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PETITION TO THE FDA

REGARDING HYPNOTIC DRUGS

The undersigned, Daniel F. Kripke, M.D., submits this Citizen Petition under the Federal Food, Drug & Cosmetic Act, 21 C.F.R. §§ 10.30, to request that the Commissioner of Food and Drugs take the following administrative actions with respect to the so-called hypnotic drugs listed herein. For at least the following drugs: zolpidem, temazepam, eszopiclone, zaleplon, triazolam, flurazepam, and quazepam, in all brands and forms prescribed to treat insomnia or patient-reported sleep disorders, and any barbiturates including pentobarbital, amobarbital, and secobarbital still prescribed, either on- or off-label, to induce sleep, Petitioner requests the following actions.

A. Action Requested

Because the risks of these hypnotic drugs, which include significantly increased patient morbidity and mortality, greatly outweigh the minimal demonstrated clinical benefits, Dr. Kripke ("Petitioner") requests that the Commissioner of Food and Drugs take the following administrative actions:

A.1. Require that manufacturers of each of these drugs conduct comprehensive post-market randomized placebo-controlled trials quantifying risks and benefits to patients. These studies should be designed and implemented under FDA supervision, should include long-term follow-up, and should measure the drug-induced hazard ratios for the following:

- all-cause mortality, and specifically, death at night
- cancer incidence
- depression
- serious infections
- accidental injuries, especially falls causing injury and driver-caused accidents
- suicidality, suicide attempts, and suicides.

These trials should be performed with adequate power to demonstrate with 95% confidence that the manufacturer's hypnotic drug does not cause an excessive increase in mortality.

The studies should include examination of the risks and benefits of hypnotic use by vulnerable patients such as frail elderly, obese patients, patients with comorbidities such as chronic obstructive pulmonary disease, and patients with active sedative or narcotic prescriptions and/or use of alcohol. Hypnotics are frequently taken by persons with comorbidities and those taking multiple prescription medications including sedatives and narcotics. Hypnotics are also widely used in hospitals, veterans' homes, and nursing homes.

Patients with comorbidities and those taking multiple prescription medications and frail elders are under-represented in pre-market clinical trials and are at particular risk of injury, illness, and death due to hypnotics. The risks and benefits of hypnotics for these vulnerable populations must be quantified and better understood.

A.2. Require that manufacturers of each of these drugs promptly issue "Dear Doctor" letters regarding the known and suspected risks to patients of long-term use of these drugs. Those letters should call to prescribing doctors' attention the greatly increased risks of serious side effects of use of these hypnotic drugs, including lethality, infection, cancer, depression, and suicide.

A.3. Implement enhanced reporting of all prescription use of hypnotics. Most hypnotics are indicated only for occasional, short term use. Yet market data suggest that many patients receiving these drugs use them continuously for extended periods of time, and this long-term use constitutes the majority of prescriptions and consumption. The FDA should therefore implement an enhanced reporting system for these drugs that records all prescriptions. Any renewals of prescriptions or any original prescription for greater than a two-week supply of any of the listed drugs should be subject to mandatory reporting to the FDA. Likewise, all U.S. importing and manufacture of these drugs should be reported to FDA to obtain reliable national data on total U.S. consumption, both legal and illegal.

A.4. Restrict off-label prescription of listed hypnotic drugs. Prescriptions of any of the listed drugs for any off-label use should be curtailed until the results of post-market studies have been analyzed and the FDA makes a final determination that clinical benefits exceed patient risks.

A.5. Require labeling of mortality hazards. Require labeling of all medication containers of all of the listed drugs to indicate that use of sleeping pills is hazardous to health and can cause serious illness or death from respiratory depression, infection, cancer, suicide, or other illnesses. Repeat such labelling in all prescribing information and advertising. Such labeling may include, as appropriate, so-called "Black Box" warnings.

A.6. Require enhanced informed-consent for listed hypnotics. Require prescribing doctors to discuss with patients requesting or being considered for prescriptions for the listed drugs, all of the known and suspected risks of use of these drugs. The informed consent discussion should specifically address increased risks including death, cancer, serious infections, mood disorders, and suicidality.

A.7. Restrict indications for the specified hypnotics to hospice care and controlled trials pending the results of post-market studies. For the listed drugs, restrict indications, marketing approval, and labeling to treatment of insomnia within hospice care and to placebo-controlled trials. Delay enforcement of this restriction until January 1, 2018 for any manufacturer engaged in providing by that date adequate controlled-trials assessment of the long-term safety of the drug.

A. 8. Relax indications beyond hospice care only if the manufacturer of each of the hypnotics specified proves that the hypnotic has minimal mortality or cancer risk and has clinically significant benefit. The above restriction in marketing may be removed from a particular hypnotic drug and manufacturer if Phase IV randomized clinical trials provided by that manufacturer prove with 95% confidence that the hypnotic drug in the average dosage prescribed causes no more than a negligible increase in mortality compared to appropriate placebo.

B. Statement of Grounds

Because the listed hypnotic drugs demonstrate little to no clinical benefit to patients, but significantly increase patients' risks of mortality, cancer, depression, accidental injuries, serious and systemic infections, and suicidality, their risk to patients greatly outweighs these drugs' minimal clinical benefit.

RISKS

Hypnotic Drugs Greatly Increase the Risk of Serious Illness and Death

B.1. Hypnotic drugs greatly increase all-cause mortality. Use of hypnotic drugs is associated with a greatly increased risk of all-cause mortality. Some of this mortality has been proven by Medical Examiner data to be causal. In addition to respiratory depression, these drugs appear to be causally related to serious illnesses and premature deaths from cancer, serious infections, mood disorders, accidental injuries and suicides.

B.2. Hypnotics produce an excess of deaths at night. In the first Cancer Prevention Study, deaths at night were found to be increased by 15.6% among those taking hypnotics (P=0.01), presumably due to respiratory suppression.[1] In that study, excess deaths at night accounted for about one third of the excess mortality observed among participants using hypnotics. Mortality was attributed to other causes, even though quiet respiratory suppression is one of several covert ways that hypnotics cause excess deaths and was apparently a cause of some of these nocturnal deaths.

