August 1, 2017

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

The undersigned submit this petition pursuant to Title 21, Chapter 9, Subchapter V, Part A of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 10.30 to request that the Commissioner of the U.S. Food and Drug Administration (FDA) place a black box warning on pharmaceuticals in the CII opioids warning that the use of this kind of opioid carries greater risk of addiction and overdose death than the use of a CIII opioid.

ACTION REQUESTED

The Petitioner requests the FDA to:

1. Amend current black box warnings on all CII opioid analgesics to state:
    a. *Labeling for all CII Opioid Class Medications should read:*

        WARNING: In order to reduce the risk of addiction and death due to overdose, you are advised to try a CIII opioid to control your patient's pain before prescribing this CII opioid.

2. Require medication guides for CII opioids that explain the increased risk of addiction and overdose deaths compared to CIII opioids, and that they should be used sparingly and only when a CIII opioid cannot control the pain. Emphasize the correlation between days of usage for a CII opioid and risk of addiction.

STATEMENT OF GROUNDS

I. OVERVIEW

Overprescribing of prescription CII opioids is contributing to the opioid addiction epidemic of fatal overdose in the United States. Biological and epidemiological data indicate that the CIII opioids (buprenorphine) are much less addictive and much less likely to lead to respiratory depression and death.

FDA guidance indicates that a black box warning is appropriate in several circumstances, including when[1]:

- "There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug;"

OR

- "There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)"

Both of these conditions are met in this case. Clinicians should consider the significantly greater risk of addiction when assessing the risks and benefits of prescribing a CII opioid rather than a CIII opioid. Moreover, clinicians can prevent fatal overdose by prescribing CIII opioids in lieu of CII opioids.

Accordingly, we are petitioning the FDA to add black box warnings to all medications in the CII opioid class that appropriately warn prescribers and patients that it is advisable to use a CIII opioid for pain control before resorting to a CII opioid because of an increased risk of addiction and overdose death when using a CII opioid.

[1] Food and Drug Administration. "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format." 6 October 2011

II. BIOLOGY

Opioids, in addition to acting as potent analgesics, cause sedation up to and including complete loss of consciousness and respiratory arrest. Opioids function primarily through stimulation of the Mu (μ), Kappa (κ), and Delta (δ) receptors that are normally activated in response to noxious stimuli by endogenous molecules (endorphins, enkephalins, and dynorphins). In addition to analgesia, stimulation of Mu receptors in the brainstem and medial thalamus causes respiratory depression and sedation, particularly in non-tolerant individuals. Kappa receptors (found in limbic and other diencephalic areas of the brain, the brainstem, and spinal cord) mediate spinal analgesia, sedation, dyspnea, and respiratory depression.[2]

CII Opioids Examples- Morphine, Hydrocodone(Vicodin), Oxycodone(Oxycontin)
CIII Opioids- Buprenorphine (Belbuca, Butrans)

CII and CIII opioids bind to the Mu opioid receptors in the central nervous system. The CII opioid are so called "pure agonists" so binding to the Mu receptor is associated with analgesia and euphoria. It is the latter effect that leads to addiction. Moreover, the binding of the CII opioid to the Mu receptor depresses the respiratory rate. In an overdose situation, then, the CII opioid causes fatal respiratory arrest.

CIII opioids (buprenorphine) are "partial agonists" for the Mu receptors. Accordingly, at relatively low doses they induce analgesia but not much in the way of euphoria which reduces the cravings and addiction. Moreover, their effects on respiratory depression exhibit a "ceiling effect" meaning giving more buprenorphine does not lead to greater respiratory depression.[3] Overdose death due to buprenorphine is very rare and it is associated with large doses in opioid naïve individuals, and often associated with concurrent use of other sedatives such as benzodiazepines.

Human Subject Studies Comparing CII and CIII (buprenorphine) opioids.

1. CIII opioids (buprenorphine) have been shown to be the least likely to produce the euphoria that leads to addiction. Among a group of morphine dependent subjects, buprenorphine was ranked the least "liked" compared to other opioids.[4]

[2] Trescot, AM, Datta, S, Lee, M, Hansen, H. Opioid Pharmacology. *Pain Physician: Opioid Special Issue.* 2008; (11): S133-S153.

