DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Nuo (Nolan) Wang, PhD
President
Sciecure Pharma, Inc.
11 Deer Park Drive, Unit 120
Monmouth Junction, NJ 08852

RE: NDA 018708
DORAL® (quazepam) Tablets for oral use C-IV
MA #46

Dear Dr. Wang:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (PM-271-01) (sales aid) for DORAL® (quazepam) Tablets for oral use C-IV (Doral). The sales aid is misleading because it omits important risk information associated with Doral, contains unsubstantiated superiority claims, and omits material facts. Thus, the sales aid misbrands Doral within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(ii). Sciecure Pharma also did not comply with 21 CFR 314.81(b)(3)(i).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Doral.[1] According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Doral:

> DORAL® (quazepam) is indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of Doral has been established in placebo-controlled clinical studies of 5 nights duration in acute and chronic insomnia. The sustained effectiveness of Doral has been established in chronic insomnia in a sleep lab (polysomnographic) study of 28 nights duration. Because insomnia is often transient and intermittent, the prolonged administration of Doral tablets is generally not necessary or recommended. Since insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Doral is contraindicated in patients with known hypersensitivity to quazepam or other benzodiazepines, established or suspected sleep apnea, or pulmonary insufficiency. The PI for Doral contains warnings and precautions regarding central nervous system (CNS) depressant effects and daytime impairment, benzodiazepine withdrawal syndrome, the need to evaluate for co-morbid diagnoses, severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavior changes, and worsening depression. The most common adverse reactions observed with Doral were daytime drowsiness, headache, fatigue, dizziness, dry mouth, and dyspepsia.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The four page sales aid includes numerous claims and presentations regarding the benefits of using Doral for the treatment of insomnia, yet omits all of the contraindications for the use of Doral. The sales aid also omits the warnings and precautions regarding benzodiazepine withdrawal syndrome, the need to evaluate for co-morbid diagnoses, severe anaphylactic or anaphylactoid reactions, abnormal thinking and behavior changes, and worsening of depression. The omission of these serious risks associated with the drug is further exacerbated by the claims on pages[2] two and four characterizing Doral as having a "[f]avorable safety profile."

Additionally, while page four of the sales aid presents some risk information regarding CNS-depressant effects and daytime impairment associated with Doral, it omits material information from the WARNINGS AND PRECAUTIONS section of the PI regarding this risk. Specifically, the sales aid fails to disclose that patients should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness; that downward dose adjustment of Doral and concomitant CNS depressants should be considered; and that there is an increased risk of next-day psychomotor impairment if Doral is taken with less than a full night of sleep remaining (7 to 8 hours).

Furthermore, although the sales aid presents some of the common adverse reactions of Doral such as daytime drowsiness and headache, it completely omits other common adverse reactions associated with the drug. According to the ADVERSE REACTIONS section of the PI, the most common adverse reactions reported with Doral were daytime drowsiness, headache, fatigue, dizziness, dry mouth, and dyspepsia.

We acknowledge that the sales aid includes the statement, "Please see accompanying full prescribing information" on the bottom of page four; however, this does not mitigate the omission of the aforementioned risk information. By omitting serious and common risks associated with the drug, the sales aid misleadingly suggests that Doral is safer than has been demonstrated.

[2] Please note that for the purpose of this letter, we have numbered the pages in the sales aid, one through four, with page one representing the front cover of the sales aid, page two representing the second page of the sales aid, and so on.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The sales aid includes the following claims and presentations (emphasis original):

- Image of a single white sheep among a group of four black sheep (front cover)
- "**Discover a surprisingly unique sleep agent**" (page one)
- The tagline claim, "**Uniquely Selective**" is presented in direct conjunction with the Doral logo (pages one, three, and four)
- "DORAL IS THE ONLY BENZODIAZEPINE THAT IS
  Uniquely BZ_1 selective
  Doral® (quazepam tablets, USP) – the only
  benzodiazepine that provides BZ_1 receptor selectivity[3]
    - BZ_1 receptor selectivity offers the benefits of a hypnotic agent without many of the drawbacks of typical benzodiazepines[3]
    - BZ_1 receptors are believed to be associated with sleep function[4]" (page two)
- Image of the white sheep in association with the logo for Doral (page three)
- A bar graph which compares the "[r]elative abuse liability of common sleep agents[5]" including quazepam (Doral) (page three)
- A line graph which presents the results of the digit-symbol substitution test (DSST) after administration of Doral 15 mg, triazolam 0.1875 mg, triazolam 0.375 mg, or placebo, under the header "**Effect on cognitive-neuromotor performance**[6]" (page three)
- "**DORAL**. . . .
  For the effective treatment of insomnia
  Acts selectively on BZ_1 receptors[3]" (page four)