The mechanism of dangerous hypnotic respiratory depression is well-understood. The common hypnotics including barbiturates, benzodiazepines, the "Z" drugs and other benzodiazepine-receptor agonists bind to GABA receptors. These ligands/agonists alter the configuration of the receptors to allow negative chloride ions to more readily enter the neurons, where the chloride hyperpolarizes the membranes and inhibits the neurons from firing. When they depress neural respiratory center firing, such drugs can acutely suppress respiration and in large enough dose, or when individuals are particularly sensitive, may effectively arrest respiration, which leads rapidly to cardiac arrest and consequent death.[2-4] Respiratory depression is accordingly, and accurately, listed among zolpidem's warnings and precautions.[5] The barbiturates and alcohol bind to different locations on GABA receptors, where they exert additive or perhaps synergistic respiratory depression effects which may add to benzodiazepine-agonist effects.

B.3. Hypnotics cause serious and potentially lethal infections. A meta-analysis of available placebo-controlled randomized clinical trials showed that hypnotics cause infections

($p<0.00001$).[6] Because the clinical trials randomized hypnotics versus placebos, the 44% higher infection rate among participants who were given hypnotics was certainly caused by the hypnotics. The lead manufacturer of zolpidem has acknowledged that zolpidem induces infections, based on the manufacturer's own trial data.[7] The FDA also found dozens of reports of zolpidem-related severe infections among post-marketing reports.[5]

Extensive epidemiologic data demonstrate that hypnotics are associated with increased pneumonia including fatal pneumonia.[8] This pneumonia finding was not confirmed by one Taiwanese study,[9] but a Taiwanese study focusing on patients with sleep disturbances found that use of zolpidem was associated with 62%-91% increased hospitalizations for serious infections.[10] A Taiwan study of patients with chronic obstructive pulmonary disease found highly significant odds ratios associated with benzodiazepine use of 9.3 for pneumonia, 10.4 for acute COPD exacerbation, 45.0 for acute respiratory failure, and 18.6 for cardiopulmonary arrest; whereas the odds ratios for "Z" drugs such as zolpidem were of almost similar magnitude.[11] In confirmation, note in the Geisinger Health Study supplement, Table 7,[12] mortality hazard ratios were likewise specifically elevated among hypnotics users with COPD. Another Taiwanese study showed that use of zolpidem was associated with increased risk of pyogenic liver abscess.[13] British data showed that use of benzodiazepines and use of the hypnotic zopiclone (containing 50% eszopiclone as the active ingredient) were significantly related to asthma exacerbation and to all-cause mortality following exacerbation.[14] This study described some of the benzodiazepine-agonist-mediated impairments of immune surveillance.[14] Likewise, use of benzodiazepines was associated with 23% increased hospital readmission in North Carolina.[15] In summary, the epidemiologic evidence indicates that hypnotics not only cause the mild upper-respiratory infections mainly represented in available controlled clinical trials,[6] but also more severe and life-threatening infections. Since such infections demonstrably impair survival, infection is shown to be an additional mechanism by which hypnotics covertly increase mortality.

Animal studies confirm these findings. A controlled trial demonstrated in mice that diazepam exacerbated Streptococcus pneumoniae infection through GABA A receptors, partly explaining the underlying immune mechanisms.[16] Diazepam also exacerbates cowpox in mice, a viral infection.[17] Midazolam impairs equine immune responses, attributable to effects on macrophage peripheral benzodiazepine receptors (now called TSPO).[18] Evidence for involvement of TSPO in immune impairment also came from specific test compounds in mice.[19] Thus, hypnotic drugs cause increased risk of potentially lethal infections in controlled laboratory experiments.

B.4. Hypnotics cause cancer.

Human clinical trials strongly suggest hypnotics cause cancer in humans.

A compilation of randomized controlled trials of hypnotics showed 12 cancers or tumors of uncertain malignancy among participants randomized to a hypnotic but none (zero) among those randomized to placebo ($P=0.032$, two-tailed Fisher Exact Test).[20] When the FDA repeated this audit of their controlled trials data, the FDA counted 13 cancers from hypnotics versus none (zero) from placebo.[20] The conclusion from this FDA evidence that hypnotics caused cancer was significant ($P=0.025$ for two-tailed Fisher Exact Probability test incorporating duration of observation, or Fisher Exact Test $P<0.015$ excluding duration of observation.) Since the FDA

did not supply the numbers of participants and years of observation corresponding to their cancer tabulation, these latter Fisher Exact Tests were based on the numbers of participants and estimated years of observation from the petitioner's tabulation.[20]

These controlled-trials compilations did not include indiplon, an unlicensed zaleplon-like benzodiazepine agonist and hypnotic, for which studies published subsequently indicated 3 incident cancers in the indiplon groups and none in the randomized control groups.[21,22] The compilations did include trials of the marketed hypnotic ramelteon, for which this petition does not requested regulatory action, due to the absence of adequate epidemiologic data.

The FDA was not persuaded that these human controlled-trials data required regulatory action, because most of the definite cancers were only minor skin cancers, because of heterogeneities in the data, and because the cancers were recognized after such short observation periods. Nevertheless, the controlled trials data suggested more than skin cancer. There were cancers of organs apart from skin noted among those treated with hypnotics but none among those randomized to placebo. Reconsideration of FDA's deferral of action is now required by new animal testing and new epidemiologic findings: over half of the research referenced in this petition appeared after that FDA deferral of action.

Because hypnotics cause cancers to be suddenly recognized during short clinical trials, e.g., from one month to one year, the short-term results are likely to arise more from hypnotics promoting progression of tiny preexisting cancers rather from an effect upon cancer initiation. That progression may become a cause of death, whether or not the hypnotics initiated the cancer.

Animal studies strongly suggest hypnotics cause cancer.

