EXHIBIT "B"

Statement of Grounds

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STATEMENT OF GROUNDS

I. INTRODUCTION

As a drug product class, dual orexin receptor antagonists ("DORAs") should be removed from the controlled substance schedules. The U.S. Food and Drug Administration ("FDA") process for evaluating whether a new drug product has abuse potential and therefore should be scheduled is outlined in FDA guidance.[1] That guidance details the role of human abuse potential ("HAP") studies and the eight-factor analysis ("8FA") employed by FDA in providing its recommendation for the appropriate scheduling of new drug products under the Controlled Substances Act ("CSA"). Per the FDA guidance, "[d]rug products with abuse potential generally contain drug substances that have central nervous system (CNS) activity and produce euphoria (or other changes in mood), hallucinations, and effects consistent with CNS depressants or stimulants."[2] The DORAs approved by FDA for the treatment of insomnia are classified as Schedule IV controlled substances—i.e., drug products with a currently accepted medical use in treatment in the United States, low potential for abuse, and low potential for physical or psychological dependence.[3] Suvorexant (approved in 2015), lemborexant (approved in 2020), and daridorexant (approved in 2022) constitute the class of DORAs.

A recent review of available data demonstrates the limited applicability of HAP studies to the DORA Schedule IV classification. Additionally, a refreshed 8FA that includes a comparison of the DORAs to other Schedule IV drug products supports the conclusion that the DORA class should not be subject to CSA scheduling. Finally, placement of the DORA class into Schedule IV distorts the risk versus benefit analysis relative to other insomnia products, by overstating the abuse potential of DORAs and creating possible access and prescribing barriers for DORAs used to treat insomnia.

During the review of the new drug application ("NDA") submitted by Idorsia Pharmaceuticals Ltd. ("Idorsia") for QUVIVIQ™ tablets (daridorexant; NDA #214985), FDA specifically stated that "pharmacologic rationales" presented by Idorsia and "post-marketing experience suggesting lower abuse of orexin antagonists than GABA agonists approved for sleep . . . could support a citizen's petition to DEA for rescheduling of the dual orexin receptor antagonist class."[4]

Idorsia therefore respectfully requests that the DORA drug product class be removed from the CSA's controlled substance schedules. This request is based on the following:

1. The class has (i) insignificant abuse, potential for abuse, and non-medical use characteristics; and (ii) a lack of physical or psychological dependence.

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[1] *See* FDA, Guidance for Industry, *Assessment of Abuse Potential for Drugs* (Jan. 2017), https://www.fda.gov/media/116739/download [hereinafter "*Abuse Potential Guidance*"].

[2] *Id.* § I.

[3] *See* 21 U.S.C. § 812(b)(4); *accord* DEA, *Drug Scheduling* (visited Mar. 29, 2023), https://www.dea.gov/drug-information/drug-scheduling#.

[4] Pamela Horn, M.D., Cross-Discipline Team Lead, Division of Psychiatry, Office of Neuroscience, Center for Drug Evaluation and Research, FDA, to Idorsia Pharmaceuticals Ltd., re: *Late-Cycle Meeting Minutes* (Dec. 2, 2021).

2. The rates of abuse and dependence-related reports, serious adverse events ("SAEs"), and adverse events ("AEs") requiring hospitalization associated with approved DORAs are low—and substantially lower than rates for Schedule IV benzodiazepines and related drugs, including those sometimes referred to as "Z-drugs" (namely zopiclone, zolpidem, and zaleplon).

3. Re-analysis of the eight factors supports removal of daridorexant, lemborexant, and suvorexant from the CSA's controlled substance schedules.

Our detailed analysis is set forth below.

II. THE ADMINISTRATOR OF THE DRUG ENFORCEMENT ADMINISTRATION SHOULD INITIATE A RULEMAKING PROCEEDING TO REMOVE DARIDOREXANT, LEMBOREXANT, AND SUVOREXANT FROM THE CONTROLLED SUBSTANCE SCHEDULES.

A. Daridorexant, Lemborexant, and Suvorexant Share Similar (i) Insignificant Abuse, Potential for Abuse, and Nonmedical Use Characteristics, and (ii) Lack of Physical or Psychological Dependence.

1. Post-marketing Surveillance Data Shows that DORAs Have Similarly Insignificant Abuse, Potential for Abuse, and Nonmedical Use Profiles.

The independent FDA approvals of daridorexant, lemborexant, and suvorexant for therapeutic use each included a recommendation that the drug products be scheduled under the CSA. With input from the National Institute on Drug Abuse ("NIDA"), FDA recommended, and DEA agreed, that daridorexant, lemborexant, and suvorexant have a potential for abuse and warrant control.

All three marketed DORAs share similar mechanisms of action. In post-marketing surveillance data and other experience, minimal differences exist in the products' pharmacological and safety profiles, suggesting that differential scheduling among the class is not warranted.[5] As such, the collective sum of the post-marketing surveillance data of the DORA class can be used to highlight the low abuse potential of DORAs as a class.

At the time of this submission, post-marketing surveillance data included approximately eight years of data for suvorexant (U.S. marketing launch in February 2015), approximately 20 months of data for lemborexant (U.S. marketing launch in July 2021), and almost one year of data for daridorexant (U.S. marketing launch May 2022).

[5] All three drug products were approved for the treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. BELSOMRA® (suvorexant) was approved by FDA in August 2014 (NDA #204569); DAVIGO® (lemborexant) was approved by FDA in December 2019 (NDA #212028); and QUVIVIQ™ (daridorexant) was approved by FDA in January 2022 (NDA #214985).

