NDA 214985

NDA APPROVAL

Idorsia Pharmaceuticals Ltd.
Attention: Bradford Kirk Perry, PharmD
Director, US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:

Please refer to your new drug application (NDA) dated and received January 8, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Quviviq (daridorexant) tablets.

This NDA provides for the use of Quviviq (daridorexant) tablets for treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of Quviviq (daridorexant) tablets under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for Quviviq (daridorexant) tablets shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of daridorexant.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information, Medication Guide, and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of daridorexant, as the scheduled substance in Quviviq tablets, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Quviviq (daridorexant) tablets may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of daridorexant and you submit a supplement to your NDA to revise all applicable drug

labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information, Medication Guide, and carton and container labeling to describe the scheduling of Quviviq (daridorexant) tablets, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for Quviviq (daridorexant) tablets described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

We note that Quviviq (daridorexant) tablets will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of daridorexant.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214985.** Approval of this submission by FDA is not required before the labeling is used.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Quviviq (daridorexant) tablets shall be 24 months from the date of manufacture when stored at 20 to 25 °C.

ADVISORY COMMITTEE

Your application for Quviviq was not referred to an FDA advisory committee because this drug is not the first in its class, the clinical trial designs are similar to those for previously approved products in the class, evaluation of the data did not raise significant safety or efficacy issues that were unexpected for a drug in this class, and outside expertise was not necessary.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for children below 10 years of age because necessary studies are impossible or highly impracticable. This is because assessing sleep in children below 10 years of age is complex and challenging, due to the high variability of sleep and napping time, both across the age range, and between children of the same age.

We are deferring submission of your pediatric studies for ages 10 to <18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4150-5 Conduct a randomized, double-blind, dose-finding study to identify the optimal dose for a confirmatory efficacy and safety study in patients with insomnia disorder aged 10 to <18 years.

Draft Protocol Submission,: 07 /2021 (submitted)
Final Protocol Submission: 04 /2022

Study Completion:	04 /2024
Final Report Submission:	10/2024

4150-6 Conduct a randomized, double-blind, placebo-controlled efficacy and safety study of daridorexant for the treatment of insomnia disorder in children 10 to <18 years of age.

Draft Protocol Submission,:	11/2024
Final Protocol Submission:	05/2025
Study Completion:	10/2027
Final Report Submission:	04/2028

4150-7 Conduct a study to evaluate the longer-term safety of continued treatment of insomnia disorder with daridorexant for at least one year in patients 10 to <18 years of age at study entry.

Draft Protocol Submission,:	11/2024
Final Protocol Submission:	10/2025
Study Completion:	07/2028
Final Report Submission:	01/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 128789 with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA would not be sufficient to assess a

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

signal of or identify an unexpected serious risk of impairment of arousability from night sleep or psychomotor impairment following such arousal or adverse maternal, fetal, or infant outcomes resulting from the use of daridorexant during pregnancy or with breastfeeding.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4150-1 Conduct a lactation study in lactating women who have received daridorexant to assess concentrations of daridorexant in breast milk using a validated assay.

The timetable you agreed to on December 20, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission,:	09/2022
Final Protocol Submission:	12/2022
Study Completion:	12/2023
Final Report Submission:	06/2024

4150-2 Conduct a prospective, registry based cohort study that compares the maternal, fetal, and infant outcomes of women exposed to daridorexant during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you agreed to on December 20, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2022
Final Protocol Submission:	02/2023
Study Completion:	02/2033
Interim/Other:	02/2024, 02/2025, 02/2026, 02/2027, 02/2028, 02/2029, 02/2030, 02/2031, 02/2032, 02/2033
Final Report Submission:	08/2033

4150-3 Conduct an additional pregnancy study that uses a different observational design from the pregnancy registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to daridorexant during pregnancy compared to an unexposed control population.

The timetable you agreed to on December 20, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	04/2023
Study Completion:	04/2028
Interim/Other:	04/2024, 04/2025, 04/2026, 04/2027, 04/2028
Final Report Submission:	04/2029

4150-4 A randomized, double-blind, placebo-controlled, middle-of-the-night safety study in females and males aged 18-65 and >65 years to assess the ability to awaken to sound in the middle of the night and postural stability and cognitive function following awakening.

The timetable you agreed to on December 20, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission,:	07/2022
Final Protocol Submission:	10/2022
Study Completion:	04/2023
Final Report Submission:	09/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 128789 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the regulatory project manager for this application.

If you have any questions, call LCDR Jasmeet (Mona) Kalsi, Regulatory Project Manager, at 240-402-8977.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
01/07/2022 03:16:12 PM
signing on behalf of WILLIAM H DUNN