The animal data in the FDA files for zolpidem indicated that increasing doses of zolpidem fed to rats resulted in increasing numbers of renal liposarcomas and lipomas combined (statistically significant). These data also showed increased thyroid follicular adenomas and carcinomas combined, and increased testicular interstitial cell adenomas, but these findings did not reach statistical significance.[23] There were no such tumors – that is, zero tumors – in the placebo group. These studies were too small, however, to have substantial power for these neoplasms. Expert FDA pharmacy examiners interpreted the data as suggesting an unknown degree of cancer risk for humans.

These experiments, which showed tumors resulting from feeding zolpidem to rats and suggested a dose-dependent relationship, apparently were never extended, clarified, published, or otherwise followed up.

Similarly, the animal data used for eszopiclone evaluation relied largely on zopiclone data, since eszopiclone is roughly 50% of zopiclone, and eszopiclone is thought to be the active isomer. The animal evidence that zopiclone caused animal cancers was of great enough concern to FDA's scientists, with additional issues, that at least 5 FDA scientists and medical officers recommended against approval of eszopiclone.[24] Tumors of the lung in rodents were of special concern; these findings also anticipated the human-specific association of hypnotics with lung and esophageal cancers.

Since zolpidem and eszopiclone were evaluated, much additional evidence has appeared relating hypnotics to cancer. Amerio et al. systematically surveyed FDA records including much animal data not included in the earlier compilation of hypnotics trials and concluded that hypnotics and sedatives had among the most elevated cancer hazards among psychotropic drugs.[25]

In vitro studies strongly suggest hypnotics cause cancer.

Zopiclone, zaleplon, and ramelteon are clastogenic[24,26,27] – these hypnotics damage chromosomes. Clastogens are potentially mutagenic agents that induce disruption or breakages of chromosomes. This process can lead to carcinogenesis. Cells that are not killed by the clastogenic effect may become transformed to cancer.[28] One of the several forms of zolpidem was said from in vitro studies not to be clastogenic.[29] Other than the four drugs mentioned, no information could be located that other drugs included in this petition have ever been adequately tested for clastogenicity.

Clastogenicity is only one mechanism by which hypnotics are likely to be carcinogenic, through either initiating cancers or promoting progression through additional mutations of cancer cells, or both. The alterations of immune surveillance produced by benzodiazepine agonists, discussed in relation to infection in section B.3., suggest additional mechanisms by which cancer initiation and progression might be facilitated or disinhibited.[30] Hypnotic-initiated increases in infections and consequent inflammation is another potential carcinogenic mechanism. These animal-demonstrated and in-vitro mechanisms for carcinogenicity of hypnotics—that have been widely ignored—support evidence that hypnotics cause human cancer.

Human epidemiology studies show elevated cancer incidence associated with hypnotics.

A 2008 paper[20] listed three previous publications showing associations of hypnotics with cancer deaths.[31-33] Analysis of CPSII data found that the elevation in deaths associated with hypnotics was comparable to that associated with cigarettes.[33] The report of Merlo et al. was unique in that the small study showed significantly increased cancer deaths among hypnotics users, but the increase in overall deaths associated with hypnotics was not significant.[31] Mallon, Broman, and Hetta (2002) found a much higher cancer adjusted hazard ratio for habitual sleeping pill use of 5.3 (95% C.I. 1.8-15.4) than for smoking among males; none of the specific causes of death were individually significant among females.[32] A similar result was found in a later paper for males, but the simple significant mortality elevation of regular hypnotic use among females was lost after multivariate adjustment in the second study.[34] More recently, a number of new studies have appeared reporting that hypnotic usage is related to cancer incidence and mortality. Hartz and Ross found a significant association of hypnotic use with melanoma and close-to-significant associations for lung and breast cancers.[35] Kao et al. found a remarkable 6.24 (4.13-9.43, 95% CI) hazard ratio for cancer incidence among those using at least 300 mg of zolpidem per year without other-benzodiazepine consumption (this would correspond to slightly more than one 5 mg dose per week).[36] In this Taiwanese national study, smoking and BMI were not controlled, but the overall cancer hazard ratios for zolpidem users were almost identical among men and women, despite an almost 11-fold greater prevalence of smoking among adult men compared to Taiwanese women at the time.[37] Body mass index was not controlled, but at that time in Taiwan,

although being overweight was more common among women, obesity was more common among men.[38] In a similar Taiwanese study, use of benzodiazepines was associated with a 1.19 (1.08-1.32 95% CI) cancer incidence hazard ratio, with over twice the benzodiazepine-associated hazard among men as among women. Similarly, a brief analysis of the national data from Taiwan found a significant cancer adjusted odds ratio for 2 of 3 benzodiazepine hypnotics.[39]

In a study using electronic medical records, Kripke et al. found a hazard ratio for cancer incidence of 1.35 (1.18-1.55 95% CI) associated with use of >132 hypnotic doses per year, with specific hazard ratios of 1.28 (1.03-1.59) for high-dose zolpidem and 1.99 (1.57-2.52) for high-dose temazepam.[12] This study was carefully controlled for age, gender, smoking, BMI, and by matching comorbidities among cases and controls. Jiao et al. found no excess of colorectal cancer among those reporting sleeping pill usage <3 times per week versus ≥3 times per week in the Women's Health Initiative data set,[40] a result consistent with the Hartz and Ross report on the same data set,[35] but since the contrast of frequencies of usage was weak and the type and quantity of hypnotic consumption were not determined objectively, the finding is not very informative. We would not expect hypnotics to promote all cancers equally. Specificity among cancer types would be anticipated if the mechanisms are causal. Pottegard et al. and Sivertsen et al. found small but significant associations of hypnotic usage with cancer, especially lung cancer,[41,42] but since they had not controlled for cigarette smoking, both groups thought their result might have arisen from confounding, a conclusion that is questionable.[43] That investigators failed to control for important confounders is no proof that confounding explains the significant hazard. Several U.S. and European groups,[41,42] and also Kao et al.[36] found high hazard ratios for lung and esophageal tumors, but the two San Diego studies had carefully controlled for smoking.[12,33] We had proposed that effects of hypnotics on weakening the gastro-esophageal sphincter and permitting more gastro-esophageal regurgitation[44] might account for the high specific rates of esophageal and lung tumors.[12] Multiple studies finding hypnotics associated with human lung cancer was consistent with concerns of FDA scientists about lung cancers found in animal studies of zopiclone. The cancer specificity supports causality.