- An FDA Adverse Event Reporting System ("FAERS") database query from 2014 through 2022 for suvorexant indicated a total of 11 cases (over eight years) that were coded as drug dependence, two cases of drug abuse, and one case of drug withdrawal symptoms.[6] Additionally, data from the U.S. Poison Control Center showed a total of 14 reported suvorexant abuse cases from 2015 through 2019.[7]
- Additionally, in a pooled safety analysis of clinical trials, lemborexant showed similarly low amounts of abuse-related cases. When adjusted by the duration of exposure, the overall incidence (subjects per patient-year) of treatment-emergent adverse events ("TEAEs") related to abuse potential was 0.2 for placebo, and 0.3 and 0.4 for lemborexant 5mg and 10mg doses, respectively. The overall rates (events per patient-years) of TEAEs related to abuse potential were 0.3 for placebo, and 0.5 and 0.6, respectively, for the 5mg and 10mg doses.[8]
- Daridorexant had only one reported case of drug withdrawal symptoms in 2022, based on roughly six months of data.[9]

Although the post-marketing experience is less extensive for lemborexant and daridorexant, the similarities of these substances to suvorexant in their pharmacology, abuse potential assessments, and FDA labeling suggest that recreational use patterns and abuse-related risks are similar across all three products. Importantly, as a class, post-marketing surveillance data regarding safety and abuse and dependence indicates that real-world rates of nonmedical use or abuse of DORAs are low, as reflected in the low number of AEs related to abuse or recreational use.

2. Post-marketing Surveillance Data Shows a Lack of Physical or Psychological Dependence on DORAs as Compared to Conclusions Drawn from Human Abuse Potential Studies.

As described in the published DEA scheduling recommendations, FDA required the sponsors of the NDAs for suvorexant, lemborexant, and daridorexant to submit HAP study data with their respective applications.[10] Based on the HAP study data that was submitted, all three products were designated as Class IV controlled substances. Preclinical and other clinical data, however,

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[6] On behalf of Idorsia, Pinney Associates conducted an analysis of FAERS data based on the FAERS Public Dashboard accessed on February 9, 2023. The analysis covered January 1, 2014 through December 31, 2022. The products searched included: suvorexant, lemborexant, daridorexant, zolpidem, and alprazolam. The *Medical Dictionary for Regulatory Activities* ("MedDRA") preferred terms that were searched included: intentional product misuse, drug abuse, drug dependence, drug withdrawal syndrome, drug withdrawal neonatal, and withdrawal syndrome. Findings were presented as aggregate counts.

[7] *See* Caro, et al., *Human Abuse Potential Study Results in the Context of Abuse Detected Postmarketing*, COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, 84th Annual Scientific Meeting (June 11-15, 2022).

[8] *See* Moline, et al., *The abuse potential of lemborexant, a dual orexin receptor antagonist, according to the 8 factors of the Controlled Substances Act*, PSYCHOPHARMACOLOGY (2023) (citing Yardley, et al., *Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial*, SLEEP (2021)).

[9] *See* Note 6, *supra*.

[10] *See* DEA, Proposed Rule, *Schedules of Controlled Substances: Placement of Suvorexant into Schedule IV*, 79 Fed. Reg. 8,639 (Feb. 13, 2014); DEA, Interim Final Rule, *Schedules of Controlled Substances: Placement of Lemborexant in Schedule IV*, 85 Fed. Reg. 19,387 (Apr. 7, 2020); DEA, Interim Final Rule, *Schedules of Controlled Substances: Placement of Daridorexant in Schedule IV*, 87 Fed. Reg. 20,313 (Apr. 7, 2022).

suggest that there is an absence of abuse potential and dependence among the class of DORAs. Nonclinical data suggest that the chemical structure of the DORAs is such that (i) the products do not evoke a risk of interaction with opioid receptors, (ii) the products do not cause an increase in dopamine, and (iii) there is a total absence of findings in specific animal models assessing reinforcing effects, interoceptive effects (bodily sensations), and withdrawal signs indicative of physical dependence.[11] Further, clinical data did not reveal any signals of physical dependence or of abuse potential, including absence of withdrawal syndrome at drug cessation. The HAP studies indicated a drug-liking effect superior to placebo; in contrast, however, the AEs collected across clinical trials suggested insignificant potential for abuse and abuse-related effect, including low or absent euphoria-related AEs.

New consensus among experts in HAP assessments suggest that the HAP studies of suvorexant, lemborexant, and daridorexant overestimated the potential for real-world recreational use and abuse in the community.[12] FDA's Controlled Substance Staff ("CSS") first published and presented an evaluation of HAP findings for suvorexant at the Annual Scientific Meeting of the College on Problems of Drug Dependence ("CPDD").[13] In its presentation, the authors called for a better understanding of the clinical significance of HAP study findings for drugs with a novel mechanism of action and for which animal behavioral studies did not suggest abuse potential.[14]

In 2022, the CSS authors presented their evaluation of post-marketing abuse-related evidence as compared to pre-marketing HAP studies at the CPDD meeting on selected anticonvulsants and DORAs.[15] The CSS authors' evaluation concluded:

> Overall, HAP studies are highly sensitive in detecting important differences between drug effects and predicting the likelihood of drug abuse in people who recreationally use drugs. Although the current preclinical and clinical methodology for assessing abuse liability have demonstrated high predictive validity, there is a *discrepancy* between post-marketing indicators of abuse and data from HAP studies.[16]

Within the DORA class, the authors concluded that post-marketing data for daridorexant, lemborexant, and suvorexant were inconsistent with the positive signals previously reported in HAP studies. In the HAP studies, a "drug liking" effect may not be interpreted as being similar to a "drug wanting" effect. Indeed, there is a clear differentiation of the two effects, where "drug wanting" mobilizes very different brain circuits (as compared to "drug liking") and is solely

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[11] *See* Born, et al., *Preclinical assessment of the abuse potential of the orexin receptor antagonist, suvorexant*, REGULATORY TOXICOLOGY & PHARMACOLOGY (2017) (suvorexant); Asakura, et al., *Nonclinical evaluation of abuse liability of the dual orexin receptor antagonist lemborexant*, REGULATORY TOXICOLOGY & PHARMACOLOGY (2021) (lemborexant); FDA, Summary Basis for Approval, Quviviq™ (daridorexant), NDA 214985 (visited Mar. 29, 2023) (daridorexant), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000OtherR.pdf.

