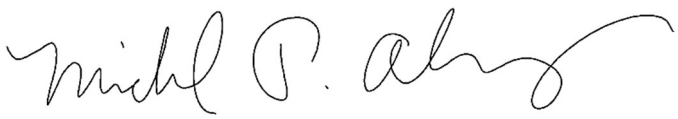
Table 1 Frequency counts of opioids and associated deaths in the FAERS database

Opioid Drug Name	No. of Records (Frequency)	% of Total	No. of Deaths (Frequency)	% of Total	Deaths to Drug Count (%)
Oxycodone	158,181	20.16	32,661	21.30	20.65
Hydrocodone	141,990	18.10	23,474	15.31	16.53
Fentanyl	105,381	13.43	23,180	15.12	21.99
Tramadol	104,000	13.26	13,637	8.89	13.11
Morphine	86,984	11.09	23,280	15.18	26.76
Buprenorphine	50,968	6.50	3275	2.14	6.43
Codeine	40,910	5.21	7210	4.70	17.62
Hydromorphone	30,792	3.92	6123	3.99	19.89
Methadone	28,659	3.65	10,649	6.94	37.16
Diphenoxylate	9175	1.17	1135	0.74	12.37
Propoxyphene*	7784	0.99	1848	1.21	23.74
Meperidine	7178	0.91	1177	0.77	16.39
Oxymorphone	5854	0.75	1272	0.83	21.73
Heroin**	4500	0.57	3230	2.11	71.78
Dextromethorphan	2161	0.28	1201	0.78	55.58
Total	784,517***	100	153,352	100	—

Notes: *No longer marketed in the US. **Illegal Controlled Substance (Schedule I of the US Controlled Substances Act). ***Represents Approximately 2.46% of the Drug Name Records in the FAERS database.

We hope this supplemental information will help you to decide to reschedule tramadol to schedule II in the very near future. We appreciate your consideration and look forward to your response.

Sincerely,



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