There was one pair of studies that was neither clearly confirmatory nor negative. A large-scale survey screening many drugs with a questionable scheme for reusing controls for multiple tests and incorporating a questionable 2-year drug-to-cancer lag remarked no significant association of cancer with temazepam or zolpidem but did find significant associations with oxazepam and perhaps lorazepam, using $P<0.01$ and relative risk >1.50 as criteria.[45] In that study, it was not always possible to control for smoking, and control for other confounders was crude and not well-standardized. A similar study added a possible association for phenobarbital.[46]

In summary, the great majority of relevant epidemiologic studies have noted either small or large hazards for new cancers associated with hypnotics. Epidemiologic studies of hypnotics and cancer incidence have had many limitations, and some of these studies were not well-controlled for important confounders such as smoking and obesity, but the preponderance of evidence suggests a causal elevation of cancer incidence among those who take hypnotics.

The findings from human epidemiology studies confirm and reinforce findings from animal studies, controlled clinical trials, and the in-vitro clastogenicity data. The available animal data, clastogenicity data, randomized placebo-controlled clinical trials, and human epidemiology

studies demonstrating an association with cancers and hypnotics use consistently, if not conclusively, suggest that hypnotics likely cause human cancers and cancer deaths.

B. 5. Hypnotics increase incidence of clinical depression. In combined clinical trials, participants randomized to hypnotics suffered 2.1 times as many incident (new) depressions as those randomized to placebo ($P<0.002$).[47] These were not exacerbations of pre-existing depressions. These were depressions caused by the hypnotics. There are other data demonstrating worsening of depression with a wider variety of popular benzodiazepine and GABA agonists.[48]

Some studies have appeared designed to show that a hypnotic reduced depression scores among patients given an antidepressant known to cause insomnia.[49,50] In the first of these studies, the benefit of the hypnotic for depression was not significant at Week 4 after the investigators removed the rating scale items related to insomnia, whereas the Week 8 benefit was only significant at the $P=0.04$ level not correcting for multiple comparisons. In other words, using rigorous Bonferroni correction for multiple comparisons, the alleged benefit of hypnotic for depression symptoms was not significant. In the second study the authors more readily conceded that the hypnotic had no significant benefit for depression. In summary, these studies failed to rebut the evidence that hypnotics cause new depressions.

Depression is the major cause of suicide. Also, short-acting benzodiazepine agonists such as triazolam and zolpidem may cause withdrawal anxiety and even panic attacks during the daytime.[51] Panic attacks are a risk factor for suicide.[48] Suicide is the 8th or 10th leading cause of death in the United States.[52] Hypnotic use is associated with high rates of suicide.[3,33] Indeed, comprehensive toxicological studies have found intoxicating abusable substances (mainly sedative-hypnotics) in a majority of suicides, often combined with alcohol in 30-40%.[48] Suicides due to overdoses have increased dramatically from 1999 to 2010 in the U.S.,[53] but there are an even larger number of deaths of undetermined manner in which suicide through overdose must be suspected.[54] A very recent report estimated that in 2013 there were 7,000 overdose deaths related to anxiety and sleep medications,[52] but this did not include all suicides in which the most rigorous toxicology shows a sedative or anxiolytic often mixed with alcohol to be present.[48] The adjusted odds rate for suicide was 4.2 among hypnotic users as compared to nonusers in one study of elderly people, whereas the odds were not elevated among anti-depressant users (tending to exclude depression and other comorbidities as confounders.)[55] Prescription sleeping pill use was a stronger predictor of suicide attempts than insomnia symptoms in the National Comorbidity Survey Replication.[56] In a large study from Taiwan, the adjusted suicide hazard ratio for "needing sleeping pills" was 11.1, whereas the hazard ratio for those reporting sleeping only 0-4 hours adjusted for sleeping pill use was only 3.5, and none of the hazard ratios for insomnia symptoms exceeded 2.0.[57] The findings indicate that the association of suicides with hypnotic use cannot be entirely attributed to confounders, especially since the association of hypnotic usage with depression is known to be largely caused by the hypnotics.[47]

Zolpidem specifically has been implicated as a causal agent in a number of suicides, some of which involved kinds of dissociative behavior often attributed to zolpidem or to combined use of zolpidem with other drugs or alcohol.[58] Impairments of cognition and judgment that may be caused by sleeping pills[59] as well as hallucinations,[60] irrational behaviors,[53,61-63] and behavioral

disinhibition[48] may all contribute to suicides, violence, and accidents, even among persons who are not severely depressed.

B. 6. Hypnotics greatly increase the risk of injuries due to automobile accidents, falls, and other accidents. Hypnotic drugs impair next-day alertness, motor skills, reasoning, and overall performance. Accidents of all sorts are associated with use of benzodiazepines and benzodiazepine agonists such as zolpidem.[64-66] Most hypnotics impair automobile driving, as indicated by on-the-road controlled performance testing.[67] This impairment in some instances exceeds the impairment produced by a blood alcohol concentration of 0.05%.[68] Drivers' ability to predict their own impairment is poor.[69] The use of hypnotics and other sedatives is strongly associated with on-the-road driver-at-fault crashes.[70-74] In addition to accidents attributable to impaired coordination impaired motor skills and loss of alertness, hypnotics may also lead to fatal crashes due to drug induced suicidal thinking, impaired judgment or recklessness on the part of intoxicated drivers.[75] Some of these crashes result in deaths of passengers and other drivers not themselves using hypnotics.

It is well known that falls and accidental injuries are strongly associated with hypnotic usage, in particular hip fractures among aging patients.[76-83] Hip fracture is a sometimes-lethal injury. The preponderance of studies indicate a true association of the use of hypnotics and falls, that is thought to be due to the properties of benzodiazepine agonists in inhibiting psychomotor skills and in causing weakness, slowed reflexes, and impaired judgment, especially less than 8 hours after ingestion.