[12] *See* Calderon, et al., *Evaluation of Human Abuse Potential (HAP) Studies for Drugs with Novel Mechanisms of Action*, COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, 82nd Annual Scientific Meeting (June 20-24, 2020).

[13] *See id.*

[14] *See id.*

[15] *See id*.

[16] *Id.* (emphasis added).

associated with addiction.[17] In the absence of any other signal of drug abuse or drug dependence potential, the drug-liking effect of DORAs identified in HAP studies may not represent "drug wanting" and therefore may not indicate a potential for abuse.

Although scheduling recommendations consider all data related to the abuse potential of a drug, a positive signal in HAP study data will result in a scheduling recommendation in most cases. Drugs with a novel mechanism of action and lack of a positive signal indicative of abuse in nonclinical studies that are scheduled primarily based on HAP study findings should be carefully and continuously evaluated as post-marketing surveillance data becomes available. While HAP studies may initially serve as a potential signal of drug abuse in people who use drugs recreationally, actual patterns of abuse post-marketing may be influenced by multiple factors, such as availability, economic considerations, and the drug's approved indication.

B. The Rates of Abuse and Dependence-related Reports, Serious Adverse Events, and Adverse Events for Approved DORAs Are Substantially Lower Than Rates for Other Schedule IV Drugs, Including (i) Benzodiazepines and (ii) "Z-drugs" (i.e., Zopiclone, Zolpidem, and Zaleplon).

When compared to Schedule IV benzodiazepines and so-called Z-drugs (zopiclone, zolpidem, and zaleplon), the pharmacological properties and real-world experience of DORAs suggest negligible abuse potential and no other safety-related risks. In this petition, the term "benzodiazepines" is used to refer to GABA-agonist benzodiazepines approved for the treatment of insomnia. Z-drugs, which also are GABAergic, are drugs that also are indicated for insomnia and carry a "black box warning" related to safety issues other than abuse.

1. Surveillance and Other Data Demonstrate That Benzodiazepines Have Higher Rates of Abuse Potential, Withdrawal Symptoms and Rebound Effects, and Potentiation of the Risk with Opioids.

There is limited evidence of DORA abuse in opioid and other substance-abusing populations, whereas benzodiazepines and similar Schedule IV drugs are widely abused along with opioids.[18] Over time, key trends have emerged regarding the concomitant use of benzodiazepines and opioids. First, fatal and non-fatal overdoses involving benzodiazepines and opiates have increased. In addition, there has been a marked increase in illicit benzodiazepine prescriptions, though legitimate benzodiazepine prescriptions far outnumber illicit prescriptions. From 2019 to 2020, benzodiazepine overdose visits per 100,000 emergency department visits increased (23.7%), both with (34.4%) and without (21.0%) opioid co-involvement.[19] From April 2019 to April 2020, prescription and illicit benzodiazepine-involved overdose deaths increased 21.8%

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[17] *See* Berridge & Robinson, *Liking, Wanting, and the Incentive-Sensitization Theory of Addiction*, AMERICAN PSYCHOLOGIST (2016).

[18] *See* NIDA, *Benzodiazepines and Opioids* (Nov. 7, 2022), https://nida.nih.gov/research-topics/opioids/benzodiazepines-opioids; NIDA, *Drug Overdose Death Rates* (Feb. 9, 2023), https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates.

[19] *See* Liu, et al., U.S. Dep't of Health & Human Servs./Ctrs. For Disease Control & Prevention, *Trends in Nonfatal and Fatal Overdoses Involving Benzodiazepines—38 States and the District of Columbia, 2019-2020*, MORBIDITY AND MORTALITY WEEKLY REPORT (Aug. 27, 2021).

and 519.6%, respectively. From January to June 2020, 92.7% of benzodiazepine-involved deaths also involved opioids, and 66.7% involved illicitly manufactured fentanyl products.[20]

Additional data suggests evidence of benzodiazepine-related serious withdrawal and rebound effects for insomnia treatment. The phrase "drug dependence and withdrawal" most often and traditionally relates to substance abuse, but it also relates to a person's ability to restore normal function despite the presence of the drug. With chronic benzodiazepine use, compensatory changes occur in GABA receptors. Such changes consist of decreased sensitivity of these receptors to GABA, leading to tolerance development. Additionally, protracted withdrawal symptoms for benzodiazepines include anxiety, depression, psychotic reactions, memory impairment, motor symptoms (muscle jerking, blepharospasm), paresthesia, formication, tinnitus, and irritable bowel syndrome, and there is a characteristic fluctuation of symptoms that may wax and wane.[21] Rebound phenomenon is a rapid return of the patient's original symptoms at a greater intensity than before the treatment. One of the most common examples is anxiety and insomnia rebound following abrupt discontinuation of treatment with benzodiazepines. The most serious AEs which may occur are psychosis, delirium, suicidality, seizures, and, in older people, catatonia.[22]

As compared to benzodiazepines, DORAs have relatively minimal, if any, evidence of abuse with opioids or illicit prescriptions. Similarly, DORAs do not demonstrate withdrawal and rebound effects for insomnia treatment to the extent of benzodiazepines. For example, the daridorexant labeling states: "In animal studies and clinical trials evaluating physical dependence, chronic administration of daridorexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that daridorexant does not produce physical dependence."[23]

2. GABAergic "Z-drugs"—i.e., Zopiclone, Zolpidem, and Zaleplon—Carry Additional Risks for the Treatment of Insomnia.

Zolpidem, zopiclone, and zaleplon have a spectrum of adverse effects comparable to benzodiazepines. For example, these Z-drugs have demonstrated effects on cognition, behavior, psychomotor performance, and driving ability. As short-acting GABA agonists, Z-drugs have also demonstrated bizarre behavioral effects that have prompted black box warnings.[24] Psychomotor impairment, falls, and hip fractures are more likely to occur with Z-drugs that have longer half-lives, are taken at higher-than-recommended doses, and are mixed with other psychoactive substances, including alcohol.[25]

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[20] *See id.*

[21] *See* Lerner, et al., *Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development*, BRAIN COMMUNICATIONS (2019).

