DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Bharat Patel, Pharm.D.
CEO and Co-Founder
Galt Pharmaceuticals, LLC
3350 Riverwood Parkway, Suite 1900
Atlanta, GA 30339

RE: NDA 018708
DORAL (quazepam) tablets for oral use C-IV
MA 51

WARNING LETTER

Dear Dr. Patel:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional email[1] (GLT-DOR-016) for DORAL (quazepam) tablets for oral use C-IV (Doral) submitted by Galt Pharmaceuticals, LLC (Galt) under cover of Form FDA 2253. The email makes false or misleading claims and/or representations about the risks associated with and efficacy of Doral. Thus, the email 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), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). These violations are extremely concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Doral, a drug that is a controlled substance and bears a Boxed Warning due to serious, life-threatening risks from concomitant use with opioids.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Doral.[2] According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI)[3] for Doral:

[1] The email includes an active hyperlink to open the email in a web browser http://www.doralrx.com/Campaigns/Emails/Doral_Least_Abuse_Potential/ (Last accessed September 13, 2019)
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.
[3] The version of the Doral PI that was submitted to FDA when the piece was disseminated, and the version referred to in this letter is dated August 2017. Subsequently, a new version of the PI was approved in February 2019. We note that the current version of the PI, approved in February 2019, includes additional risk information in the WARNINGS AND PRECAUTIONS section.

> DORAL 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.

Doral is contraindicated in patients with known hypersensitivity to Doral or other benzodiazepines, established or suspected sleep apnea, or pulmonary insufficiency. The PI for Doral contains a Boxed Warning regarding risks from concomitant use with opioids. In addition, the WARNINGS AND PRECAUTIONS section includes risk information 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 of depression. The most common adverse reactions observed with Doral were drowsiness, headache, fatigue, dizziness, dry mouth, and dyspepsia.

Prior Communication(s)

OPDP has expressed concerns regarding promotional materials for Doral in a previous letter. On October 29, 2014, OPDP sent Sciecure Pharma, Inc. (Sciecure) an Untitled Letter for a Doral professional sales aid (2014 Untitled Letter) that omitted important risk information, contained unsubstantiated superiority claims, and omitted material facts. While Sciecure is no longer the application holder,[4] OPDP is concerned that Galt is continuing to promote this product in a similarly violative manner.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk or benefits. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The email includes numerous claims and presentations regarding the benefits of using Doral for the treatment of insomnia. However, it completely omits the warning and precaution regarding benzodiazepine withdrawal syndrome.

Additionally, while the email presents some risk information regarding the serious risks

[4] On April 19, 2016, FDA acknowledged receipt of Cutis Health, LLC's correspondence notifying FDA of the change of ownership of Doral from Sciecure Pharma. Inc., to Cutis Health, LLC. On March 7, 2018, FDA acknowledged receipt of your correspondence notifying the FDA (in pertinent part) that the corporate name had been changed from Cutis Health, LLC to Galt Pharmaceuticals, LLC.

associated with Doral, it omits certain material information pertaining to these risks. Specifically, the email fails to disclose information from the WARNINGS AND PRECAUTIONS, CNS-Depressant Effects and Daytime Impairment section of the PI 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, that use of Doral with other sedative-hypnotics is not recommended, 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). The email also fails to disclose material information from the WARNINGS AND PRECAUTIONS, Severe Anaphylactic and Anaphylactoid Reactions section of the PI that some patients have required medical therapy in the emergency department, if angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal, and that patients who develop angioedema after treatment with Doral should not be rechallenged. In addition, the email fails to disclose material information from the WARNINGS AND PRECAUTIONS, Abnormal Thinking and Behavior Changes section of the PI regarding the types of behavior changes and some complex behaviors that may occur, as well as information about discontinuing Doral if "sleep-driving" occurs. Lastly, the email fails to disclose material information from the WARNINGS AND PRECAUTIONS, Worsening of Depression section of the PI regarding appropriate precautions that should be considered in this patient population (e.g., limiting the total prescription size and increased monitoring for suicidal ideation).

We acknowledge that the email includes the statement, "For a full list of warnings and precautions, please refer to the full prescribing information." However, this does not mitigate the omission of the aforementioned risk information from the email. By omitting this material information related to serious risks associated with the drug, the email, similar to the professional sales aid at issue in the 2014 Untitled Letter, misleadingly suggests that Doral is safer than has been demonstrated.

The email includes the following claims and presentation under the bolded header, "**Concerned about Abuse potential of sleep medications?**" (emphasis original; asterisk content below):

- "Doral's relative likelihood of abuse is considerably lower than some of the widely used sleep aids (i.e. Zolpidem & Temazepam)*"
- "Doral was ranked even lower than OTC product Diphenhydramine for relative abuse potential*"
- A figure comparing the "**Relative Likelihood of Abuse**" of 19 drugs, with Quazepam shown as having a score lower than 16 of the drugs depicted
- "**Doral**'s abuse potential is **1/2** of Zolpidem & **1/3** of Temazepam"

These claims and presentation are misleading because they minimize the risks of abuse and dependence associated with Doral and suggest that this C-IV scheduled drug is superior in safety to other prescription and over-the-counter (OTC) products. The cited reference by Griffiths et al.,[5] provides an algorithm that purportedly differentiates the likelihood of abuse and relative toxicity among 19 compounds, including Doral (quazepam). However, as FDA pointed out in 2014, "the 'algorithm' lacks actual abuse data in human subjects and has not

[5] Griffiths RR, Johnson 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.

been validated." While we acknowledge the figure includes the following statement, "*Please see complete prescribing information for detailed information on each product. The above chart is not intended for efficacy comparison. The authors algorithm, while comprehensive, does lack prospective abuse data in human subjects and had not been validated in subsequent research," this statement does not mitigate the overwhelming impression that Doral is superior in safety to other prescription and OTC products.

Furthermore, this misleading impression is compounded by the fact that the email fails to disclose Doral's potential for abuse and dependence, including that Doral is classified as a schedule IV controlled substance. This is alarming as it appears that Galt is intentionally attempting to promote Doral as a non-controlled product that is safer than over-the-counter medication.

False or Misleading Claims about Efficacy

The email includes the following claim (bold emphasis original, underline emphasis added):

> **Doral is the <u>only</u> marketed medication for Insomnia that helps with all three important components of sleep:**
> - Difficulty falling asleep
>   - Difficulty staying asleep
>   - Early morning awakening

This claim is false because it suggests that Doral is the **only** marketed medication indicated for the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. However, there are other marketed medications indicated for all three of these components of sleep.

Omission of Material Facts

The email includes claims about the use of Doral such as (emphasis original):

- "For your patients with insomnia, Prescribe **Doral** (*Quazepam*) for a complete night's sleep"
- "Doral (Quazepam) is indicated for the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings."

These claims are misleading because the email omits the following material information from the INDICATIONS AND USAGE section of the PI:

> 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.

By omitting this information, the email creates a misleading impression about the use of Doral. These omissions are particularly concerning from a public health perspective due to

the serious health risks associated with Doral that should be considered when prescribing the product.

Conclusion and Requested Action

For the reasons discussed above, the email misbrands Doral within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5).

OPDP requests that Galt immediately cease misbranding Doral and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before September 27, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Doral that contain statements such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Doral. Because the violations described above are serious and repeated, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

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**. A courtesy copy can be sent by facsimile to (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 51 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 Warning Letter.

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

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D.
Director
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

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/

ANDREW S HAFFER
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