A nursing-home study challenged these conclusions, arguing that it was insomnia, not hypnotics, that was associated with falls. This study did not appear to control for confounding sleep apnea, Alzheimer's disease, or cognitive-behavioral disorders.[84] It should be conceded that confounders are likely have some influence on risk ratios associating hypnotics with accidental injuries, but the scientific consensus suggests that the association is nevertheless partly causal, based in part on controlled trials showing hypnotic impairments of driving and other forms of psychomotor performance. A causal element is therefore inferred by the majority of authorities.

B. 7. Safe doses of hypnotics for target populations are unknown. Animal studies indicate that some individuals in a population may succumb to a lethal hypnotic-drug effect at doses as low as one-fifth that which is universally lethal.[85] Variations in susceptibility in a human population varying in age, gender, genetics, and health status is likely to be greater than that among laboratory animals. The minimum lethal dose of hypnotic drugs in humans – the dose that might produce fatal respiratory arrest in one person out of one thousand in a representative population, or one in ten thousand, is unknown. Moreover, there are no human dose-response data and very little animal data concerning what doses of hypnotics may be lethal in the presence of narcotics, other sedatives, alcohol, aging, obesity, and other comorbidities. Yet most recognized hypnotic-related deaths are observed in the presence of such other factors. More study is needed to establish safe doses of hypnotics (if any) when taken with other medications and in the presence of potential comorbidities.

Hypnotics cause covert deaths in combination with numerous other factors, including opioid analgesics, other sedatives, alcohol use, advanced age, and obesity.

B. 8. Obesity and aging exacerbate hypnotic risks. Obesity and aging are perhaps the two most important risk factors for sleep apnea, that is, cessations of breathing during sleep.[86] Even apart from apneas, mechanical problems produced by obesity may impair ventilation. Thus, hypnotic-related hazard ratios are higher among obese patients (see Geisinger Health study supplement Table 2.[12]) Since there is no evidence that the huge increase in hypnotic hazards among obese patients can be attributed to overdoses, it appears that obesity predisposes to covert hypnotic-related deaths. It is plausible that among susceptible patients, combinations of obesity, hypnotics, opiates and other sedatives, alcohol and aging could produce quiet respiratory cessations followed by cardiac cessation and death even without any ingested overdoses being taken. In effect, the "overdose" comes from the overload of combined factors, not from excessive dose of hypnotic considered by itself.

B. 9. Prescription or non-prescription opiate use increases hypnotic risk. The use of opiates has become increasingly common in recent years.[87] Opiates are respiratory suppressants that (like pentobarbital) in overdose can produce respiratory arrest and cardiac arrest. A milder form of brief respiratory arrests during sleep, called sleep apnea, occurs at least a few times an hour in the majority of adults over age 40 years and in a very large percentage among those over age 65.[86,88] Among patients taking both benzodiazepines and opiates, a remarkable 75% were found to have sleep apnea, and causality was suggested by significant dose-response correlations both for the opiates and for the benzodiazepines.[89] In some patients, this combination of benzodiazepine and opiate causes profound hypoxemia (low oxygen).[90] The petitioner has seen polysomnographic data from patients who suffered profound almost continuous apnea with severe hypoxemia due to combinations of hypnotics and opiates. Patients receiving a combination of benzodiazepines and opiates have increased mortality.[91,92] The combination of opiates and benzodiazepines has caused a growing overdose problem in emergency rooms.[87] Moreover, the most serious overdose problems are seen when opiates and benzodiazepines are combined with alcohol in older patients, reflecting combined effects of opiate, benzodiazepine, alcohol, and aging.[93]

B. 10. Quiet deaths from hypnotic combinations with other factors go undetected, because the individual drug concentrations present in blood may appear within the therapeutic ranges. Especially when death occurs quietly at night, for example in an elderly obese patient known to have various comorbidities, there often is no autopsy. Physicians signing the death certificates are likely to list a cardiac event or a stroke or some long-standing comorbidity as the cause of death without knowing that hypnotic-induced respiratory suppression was the precipitant. Even if the physician suspects that a hypnotic had a role, the physician has little motivation to list the hypnotic as a cause of death when it cannot be proven and may reflect negatively on the physician prescribing the drug. Even if a patient is undergoing cardio-respiratory monitoring at the time when respiratory cessation followed by cardiac cessation occurs, there is usually no way of determining that the fatal respiratory cessation was due to hypnotic drugs in combination with the other factors.

B. 12. Commonly-prescribed hypnotics are used in unsafe combinations. Zolpidem, reportedly the most commonly-prescribed hypnotic in the U.S., with an estimated 40 million outpatient prescriptions in 2013,[94] ranked first for emergency department visits among

psychotropic drugs according to CDC data.[94,95] According to AHRQ data, 68% of zolpidem patients were sustained users (3 or more prescriptions), and of those 22% were also sustained users of opioids.[94] Although the FDA had recommended that women use only 5 mg or 6.25 mg of zolpidem, only 5% of women and 10% of elderly were dispensed these low doses.[94] Moreover, 23% of patients with sustained use took another drug targeting the same receptors. A high percentage were depressed, as indicated by 34% of sustained users also receiving antidepressants.[94]

B. 13. Hypnotics significantly increase overall risks of death for all users.[1]

In 34 of 36 epidemiologic studies that provided comparable risk ratios for mortality associated with hypnotics, 33 showed hypnotics were associated with excess mortality (Kripke, *Drug Safety,* accepted for publication.) The Petitioner identified 36 epidemiologic examinations of associations of hypnotics and anxiolytics with mortality, of which 34 provided odds ratios, risk ratios, or hazard ratios. Fully 33 of these 34 studies found elevated risk ratios greater than 1.0. The only exception was a small study by Merlo et al. that nevertheless found hypnotics associated with cancer deaths.[31] The 36 published epidemiologic studies associating hypnotics with mortality are listed in Appendix A.