[22] See *id.*

[23] QUVIVIQ® (Daridorexant), Package Insert (rev. Mar. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214985s000lbl.pdf.

[24] *See* FDA, Safety Communication, *FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines* (Feb. 18, 2022), https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia.

[25] *See* Gunja, *In the Zzz zone: the effects of Z-drugs on human performance and driving*, J. MED. TOXICOL. (2013).

A search of the FAERS database for zolpidem-related AEs revealed 2,180 reports of drug abuse, 1,119 cases of drug dependence, and 194 cases of drug withdrawal syndrome.[26] While the greater numbers of zolpidem and other Z-drug AEs compared to DORA class AEs may be attributed to overall use, research has shown that GABAergic treatments, like Z-drugs, are not good first-tier candidates for managing sleep problems given their safety profile and abuse potential. Indeed, FDA has even referenced the issues with Z-drugs in a communication to consumers, stating:

> Considering the large number of individuals who take the drugs, FDA wants people to be aware of the potential dangers, including death, that can occur as a result. Patients may not remember these behaviors when they wake up the next morning. Moreover, they may experience these types of behaviors after their first dose of one of these Z-drugs, or after continued use.[27]

The European Medicines Agency ("EMA"), through its EudraVigilance system, has reported growing numbers of Z-drug clinical concerns relating to their potential of abuse, dependence, and withdrawal. From 2003 to 2017, there were a total of 33,240 (23,420 zolpidem, 9,283 zopiclone, and 537 zaleplon) cases of misuse, abuse, dependence, and withdrawal-related adverse drug reactions, corresponding to some 6,246 unique patients given Z-drugs.[28] Cases were studied and described, including demographic characteristics and clinical data, such as concomitant drugs, doses, routes of administration, and outcomes of the reactions (including fatalities).[29]

Additionally, among over 500,000 U.S. patients who received a prescription opioid medication (as identified in an epidemiologic analysis of a prescription database from 2007-2019), exposure to Z-drugs was associated with an increased risk of unintentional overdose.[30] Although absolute risks were found to be small, given the data subset, the potential implications of these findings are substantial considering the total number of opioid-treated patients also receiving Z-drugs. In another review of a U.K. database, among 2,118 patients aged 15-64 years prescribed opioid abuse therapy between 1998 and 2014, the co-prescription of Z-drugs and gabapentinoids was also associated with increased mortality risk.[31] With concurrent opioids, benzodiazepines and Z-drugs are strongly associated with increased hospital emergency department visits and total

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[26] *See* Note 6, *supra*.

[27] FDA, *Taking Z-drugs for Insomnia? Know the Risks* (visited Mar. 29, 2023), https://www.fda.gov/consumers/consumer-updates/taking-z-drugs-insomnia-know-risks.

[28] *See* Schifano, et al., *An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions*, INT. J. NEUROPSYCHOPHARMACOLOGY (2019).

[29] *See id.*

[30] *See* Szmulewicz, et al., *The Risk of Overdose With Concomitant Use of Z-Drugs and Prescription Opioids: A Population-Based Cohort Study*, AM. J. PSYCHIATRY (2021).

[31] *See* Macleod, *Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records*, PLOS MEDICINE (2019).

mortality. Indeed, FDA listed zolpidem as a CNS-depressant in its list of potential drugs that carry serious risks when combined with opioids.[32]

Interpreting epidemiological drug overdose data with respect to different classes of drugs and considering other confounding factors may not be sufficient to rule out increased risk of overdose and other safety issues in certain populations. Available data on DORA use to date, however, has not shown the same level of abuse potential or safety issues associated with benzodiazepines and Z-drugs.[33] Taken together, and considering the different mechanism of action of DORAs as compared to other Schedule IV drugs used to treat insomnia, the available data suggest that DORAs are associated with a lower risk of contributing to overdose deaths. Moreover, reported clinical and post-marketing withdrawal and rebound effects for benzodiazepines and Z-drugs indicates a greater risk than for the DORA class. This potential risk difference should alleviate concerns surrounding removal of the DORAs from the controlled substance schedules. Further, descheduling DORAs could result in shifting insomnia patients away from the higher abuse liability benzodiazepines and Z-drugs and allow patients greater access to a less harmful class of products. Greater access to DORAs could constitute an incremental step toward reducing opioid overdose-related deaths and other safety issues in patients combining opioids and insomnia drugs.

C. Re-analysis of the Eight Factors Supports Descheduling Daridorexant, Lemborexant, and Suvorexant.

Based on the foregoing findings, this petition respectfully requests that the DEA and FDA develop a new 8FA of abuse potential that considers (i) post-marketing evidence and (ii) the HAP studies' lack of predictive validity for assessing the real-world use of DORAs and the risk of addiction. The available evidence includes AE reporting from FAERS, DEA's National Forensic Laboratory Information System ("NFLIS"), the National Survey on Drug Use and Health ("NSDUH"), and internet monitoring of websites and "chat rooms" that include anonymous and unverifiable (but nonetheless qualitatively informative) self-reports of experiences that are relevant to understanding interest and/or lack of interest in these drugs for recreational users, often in comparison with controlled substances (see below under Factor 4).

Per the CSA, the DEA "shall consider the following factors with respect to each drug":

(1) Its actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history and current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.