The totality of these claims and presentations misleadingly suggests that Doral is both safer and more effective than other products for the treatment of insomnia because of a unique mechanism of action. However, this suggestion of superior safety and efficacy, based on the mechanism of action, has not been demonstrated by substantial evidence. Four references are cited to support these claims. Two of the references cited are review articles which provide general descriptions of the pharmacodynamics, pharmacokinetics, and efficacy of quazepam and other benzodiazepines rather than descriptions of well-controlled clinical studies.[3,4] A third reference, by Griffiths et al., provides an algorithm that purportedly differentiates the likelihood of abuse and relative toxicity among 19 compounds, including quazepam.[5] However, the "algorithm" lacks actual abuse data in human subjects and has not been validated. Finally, the fourth reference, by Rush et al., is a study evaluating cognitive-

[3] Kales A. Quazepam: hypnotic efficacy and side effects. Pharmacotherapy 1990;10(1):1-12.
[4] Hilbert JM, Battista D. Quazepam and flurazepam: differential pharmacokinetic and pharmacodynamics characteristics. J Clin Psychiatry 1991;52(suppl 9):21-26.
[5] Griffiths RR, John MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry. 2005;66(suppl 9):31-41.
[6] Rush CR, Armstrong DL, Ali JA, Pazzaglia PJ. Benzodiazepine receptor ligands in humans: acute performance-impairing, subject-rated and observer-rated effects. J Clin Psychopharmacol. 1998;18(2):154-165.

neuromotor performance based on a DSST in nine healthy subjects that lacks adequate statistical power and an appropriate patient population to draw any conclusions.[6] The four cited references do not describe adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of Doral and the comparator drugs in an appropriate patient population that would be necessary to support claims of efficacy or safety superiority for Doral. Therefore, the references cited do not constitute substantial evidence to support the suggestion that Doral is safer or more effective than other products for the treatment of insomnia.

In addition, the above claims regarding the purported BZ_1 receptor selectivity of Doral are misleading because they imply a greater degree of certainty about the mechanism of action than is currently known. The above claims also misleadingly suggest that BZ_1 receptor selectivity is "unique" to Doral. However, in direct contrast to these claims, the Clinical Pharmacology section of the PI for Doral states (emphasis added):

> Quazepam, **like other central nervous system agents of the 1,4-benzodiazepine class**, **presumably** exerts its effects by binding to stereo-specific receptors at several sites within the CNS. **The exact mechanism of action is unknown**.

If you have data to support these claims and presentations, please submit them to FDA for review.

Omission of Material Facts

The sales aid includes the following claim regarding Doral's use for the treatment of insomnia:

- "Doral is indicated for the treatment of insomnia, characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings."

The sales aid is misleading because it fails to communicate material information from Doral's full FDA-approved indication for the treatment of insomnia. In addition to the above claim, the INDICATIONS AND USAGE section of the PI also states the following, in pertinent part:

> Because insomnia is often transient and intermittent, the prolonged administration of DORAL Tablets is generally not necessary or recommended. Since insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered.

Page four of the sales aid presents the image of a prescription pad with the following claim:

- "Doral 15 mg
  @ bedtime"

However, within the context of this sales aid directed to healthcare professionals, this claim is misleading because it omits important material information necessary for the dosing and administration of Doral. Specifically, the DOSAGE AND ADMINISTRATION section of the PI states:

Use the lowest dose effective for the patient, as important adverse effects of Doral are dose related.

The recommended initial dose is 7.5 mg. The 7.5 mg dose can be increased to 15 mg if necessary for efficacy.

The 7.5 mg dose can be achieved by splitting the 15 mg tablet along the score line.

Failure to Submit Under Form FDA-2253

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. A copy of the Doral sales aid was not submitted to OPDP under cover of Form FDA-2253 at the time of initial dissemination as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the sales aid misbrands Doral within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(ii). Furthermore, Sciecure Pharma also did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Sciecure Pharma immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before November 13, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Doral that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #46 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Doral complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion

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/s/

MATHILDA K FIENKENG
10/29/2014