Not one of the 34 epidemiologic studies of hypnotic drugs found any benefit with respect to patient survival. None of the 34 studies found a hypnotic drug risk ratio less than 1.0. That is, in 34 studies there was no evidence that hypnotics ever benefit patient survival. To find 33 of 34 studies showing a positive risk ratio is very highly significant, $P < 0.000001$. There is little question that hypnotic use is associated with increased mortality. Causality has been demonstrated, in part, by Medical Examiner data. The only remaining questions concern the magnitude of the association and the magnitude of causality, which the randomized placebo-controlled trials requested in Part A will resolve.

Of the 34 epidemiologic studies, 24 individual studies found statistically significant odds ratios, risk ratios, or hazard ratios exceeding 1.0. All 14 studies reporting on samples >14,000 persons were significant, but 10 of 19 smaller studies found positive trends that were

[1] One of the original broad American epidemiological studies, an American Cancer Society study, conducted over 50 years ago, showed increased risk of death with hypnotic use. The Cancer Prevention Study I (CPSI) obtained questionnaires in 1958 from over 1,000,000 participants and their highly-reliable 6-year mortality follow-up.[96] The data showed that both long and short sleep predicted elevated mortality (with 7 hours associated with minimal mortality for each age group); insomnia had little or no additional effect although insomnia was associated with short sleep; but reported sleeping pill use was associated with about 50% increased mortality after controlling for age, gender, reported sleep duration, and reported insomnia.[97] This was statistically a highly significant result in a million participants, but uncertainty about what participants meant by taking "sleeping pills" "Often" in terms of drug type and frequency demanded more study. The American Cancer Society performed the CPSII study with participants completing over 1.1 million questionnaires in the fall of 1982, containing more explicit questions about sleep duration, insomnia, and "prescription sleeping pills." After controlling simultaneously for 32 covariates and confounders in Cox Proportional Hazards models, results again showed that use of hypnotics was associated with elevated mortality not attributable to major confounders such as cigarette smoking. Indeed, the mortality associated with taking "prescription hypnotics" was surprisingly comparable to that associated with smoking a pack of cigarettes a day.[33] Nevertheless, better studies were needed for specific identification of the hypnotics and doses implicated and specific monitoring of hypnotic usage during the mortality follow-up. Many such studies have been conducted in more recent years.

not significant. Most of the not-significant were among the earliest 15 published before 2006. Of studies analyzing follow-ups of 8 years or less, 18 of 22 studies found a significant association, but of studies with longer follow-ups, only 8 of 14 studies found significance. Evidently, this is because during long prospective follow-ups, many subjects initially taking hypnotics will discontinue hypnotic usage, whereas many controls not using hypnotics at prospective baseline may have begun using hypnotics during a long follow-up, so that the longer the follow-up, the more mixing of hypnotic-consuming and control groups is likely, thus weakening the risk-ratio contrasts observed.

The median risk ratio for the 34 studies was only 1.27 and only 12 studies had risk ratios of 1.5 or more. However, some of the highest quality studies reported among the highest risk ratios. Three of the most recent studies were particularly persuasive.

Note that these epidemiologic studies had many limitations. However, the limitations that would tend to bias the results towards *underestimating* the association of hypnotics and mortality appeared more influential than those that would bias towards overestimation of the risk (Kripke, *Drug Safety,* accepted for publication.) In particular, studies with the most careful efforts to control for confounders found that such control made little difference in the estimated risk ratios. However, the risk ratios derived, like the studies themselves, were extremely heterogeneous, probably due to differences in the size, age, gender, and ethnicity of samples and their health status, the nature of the hypnotics studied, the accuracy with which the drugs involved and their dosages were known, the control variables available, and the duration of follow-up observations to ascertain mortality. Accordingly, meta-analysis would not be clarifying.

In the Geisinger Health System in Eastern Pennsylvania, a sample of 34,205 patients was drawn with carefully controlled 2:1 matching of hypnotic users with non-user controls for age, gender, smoking, and various comorbidities. Compared to a reference hazard ratio of 1.0 for non-users of hypnotics, the fully-adjusted mortality hazard ratio for use of 0.4-18 hypnotic doses per year was 3.60 (2.92-4.44, 95% CI), for those using 18-132 doses per year, the hazard ratio was 4.43 (3.67-5.36), and for >132 doses per year, **the hazard ratio was 5.32** (4.50-6.30).[12] Each of these associations was significant with P<0.001. Sensitivity studies showed that little of the hypnotic-associated mortality could be explained by known confounders or use of hypnotics before commencement of the study. In this study, use of each of the hypnotics named in this petition was shown to be strongly associated with excess mortality in fully-adjusted hazard ratios. Barbiturates prescribed at night for sleep considered as a group had about the same empirical hazard ratios as the benzodiazepines and zolpidem, but the observed hazard ratio for eszopiclone was significantly higher than that of barbiturates.[12]

In a sample of over 100,000 hypnotic users and matched controls from the representative British General Practice Research Database,[98] users of 1-30 defined daily doses (DDD) of hypnotics and anxiolytics within a year had fully adjusted dose-responsive mortality hazard ratios of 2.55 (2.42-2.69, 95% CI) for 1-30 DDD (defined daily doses in the first year); 3.78 (3.54-4.04) for 31-60 DDD, 4.19 (3.84-4.58) for DDD 61-90, and **4.51 (4.22-4.82) for DDD >90**. Extensive full adjustment for potential confounders resulted in only very small and inconsistent decreases in the estimated hazard ratios, although many methodological details were focused on minimizing possibilities of confounding. Use of benzodiazepine

hypnotics only was associated with higher hazard ratios than use of "Z" hypnotics only. These hazard ratios were remarkably similar to those from the Geisinger Health System, considering the many differences in drugs, samples, design, confounder controls, and analyses. Note that as in the Geisinger Health System study, much of the mortality was associated with early deaths after limited doses of hypnotics, perhaps as little as 1-2 prescriptions filled or refilled.