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[32] *See* FDA, Safety Communication, *FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning* (visited Mar. 29, 2023), https://www.fda.gov/media/99761/download.

[33] *See* Ware, et al., *The association of chronic pain and opioid withdrawal in men and women with opioid use disorder*, DRUG & ALCOHOL DEPENDENCE (2022).

(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.[34]

In the following sections, each of these factors is considered for each of the DORA drug products—i.e., for daridorexant, lemborexant, and suvorexant. For reference, the 8FA for daridorexant is attached in Appendix I.

Factor 1 (Actual or Relative Potential for Abuse): For all three DORAs, pre-marketing nonclinical and clinical study data, other than HAP study data, suggested low abuse potential that does not warrant CSA control.

FDA and NIDA determined that daridorexant, lemborexant, and suvorexant had similar therapeutic sedative effects, abuse potential profiles, and favorable benefit-to-risk ratios that supported placement of the drug products in Schedule IV. The HAP study findings suggesting comparable abuse potential with Schedule IV comparators appears to have been the most important evidence resulting in the decision to place all three DORAs in Schedule IV.

HAP studies are conceptually designed to minimize the risk of false negative results (i.e., to wrongly conclude a lack of abuse potential). Participants in the DORA HAP studies were qualified based on their drug-liking of control drugs with similar properties as the test drug. Per FDA guidance, "the positive control should be an FDA-approved drug that is pharmacologically similar to the test drug and scheduled under the CSA."[35] While differences exist between the DORA HAP studies, it should be noted that for suvorexant, zolpidem was the control drug to which it was compared.[36] For lemborexant and daridorexant, another DORA was used as the comparator.[37] In the daridorexant HAP study, subjects were required to distinguish both, suvorexant and zolpidem from placebo, which resulted in a high screening failure rate.[38] This resulted in a study population that was ultra-sensitive to perceiving the drug-liking effects of the test drug but was otherwise healthy.

Post-marketing evidence in the general population, from multiple lines of surveillance (discussed below in Factors 4, 5, and 6) suggests that the "actual or relative potential for abuse" is very low compared to Schedule IV and Schedule V controlled substances.

Factor 2 (Pharmacological Effect): The pharmacology of DORAs as a class, and specifically of DORAs approved for insomnia, has been studied extensively and indicates a pharmacological mechanism of action that is distinct from other Schedule IV drugs, low in abuse potential, and relevant to the insomnia indication.

The pharmacology of daridorexant, lemborexant, and suvorexant is similar across the three substances but different and distinct from the pharmacology of other drugs in Schedule IV. The

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[34] 21 U.S.C. § 811(c).

[35] *See Abuse Potential Guidance* § V(C)(3).

[36] *See* Schoedel, et al., *Assessment of the Abuse Potential of the Orexin Receptor Antagonist, Suvorexant, Compared With Zolpidem in a Randomized Crossover Study*, JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY (2016).

[37] *See* Note 8, *supra*; *see also* Appendix I.

[38] *See* Appendix I.

DEA determined that daridorexant shares a similar pharmacological profile with other DORAs, "such as suvorexant and lemborexant,"[39] and concluded that the "abuse-related neuropharmacology profile of daridorexant is similar to that of . . . suvorexant and lemborexant and is consistent with its mechanism of action as a dual orexin receptor antagonist."[40]

DORAs block the binding of wake-promoting neuropeptides OX-A and OX-B to OX receptors type 1 and type 2 (OX1R/OX2R). As such, DORAs suppress the wake drive and promote sleep in animals and humans. DORAs and their major metabolites do not bind to abuse-related molecular targets including opioid, serotonin (5-HT), or GABA-A receptors (including benzodiazepine binding sites), dopamine transporters and receptors, nicotinic acetylcholine receptors, cannabinoid-receptors, or ion channels at clinically relevant concentrations.[41] In contrast, the physiological binding of Schedule IV substances used for the treatment of insomnia target one or more of these abuse-related molecular sites as a part of their primary mechanism of action.

In support of the conclusion that DORAs do not bind to abuse-related sites, daridorexant, lemborexant, and suvorexant do not engender a zolpidem-like response in rats trained to discriminate the GABA-A receptor positive allosteric modulator ("PAM") zolpidem. Only suvorexant produced partial generalization to zolpidem at very high exposures close to the toxic range. This suggests that the interoceptive effects elicited by these DORAs in rats do not resemble those elicited by GABA-A receptor PAMs. It can be concluded that the pharmacology of DORAs as a class, unlike other Schedule IV drugs (such as benzodiazepines), is associated with low abuse potential and does not have a propensity to produce reward, euphoria, or psychological or physiological dependence.[42]

Factor 3 (Current Scientific Knowledge): Scientific knowledge regarding DORAs as compared to other drugs in Schedule IV does not indicate similar abuse potential.

As discussed, compared to other Schedule IV drug products, DORAs act selectively on orexin receptors and do not affect other neurotransmitter systems that are involved in the reward pathway of the brain. Therefore, the abuse liability difference between DORAs and other Schedule IV drugs (e.g., GABAergic drugs) is not demonstrated via HAP studies but rather is demonstrated by (i) the lack of positive reinforcing effect on self-administration in rats compared to Schedule IV drugs, and (ii) real-world evidence as described below (see Factor 4). Moreover, the complexity of the chemical structure and synthesis of available DORAs together with their weak reinforcing and other abuse-related effects further deters efforts to tamper with the formulations to enable more rapid absorption, as is common with other potential treatments.[43]

Additionally, unlike other Schedule IV products with abuse liability, DORAs continue to be the focus of active scientific study in other disease states, with such study being primarily supported