[3] Davis, MP Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J.Support Oncol. 2012; 10(6):209-219

[4] Comer, SD, Sullivan, MA, Whittington, RA, Vosburg, SK, Kowalczyk, BS. Relative abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacology. 2008 April; 33(5) 1179-1191

2. CIII opioids (buprenorphine) are less likely to create physical dependence. In a double blind, within subject comparison of spontaneous opioid withdrawal from buprenorphine versus morphine.[5]
3. CIII opioids (buprenorphine) are the least likely to cause accidental death due to overdose. In a study of healthy volunteers, investigators demonstrated a dose-dependent effect on analgesia, but not on respiratory depression.[6] In a review of 98 unintentional lethal opioid overdose deaths in New York City, all cases involved multiple drugs, and buprenorphine exposure was found in only 2 cases.[7]
4. At higher doses, CIII buprenorphine is FDA-approved to treat opioid addiction by eliminating the physical signs of withdrawal without providing a euphoric effect.

III. EPIDEMIOLOGY

In May, 2017, Dr. Scott Gottlieb, the new FDA Commissioner, declared that addressing the opioid epidemic is his first and highest priority. In his FDA VOICE blog, he cites data unequivocally establishing prescription opioids as the major cause of opioid addiction. These medications are also gateway drugs: Some 75 percent of heroin users in treatment began their addiction with prescription opioids.

Prescription CII opioids are responsible for the majority of opioid-overdose deaths, responsible for about 22,000 of the 33,091 fatalities in 2015. The Agency for Healthcare Research and Quality reported 1.27-million emergency-room visits or inpatient stays for opioid-related issues in 2014 (the most recent year for which data is available).

The public debates over legal and regulatory policies to combat this epidemic are ongoing, with opinions continuing to evolve. Yet discussions mainly fail to consider another vital concern: the medically legitimate needs of people who require prescription opioids to help live with chronic pain. The inconvenient truth is that moderate-to-severe chronic pain typically cannot be adequately controlled with non-opioids. On the other hand, a 2016 Washington Post-Kaiser Family Foundation survey of patients using opioids to manage their chronic pain found that 1/3 of patients admit to being addicted to their opioids and ½ of those admitted to using the opioid for non-pain purposes.

One highly promising solution to this dilemma focuses on an underutilized treatment for chronic pain called buprenorphine. It is the only opioid for pain in the CIII schedule of drugs, a category recognized by the FDA as representing a reduced risk of addiction. All other opioids for pain are grouped in the riskier CII class. Yet prescriptions for CIII opioids account for less than 1% of opioid prescriptions.

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[5]Tompkins, DA, Smith, MT, Mintzer, MZ, Campbell, CM, Strain, EC. A Double Blind, within Subject Comparison of Spontaneous Opioid Withdrawal from Buprenorphine versus Morphine. J of Pharmacol Expl Ther, Feb 2014;348:217-226.
[6]Dahn, A, Yassen, A, Romberg,R, Sarton,E, Teppema, L , Olofsen,E, Danhof,M. Burprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth 2006; 96:627-632.
[7]Paone, D, Tuazon, E, Stajic, M, Sampson, B, Allen, B, Mantha, S, Kunins, H. Buprenorphine infrequently found in fatal overdoses in New York City. Drug Alc Dep 2015 August;155:298-301

Until recently, buprenorphine was only available as a once-a-week transdermal (skin) patch (Butrans), which limited its efficacy and caused some doctors to eschew it. Early last year, however, the FDA approved a twice-daily formulation of buprenorphine (Belbuca) that provides significant pain relief: a small, transparent film resembling a Listerine breath strip that dissolves against the inside of the cheek.

In this new form, buprenorphine may play a key role in fighting the prescription-opioid epidemic. It is the least addicting of all the opioids. It typically does not lead to withdrawal symptoms when stopped. Importantly, it reduces the risk of death due to overdose because it doesn't shut down respiration the way other opioids can.