A recent representative study from the Norwegian Pharmacy Database found that benzodiazepine-receptor-agonist use associated with a mortality odds ratio of 2.30 (2.20-2.40).[99] The authors argued that terminal illness caused an upturn in benzodiazepine-receptor agonist use shortly before death (which might be appropriate for hospice care), and therefore they argued that the increased hypnotic use among those who would die was demonstrated as a confound of terminal illness. To the contrary, their data demonstrated an excess of benzodiazepine use among those who would not die until 22 months or more later, so benzodiazepine use of this population was elevated before the terminal upturn in hypnotic usage that the authors had demonstrated. Also, the upturn in death-associated hypnotic use 6-10 months before subsequent death may be equally consistent with a causal lethal hazard resulting from brief exposures to hypnotics as well as from possible confounding with palliative use. The Norwegian pharmacy data base did not enable these authors to analyze comorbidities or to control for other confounders.

Several studies carefully examined insomnia and depression as potential confounders of the association of hypnotics with mortality, finding that insomnia and depression could explain little if any of this association.[34,98,100,101] Note also that the evidence does not permit us to assume that causality between insomnia, depression, and hypnotic usage is one-way when contemplating confounder control.[47,102]

In summary, the epidemiologic literature is conclusive that hypnotic use is associated with excess mortality. The better studies tend to show very high dose-response risk ratios suggesting association with a very large number of deaths. Kripke et al. in a supplement showed that the risk ratios demonstrated in the Geisinger Health System data lead to estimated U.S. deaths associated with hypnotic usage of the same order of magnitude as those associated with cigarette use, around 300,000-500,000 per year.[12] Evidence has been presented from several independent studies that most of these deaths cannot be attributed to known forms of confounding, and indeed, adjustment for the major confounders such as smoking and comorbidities produced little change in the estimated associations. Authors acknowledge that their estimates of adjusted association of hypnotics and mortality could be influenced by inadequate ascertainment of confounding factors or lack of control for a very large number of potential confounds with small or rare effects. It is because skeptics may question whether the strong associations of hypnotics with mortality are causal that large post-marketing controlled trials must be required.

B. 14. Hypnotic drugs have a long history of delayed recognition of serious risks. Despite its now-known risks of lethality, pentobarbital was nevertheless for decades a preferred hypnotic routinely prescribed for patients seeking sleep aids. Although it is believed that the more modern benzodiazepine and benzodiazepine-receptor-agonist hypnotics that replaced pentobarbital have higher acute margins of safety and therefore lower risks than pentobarbital,

Medical Examiner and epidemiologic data do not confirm that the newer drugs are significantly safer.[3]

Only a small fraction of deaths are examined by coroners. A recent *JAMA Psychiatry* Viewpoint estimated self-injury deaths largely due to drug intoxication at 68,298 for 2013, and that did not include the role of suicidally-motivated dangerous driving.[75] Hypnotics are a factor in more than half of such intoxication and dangerous driving deaths.[48]

B. Statement of Grounds: Benefits

Hypnotic drugs are of minimal benefit to patients.

B.15. Prescribed hypnotics fail to increase sleep significantly even at doses higher than currently recommended. In an authoritative NIH-sponsored meta-analysis of controlled trials, Buscemi and colleagues found that although non-benzodiazepine zolpidem-like drugs ['Z-drugs"] shortened sleep onset latency by an average of 12 min (9-17 min, 95% CI), according to objective polysomnograms, these hypnotics increased total sleep time by only 11 min (-1 to 23 min, 95% CI). That is, these drugs produced no substantial statistically-reliable increase in total sleep, even at doses higher than currently recommended. Zolpidem and zolpidem-like drugs constitute the bulk of the current U.S. hypnotics market. Most of the meta-analyzed studies of zolpidem used doses of 10 mg or more (as high as 30 mg),[103] and most of the studies of zopiclone used 7.5 mg doses or more (containing more eszopiclone than any dose approved in the U.S.), whereas the FDA-approved recommended initial dosage for most patients is now 5 mg or 6.25 mg for the sustained-release form of zolpidem[104] and 1 mg for eszopiclone. Based on all available clinical studies these lower doses would increase sleep little if at all.[94] Indeed, the primary zolpidem manufacturer advised the FDA that the 5-6.25 mg dosages were generally ineffective.[7] The newly-recommended 1-mg dosage of eszopiclone is similarly ineffective.[105,106] Patients report more increase in sleep than is measured objectively, but even this self-reported "improvement," which is not supported by objective measurement, is a mere 32 min. (26-38 min, 95% CI).[103] The discrepancies between objective and subjective data may be attributable to the amnesic properties of hypnotics, erasing patients' memories of how much time they are awake in bed. In conclusion, the FDA-recommended doses of the most popular benzodiazepine agonists are virtually ineffective for objectively increasing sleep. Older benzodiazepines are not much more effective.

B. 16. Hypnotics fail to improve next-day performance. Based on manufacturers' advertising, patients expect that a hypnotic will improve their performance the following day. In fact, the truth is just the opposite. In 1982, two experts in the field received partial support from a hypnotics manufacturer to survey the daytime performance literature and found, "Drug-related improvement in performance was not found, and, in comparing active drug to placebo, it is clear that all hypnotics, at some doses, produce decrements in performance the next day."[59] Decades later, there is still no evidence that GABA-agonist hypnotics improve objective daytime performance in treating insomnia. If there is a significant effect, it is to make performance worse.[67,107]

B. 17. Hypnotic drugs are prescribed to patients without valid clinical indication. According to the U.S. National Ambulatory Medical Care Survey, insomnia is a stated reason for a patient's visit in less than a quarter of office visits where a hypnotic is prescribed.[108] Moreover, no diagnosis of any sleep disorder at all is made on 35% of office visits when a hypnotic is prescribed, and of the 65% of such patients who are diagnosed with a sleep disorder (such as hypersomnia and most forms of sleep apnea), often a hypnotic would be contraindicated.[108] Other data have likewise shown that hypnotics are commonly prescribed for patients who have no diagnosis or complaint of insomnia.[97,109,110] Hypnotics are routinely being prescribed without any apparent valid indication in as much as three quarters of the cases.