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[39] DEA, Interim Final Rule, *Schedules of Controlled Substances: Placement of Daridorexant in Schedule IV*, 87 Fed. Reg. 20,313, 20,314 (Apr. 7, 2022).
[40] *Id.* at 20,315.
[41] *See* Appendix I.
[42] *See id.*
[43] *See id.*

by the National Institutes of Health and pharmaceutical developers.[44] For example, DORAs have been the subject of study in the following disease areas:

- Depression: Some studies have suggested that orexin may play a role in depression and that blocking orexin receptors with DORAs may have antidepressant effects.[45]
- Addiction: Orexin has been implicated in the development and maintenance of addiction to drugs such as cocaine, opioids, and alcohol. DORAs have been shown to reduce drug-seeking behavior in animal models of addiction and may have potential as a treatment for addiction.[46]
- Neurodegenerative disorders: Orexin has been shown to play a role in neurodegenerative disorders such as Alzheimer's disease. DORAs are being studied as a potential treatment for these disorders.[47]

The fact that DORAs are the subject of study for treatments in these disease areas suggests that they are unlikely candidates for clandestine synthesis regarding abuse potential.

Factor 4 (History and Current Pattern of Abuse): The history and current patterns of use and abuse-related effects do not support the conclusion that DORAs are attractive for recreational use or are associated with abuse and dependence.

The United States has the world's most multi-layered and comprehensive systems for tracking and detecting emerging trends in recreational substance use and abuse. When suvorexant was approved, there was no real-world evidence of recreational use, as DORAs were unavailable in the community from either licit or illicit sources. Since then, post-marketing surveillance from FAERS, NFLIS, and NSDUH have shown no patterns of recreational use or abuse of DORAs. Consistent with this observation, available DORAs have had very low reporting in DEA's NFLIS listing of drugs identified with (i) persons who recreationally use controlled substances or (ii) illicit marketers of CNS-active drugs for recreational uses.

Internet monitoring of discussion threads and online "chat room" discussions of recreational substances and their effects, uses, and desirability, can provide early signals of what might make some new substances more attractive than others. While these reports are qualitative and represent unverifiable anonymous reports, they provide some general direction and may reveal trends about how new substances compare to controlled substances that are widely used for recreational purposes. Searches of Bluelight, Drugs-Forum, and Reddit using search terms that included "abuse," "misuse," "nonmedical use," "NMU" are revealing. The time frame was not

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[44] *See* Mogavero, et al., *Targeting Orexin Receptors for the Treatment of Insomnia: From Physiological Mechanisms to Current Clinical Evidence and Recommendations*, NATURE AND SCIENCE OF SLEEP (2023).

[45] *See* Li, et al., *Increased Hypocretin (Orexin) Plasma Levels in Depression, Bipolar Disorder Patients*, FRONTIERS IN PSYCHIATRY (2021); Fagan, et al., *Orexin Receptor Antagonists in the Treatment of Depression: A Leading Article Summarising Pre-Clinical and Clinical Studies*, CNS DRUGS (2022).

[46] *See* Matzeu, et. al., *Understanding the Role of Orexin Neuropeptides in Drug Addiction: Preclinical Studies and Translational Value*, FRONTIERS IN BEHAVIORAL NEUROSCIENCE (2021).

[47] *See* Herring, et al., *Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial*, ALZHEIMER'S AND DEMENTIA (2020); Kang, et al., *Amyloid-beta Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle*, SCIENCE (2009).

limited as to the earliest time, but collection stopped on January 31, 2023. The first threads appeared in 2014 when approval of suvorexant was announced, with most expressing curiosity and speculating about the drug product's effects. Overall, the search indicated little interest in DORAs for recreational use. The results of the internet search are included in Appendix II. The following themes illustrate major points of discussion, including comments about effectiveness for sleep (note that these themes are similar to statements on the internet that are provided in Appendix II but are not actual quotes):

- "Don't bother using [DORA] to get high, it just puts you to sleep."
- "Why was this [DORA] scheduled? It does not give you a good high."
- "[DORA] is a waste of time compared to benzos."

In most cases, the statements on the internet used the brand name of the DORA on which they were posting.

Idorsia conducted a review of the published literature in the PubMed database on August 18, 2020, and found no reports related to the abuse, misuse, or nonmedical use of suvorexant or lemborexant.[48] Data for daridorexant in a Phase 3 study of 1,854 patients with insomnia showed that the incidence of predefined, abuse-associated events was balanced across all doses of daridorexant and placebo, and there were no symptoms of withdrawal.[49] Idorsia's review of the NSDUH database suggests that nonmedical use of suvorexant is extremely rare; per the NSDUH, between 2014 and 2018, only three unweighted cases of nonmedical use were reported for suvorexant.[50]

In contrast, in 2017 alone, there were an estimated 901,000 cases of nonmedical use reported for the Schedule IV drug zolpidem, and an estimated 24,000 cases reported for the Schedule IV drug zaleplon.[51] An updated review of NSDUH data available on February 8, 2023 found only one additional unweighted case of suvorexant misuse and no additional unweighted cases of lemborexant misuse between 2019 and 2020.[52] In contrast, in 2020 alone, there were an estimated 3,419,000 reports of misuse for alprazolam, 971,000 reports of misuse for diazepam, and 807,000 reports of misuse for zolpidem.[53]

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[48] *See* Appendix I.

[49] *See* Ufer, et al., *Assessment of the Abuse Potential of Daridorexant, a New Dual Orexin Receptor Antagonist for the Treatment of Insomnia Disorder: Data From Preclinical and Clinical Studies*, AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY, 59th Annual Meeting (Dec. 6-9, 2020).

[50] *See* Appendix I.

[51] *See id.*

[52] On behalf of Idorsia, Pinney Associates conducted an analysis of the 2020 NSDUH detailed tables accessed on February 9, 2023, found at https://www.samhsa.gov/data/report/2020-nsduh-detailed-tables. Open-ended search terms included: daridorexant and Quviviq™; suvorexant and Belsomra® (registered trademark of Merck Sharp & Dohme Corp.); and lemborexant and Dayvigo® (registered trademark of Eisai Inc. under license from Eisai R&D Management Co., Ltd.).