Buprenorphine poses much less risk than CII opioids because it doesn't produce the same kind of potentially addictive euphoria. People living with chronic pain can get relief from buprenorphine, but addicts looking for a high don't like the drug very much, according to studies.

The FDA has approved high-dose CIII buprenorphine (generally, over ten times the amount approved for pain management) as a treatment for opioid addiction. The advantage of buprenorphine is that it can eliminate withdrawal symptoms without triggering euphoria. This is in stark contrast to the use of methadone to treat heroin addiction. The dual ability of buprenorphine to both manage pain and also addiction underscores its uniqueness.

The danger posed by CII opioids is real and immediate. In an analysis by the Centers for Disease Control and Prevention, the longer the exposure of opioid-naïve patients to CII opioids, the greater the risk of becoming a chronic user.[8] With at least a one-day supply there is a 6 percent risk of continuing the opioid for at least a year; a greater than 31 day supply is associated with a 29.9 percent risk of using opioids one year later.

There are common-sense conclusions to be drawn here. For chronic-pain patients who are not getting adequate relief from non-opioids, prescribers should be encouraged to offer CIII buprenorphine as a first-line therapy before resorting to a CII opioid. For patients who have been on a CII-opioid long-term, they should be encouraged to gradually replace the medication with CIII buprenorphine.

V. CLINICAL EDUCATION

Prescribers need to consider the serious adverse reaction of fatal overdose when assessing the risks and benefits of prescribing CII opioids in lieu of CIII buprenorphine. However, existing educational measures have not been sufficient for this purpose. As a result, a black box warning would provide significant benefit. Currently, buprenorphine accounts for less than 1% of prescription opioids for chronic pain and it is clearly being underutilized.[9]

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[8]Shah, A, Hayes, CJ, MartinBC, Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use-United States 2006-2015. MMWR Morb Mortal Wkly Rep 2017; 66:265-269

[9]Khanna, IK, Pillarisetti, S. Buprenorphine-an attractive opioid with underutilized potential in treatment of

chronic pain. J Pain Res 2015; 8:859-870

Class wide REMS introduced in 2011 for the long acting CII opioids commonly used in chronic pain management do not suggest a trial of a CIII opioid (buprenorphine) before resorting to a CII opioid and these REMS are not mandatory for prescribers.

5. PUBLIC EDUCATION

A black box warning would alert patients to the risk of the extended use of CII opioids in terms of addiction and the risk of unintentional overdose death. It would inform them about the preference to try the less addictive and less dangerous CIII opioids (buprenorphine) to manage their pain before resorting to CII opioids.

6. POTENTIAL OBJECTIONS

Some may object to the lack of a prospective head to head comparison of the risk of the CIII opioids and the CII opioids. Clinical trials for drug approvals (NDA) of the CIII opioids typically used chronic pain patients on other opioids to demonstrate their ability to provide adequate pain relief. Clinical studies, furthermore, have demonstrated that CIII buprenorphine is the opioid of last resort for abuse, because it does not provide the level of euphoria associated with the CII opioids, even though the "ceiling effect" on respiratory depression reduces substantially the risk of inadvertent overdose death.

In addition to the reduced risk of addiction and overdose death, CIII buprenorphine in head to head clinical trials against CII opioids is associated with substantially less chronic constipation, markedly reduced mental confusion, and a reduction in depressive side effects of CII opioids .

7. FDA AUTHORITY

The Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Section 901(a) of the FDAAA added Section 505(o)(4) to the FDCA, granted FDA authority to mandate post- approval safety-related labeling changes for both individual drugs and classes of drugs.

ENVIRONMENTAL IMPACT

According 1921 CPR Sec. 25.31(a), this Petition qualifies for a categorical exclusion from the requirement that an environmental impact statement be submitted.

ECONOMIC IMPACT

According to 21 CPR See 10.30(b)~ an economic impact statement is to be submitted only when requested by the Commissioner following reviewing of this Petition.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition that are unfavorable to the petition.

Respectfully submitted,

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Dennis L. Ryll, MD

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