B. 18. Manufacturers misrepresent the drugs' benefit in direct-to-consumer advertising. For example, a 2006 advertisement represented that "[eszopiclone] provides a full night of sleep (7 to 8 hours)." An equivalent claim was made in a 2007 eszopiclone-hypnotic print advertisement titled "Sleep the night and seize the day. . . A better tomorrow begins tonight." In the scientific study cited by both advertisements as evidence,[111] the average sleep of patients receiving eszopiclone 2 mg was 382 min (6 hours, 22 min) and for 3 mg, it was 412 min (6 hours, 52 min). The clinical results cited did not support the manufacturer's claims to "a full 7 to 8 hours of sleep," even though the 2 mg and 3 mg doses then studied were greater than the currently-recommended starting doses.

As for the manufacturer's advertised benefits of "seizing the day," and a "better tomorrow," the eszopiclone manufacturer's study demonstrated no significant objective improvement in next-day daytime performance or accomplishment. In the study cited above by the manufacturer, an objective performance test did not demonstrate significantly better performance with eszopiclone than with placebo.

Summary of grounds for this petition

The evidence is clear: the specified hypnotics offer little to no benefit to patients. The most recent American Academy of Sleep Medicine's Clinical Guideline for Management of Chronic Insomnia[112] stated that the primary goals of treatment of insomnia should be to increase sleep quantity and to enhance daytime function. To the contrary, hypnotics do not increase productive sleep significantly, and for many patients, hypnotics cause substantial objective next-day functional impairment. In confirmation, FDA records show that the lead manufacturer of zolpidem (the most commonly-prescribed hypnotic) stated that the FDA-recommended dosage was ineffective.[7] The National Ambulatory Medical Care Survey indicated that over three quarters of hypnotics prescriptions are given to patients who do not even come to the physician for insomnia.[108] Yet the specified hypnotics do not substantially improve sleep or objective daytime performance and have no known benefits for any aspect of general health.

Overwhelming the questionable benefits, each drug specified by this petition is associated with increased mortality hazards, comparable to the hazards of barbiturates. Medical examiner data suggest that over 10,000 deaths every year are directly caused by and attributed to hypnotic drugs, and there is overwhelming evidence that hypnotics cause covert respiratory depression, suicides, infection, cancer, accidents, and other disorders that lead to a far larger number of deaths as well as non-fatal morbidities and suffering. It is well-documented that use of hypnotics kills large numbers of Americans yearly; however, the exact number of deaths caused by

hypnotics is difficult to estimate from medical examiner data alone,[87] because most of the deaths produced by hypnotics are covert or indirect due to hypnotic-induced or hypnotic-exacerbated morbidities such as respiratory depression or infection.

These risks far outweigh even the minimal benefits claimed for the specified drugs. Hypnotics are associated with many causes of early death. There is no objective evidence that hypnotics improve any important aspect of health. These hypnotics have no important benefits to balance their risks.

The hypnotics for which this petition requests mortality, safety and risk-benefit trials are zolpidem, temazepam, eszopiclone, zaleplon, triazolam, flurazepam, quazepam, and barbiturates used for sleep (such as pentobarbital, amobarbital, and secobarbital). These specified drugs have little or no benefit for insomnia, and are commonly not even prescribed for presenting insomnia or other approved indications. Each has been shown epidemiologically to be associated with high mortality hazards.[12] Other hypnotics considered but not formally included in this petition at this time include diphenhydramine, ramelteon, doxepin, and suvorexant, all of which are approved for a hypnotic indication. Also not included are trazodone (off label) and melatonin (unregulated). These un-included drugs and other sedatives sometimes used for sleep were not specified in this petition, either because the epidemiologic and controlled-trials data are not sufficient to assess their risk as hypnotics at this time or because these drugs are approved and may be effective for indications other than insomnia. Ultimately all drugs used for insomnia should undergo long-term mortality-safety and risk-benefit trials.

In the supplement to the Geisinger Health System study, the best-estimate extrapolation from the data suggested 300,000 – 500,000 deaths each year in the United States are associated with hypnotic usage.[12] The risks of under-estimation in this study were thought to be as great as the risks of over-estimation. Since this estimate was derived from risk ratios fully-adjusted for confounders, it is likely that most of the association was causal.

This mortality risk is comparable to that of cigarette smoking and many-fold greater than the risk to Americans of violent death.

Hypnotic drugs	300,000-500,000 U.S. deaths per year[12]
Cigarettes	560,000 U.S. deaths per year[113]
Murders	14,196 U.S. deaths in 2013

The Food and Drug Administration is failing to adequately regulate drugs that may cause 300,000 – 500,000 excess deaths per year, a number comparable to the number of deaths attributed to cigarette smoking (560,000), cancer (585,000), or heart disease (611,000).

The FDA Amendments Act of 2007 provides the FDA authority to require, at a minimum, additional safety studies of marketed drugs when needed, for example when any new evidence or evaluation of risks becomes available. New evidence and analysis conclusively demonstrates the greatly increased risks of hypnotic drugs with little or no clinical benefit. The FDA is therefore legally as well as ethically obligated to require additional safety studies of these drugs and other regulatory actions as requested. Petitioner therefore requests that the Commissioner mandate

such safety studies to commence immediately and to implement the other administrative actions included herein as indicated.

C. Environmental Impact

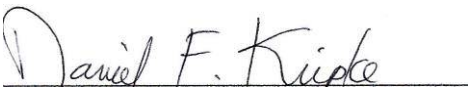
Categorical exclusion from environmental assessment is claimed under CFR 21.IA§25.30 (k): there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes. The preferred substitute is the cognitive-behavioral treatment of insomnia.

D. Economic Impact

Based on the significant risks of hypnotic drugs compared to the minimal clinical benefit, it is expected that the actions requested will be of net economic benefit to the United States, from reductions in premature deaths and morbidities from cancer, infections, accidents, mood disorders, and respiratory depression, associated health care costs and productivity losses.

E. 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 Petitioner which are unfavorable to the petition.



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Appendix A: Epidemiologic Studies of the Mortality Risks of Hypnotic Drugs

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