[53] *See* Substance Abuse & Mental Health Servs. Admin., Center for Behavioral Health Statistics & Quality, *2020 National Survey on Drug Use and Health (NSDUH) Public Use File Codebook* (Oct. 28, 2021).

Similarly, a review of the NFLIS annual report showed 1,261 drug reports related to zolpidem, as identified by forensic laboratories across the United States in 2017, and 1,001 drug reports identified in 2018. A review of data from the NFLIS Data Query System-Public ("DQS-P") on February 8, 2023, showed very few drug reports related to suvorexant (one to 10 annual reports from 2019-22), lemborexant (zero annual reports from 2020-22), or daridorexant (zero drug reports in 2022). Zaleplon drug reports were similar, ranging from one to 15 over the years 2019-22. In contrast, zolpidem (254-809 annual reports), diazepam (983-2,873 annual reports), and alprazolam (9,951-26,921 annual reports) had much higher yearly drug reports from 2019-22. Note that the NFLIS reports summarized the results of drug seizures, undercover drug buys, and other evidence analyzed at DEA laboratories across the country. In contrast, suvorexant was not listed in the top 60 of drugs that cover approximately 90% of the total drug reports collected by NFLIS in 2017 and 2018.[54] The history and current patterns of abuse of available DORAs—especially suvorexant, which has been on the market the longest[55]—reveals very few reports related to abuse, misuse, or nonmedical use. At the time of this petition, no U.S. system has identified emerging patterns of use suggestive of a known or imminent public health risk related to daridorexant, lemborexant, or suvorexant.

In summary, the very low incidence of nonmedical use and abuse of suvorexant, a product in the same DORA drug class as lemborexant and daridorexant, supports the conclusion that nonmedical use and diversion of these drugs of the DORA class is extremely rare. This is in stark contrast to the nonmedical use and diversion seen with other Schedule IV drugs used to treat insomnia.

Factor 5 (Scope, Duration, and Significance of Abuse): There is no evidence of a scope or duration of abuse of DORAs that is suggestive of an imminent or known threat to public health—and certainly not a significant threat.

DORAs have not been associated with any scope or duration of abuse that would pose a risk to the public health. In contrast, scheduling of the leading benzodiazepines was in part justified by their significant and well-established risks to the public health. Abuse and overdose-related risks of benzodiazepines are discussed by NIDA on its webpages addressing the issues surrounding concurrent use of benzodiazepines and opioids and the role of benzodiazepines in overdose deaths.[56]

As highlighted by NIDA, "[t]aking opioids in combination with other central nervous system depressants—like benzodiazepines, alcohol, or xylazine—increases the risk of life-threatening overdose."[57] The number and proportion of overdose deaths involving benzodiazepines has

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[54] *See* Appendix I. Again, because lemborexant was not made commercially available until 2020, and daridorexant was not approved until 2022, there were no cases related to lemborexant or daridorexant.

[55] The history of nonmedical use and abuse of lemborexant and daridorexant is limited, as FDA approved those drugs in 2019 and 2022, respectively. Suvorexant was approved in 2014 and therefore is the primary source of insights into the nonmedical use and abuse of these DORAs.

[56] *See* Note 18, *supra*.

[57] *See* NIDA, *Benzodiazepines and Opioids* (Nov. 7, 2022), https://nida.nih.gov/research-topics/opioids/benzodiazepines-opioids.

increased steadily since 2015, culminating in 12,499 deaths in 2021.[58] These data indicate an urgent need for approaches to limit benzodiazepine prescribing and underscore the potential importance of replacing some fraction of benzodiazepine prescribing with DORA prescribing for insomnia patients.

In contrast, there is no evidence of an imminent or known threat to the public health caused by daridorexant, lemborexant, or suvorexant. In the six years between the approval of suvorexant in August 2014 to June 2020, the FAERS database registered 32 cases of "intentional product misuse," two cases of "drug abuse," and 10 cases of "drug dependence."[59] In contrast, there were 138 cases of "drug dependence" reported to FAERS for the Schedule IV zolpidem in 2022 alone. There were also 222 cases of "drug abuse" of zolpidem reported to FAERS in the same year.[60] According to NSDUH, there were an estimated 741,000 cases of zolpidem misuse among those aged 12 or older in 2018.[61]

Factor 6 (Risk to the Public Health): An unintended negative consequence of scheduling is the possible exacerbation of healthcare disparities resulting in prescriptions indicated for insomnia that nonetheless have higher risks of abuse-related and adverse effects.

As detailed in Factor 5, DORAs do not appear to pose risks to the public health that warrant CSA scheduling. If DORAs are descheduled and then substituted for Schedule IV benzodiazepines and Z-drugs in patients with insomnia, the possible public health benefits outweigh any risks. Descheduling DORAs hopefully will cause a bias against the riskier products, resulting in an overall positive effect.

Epidemiological post-marketing data demonstrating low risks of abuse-related effects and overdose associated with available DORAs are bolstered by data from a recent study that co-administered the DORA suvorexant during a four-day buprenorphine taper to decrease withdrawal symptoms in individuals with opioid use disorder.[62] This study found no evidence of respiratory depression or psychological symptoms with suvorexant co-administration and also concluded that suvorexant was not associated with any abuse potential. Accordingly, it appears that substituting DORAs for benzodiazepines in at least a fraction of patients is a plausible strategy for mitigating the risk of opioid overdose associated with benzodiazepines. Prescribing physicians would have lower risk, non-controlled alternative drug products to prescribe to patients with insomnia.

Current scheduling contributes to the perception that DORAs are similar in overall safety and abuse-related risks as benzodiazepines, Z-drugs, and other controlled substances. DORAs' Schedule IV status present opportunities for generic Z-drugs and other generic drug products that are scheduled to be prioritized by insurers. Specifically, according to a recent query on coverage

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[58] *See* NIDA, *Drug Overdose Death Rates* (Feb. 9, 2023), https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates.

[59] *See* Appendix I.

[60] *See* Note 6, *supra*.

[61] *See id.*

[62] *See* Huhn, et al., *Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper*, SCIENCE TRANSLATIONAL MEDICINE (2022).

criteria for commercial payers, most payers require some sort of step therapy of a Z-drug or other agent not indicated for insomnia before starting a DORA.[63] Additionally, state restrictions for controlled substances may inadvertently deter physicians form prescribing DORAs. Under state-run Prescription Drug Monitoring Program ("PDMPs"), pharmacies and prescribers are required to register with the PDMP, and registered physicians are the then singled-out and monitored for prescribing patterns. There is concern among physicians who, for valid reasons, are relatively high prescribers that if they are identified by a PDMP, then they may be seen as prescribing inappropriately. High-profile criminal prosecutions of physicians prescribing large amounts of opioids may have a "chilling effect" on physicians' willingness to prescribe controlled substances.[64] Indeed, a Congressional Research Service report found that "[p]rescribers may hesitate to prescribe medications monitored by the PDMP—even for appropriate medical use—if they are concerned about potentially coming under scrutiny from law enforcement or licensing authorities."[65] Descheduling available DORA medications likely will help align prescribing incentives and reduce underutilization of new insomnia treatments with plausible benefits for public health.

Factor 7 (Psychic or Physiological Dependence Liability): In contrast to benzodiazepines and other Schedule IV drugs that have known potential for psychological and physiological dependence as recognized in their labeling, DORAs do not produce withdrawal or physiological dependence, nor do they require dose tapering following chronic use.

Section 9 of the FDA-approved daridorexant label is like the labels for suvorexant and lemborexant. The section states: "In animal studies and clinical trials evaluating physical dependence, chronic administration of daridorexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that daridorexant does not produce physical dependence."[66] This is consistent with FAERS data reflecting very low rates of withdrawal, abuse, and dependence as compared to benzodiazepines. In contrast to benzodiazepines, and to a lesser extent Z-drugs, DORAs do not lose efficacy over time. Benzodiazepines (and possibly Z-drugs) induce a loss of efficacy over time (tolerance) and thus initiate a frequent need to increase doses, further increasing the risk of dependence.[67]

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[63] *See* MMIT (Managed Markets Insight and Technology, LLC) Analytics 3 Platform. Data extracted from Idorsia internal search. March 3, 2023. Query terms: Product=Belsomra, Channel=Commercial OR Health Exchange.

[64] *See* Mofizul, et al., *An inevitable wave of prescription drug monitoring programs in the context of prescription opioids: pros, cons and tensions*, BMC PHARMACOLOGY & TOXICOLOGY (2014).

[65] Sacco, et al., *Prescription Drug Monitoring Programs*, CONGRESSIONAL RESEARCH SERVICE (May 24, 2018), https://sgp.fas.org/crs/misc/R42593.pdf.

[66] QUVIVIQ® (Daridorexant), Package Insert (rev. Mar. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214985s000lbl.pdf.

[67] *See* Edinoff, et al., *Benzodiazepines: Uses, Dangers, and Clinical Considerations*, NEUROLOGY INTERNATIONAL (2021).

Factor 8 (Immediate Precursor of a Controlled Substance): DORAs are not immediate precursors of a controlled substance, and they are not chemically similar to or derived from a controlled substance.

Because DORAs are not immediate precursors of a controlled substance and are not chemically similar to or derived form a controlled substance, this factor weighs in favor of descheduling the class.

III. CONCLUSION

Scheduling DORAs has exacerbated healthcare disparities. Given the financial incentives driving insurers and physician-prescribing deterrents, an older class of scheduled products that have significant risks of abuse-related adverse effects are more likely to be prescribed for insomnia than are DORAs. As noted by NIDA, "drug use and addiction are preventable."[68] Descheduling DORAs provides an alternative for patients with insomnia, where the benefits of treatment with unscheduled DORAs outweigh the risks of the current standard of care.

We recognize that the DEA must involve FDA (exercising authority delegated by the Secretary of the U.S. Department of Health and Human Services) in developing a scientific and medical evaluation, and recommendations, regarding whether daridorexant, lemborexant, and suvorexant should be removed from the CSA's controlled substance schedules. Per DEA regulations:

> The Administrator shall, before initiating proceedings for the issuance, amendment, or repeal of any rule either to control a drug or other substance, or to transfer a drug or other substance from one schedule to another, or to remove a drug or other substance entirely from the schedules, and after gathering the necessary data, request from the Secretary a scientific and medical evaluation and the Secretary's recommendations as to whether such drug or other substance should be so controlled, transferred, or removed as a controlled substance. The recommendations of the Secretary to the Administrator shall be binding on the Administrator as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Administrator shall not control that drug or other substance.[69]

For the reasons outlined above, we respectfully request that FDA determine that the eight factors weigh in favor of removing the DORA drug product class—daridorexant, lemborexant, and suvorexant—from the controlled substance schedules.

Finally, we respectfully request that, consistent with the CSA and DEA regulations, the DEA Administrator initiate a rulemaking proceeding to remove daridorexant, lemborexant, and suvorexant from the CSA's controlled substance schedules. We will be pleased to discuss this petition further and to share additional data and insights relevant to DORA scheduling with DEA and FDA.

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[68] NIDA, DrugFacts, *Understanding Drug Use and Addiction* (rev. June 2018), https://nida.nih.gov/download/799/understanding-drug-use-addiction-drugfacts.pdf?v=9b2d8525f0ca1b03f816eaf71ece6ef2.

[69] 21 C.F.R. § 1308.43(d).