DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

George Hampton
Chief Executive Officer
Nalpropion Pharmaceuticals LLC
10 North Park Place, Suite 201
Morristown, NJ 07960

RE: NDA 200063
CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets, for oral use
MA 516

WARNING LETTER

Dear Mr. Hampton:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a sponsored link on the internet search engine, Google.com[1] for CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets, for oral use (Contrave) manufactured by Nalpropion Pharmaceuticals LLC (Nalpropion). The FDA Bad Ad Program also received a complaint regarding a sponsored link for Contrave. The sponsored link reviewed by OPDP makes false or misleading claims about the risks associated with and efficacy of Contrave. Thus, the sponsored link misbrands Contrave within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(ii); (e)(5). These violations are especially concerning from a public health perspective because Contrave is a drug with multiple serious, potentially life-threatening risks, including a boxed warning that describes the risk of suicidal thoughts and behaviors. Obesity and excessive weight are significant public health concerns that affect millions of adults in the United States and are associated with numerous co-morbidities. Consumers and patients who seek assistance with their weight-loss goals should not be misled regarding the serious risks, expected benefits, and necessary nutritional and lifestyle modifications associated with the use of a weight management prescription drug product, such as Contrave.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Contrave.[2] According to the FDA-approved product labeling (PI) (emphasis original):

[1] Available at https://www.google.com (Last accessed September 3, 2020).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

CONTRAVE is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use:

- The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

This product is associated with a number of serious risks. The PI for the drug contains a boxed warning regarding suicidal thoughts and behaviors. Contrave is contraindicated in uncontrolled hypertension, seizure disorder or a history of seizures; use of other bupropion-containing products; bulimia or anorexia nervosa; chronic opioid or opiate agonist or partial agonists use, or acute opiate withdrawal; patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; concomitant administration of monoamine oxidase inhibitors; and known allergy to bupropion, naltrexone or any other component of Contrave. The PI also contains warnings and precautions regarding neuropsychiatric adverse events and suicide risk in smoking cessation treatment, seizures, patients receiving opioid analgesics, increase in blood pressure and heart rate, allergic reactions, hepatotoxicity, activation of mania, angle-closure glaucoma, and the potential risk of hypoglycemia in patients with type 2 diabetes mellitus on antidiabetic therapy. In addition, the PI indicates that the most common adverse reactions associated with Contrave are nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.

Prior Communication(s)

OPDP has expressed concerns regarding promotional materials for Contrave in a previous letter. On May 18, 2017, OPDP sent Orexigen Therapeutics, Inc. (Orexigen) an Untitled Letter for a Contrave broadcast television advertisement (2017 Untitled Letter) that omitted important risk information. We acknowledge that Orexigen is no longer the application holder.[3] However, we are concerned that Nalpropion is continuing promotion of Contrave in a manner that similarly fails to adequately convey risk information.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other

[3] On August 2, 2018, FDA acknowledged receipt of Nalpropion Pharmaceuticals, Inc.'s correspondence notifying FDA of the change of ownership of Contrave from Orexigen to Nalpropion Pharmaceuticals, Inc. On December 31, 2019, FDA acknowledged receipt of Nalpropion Pharmaceuticals, LLC's correspondence notifying the FDA of the change of ownership of Contrave from Nalpropion Pharmaceuticals, Inc., to Nalpropion Pharmaceuticals, LLC.

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 sponsored link is misleading because it presents efficacy claims for Contrave but fails to communicate **any** risk information. Specifically, the sponsored link includes the following claims (emphasis original):

- "**CONTRAVE® Weight Loss - (naltrexone HCl/bupropion HCl)**"
- "Lose 2-4x more weight on average than with diet and exercise alone!"

The sponsored link, however, entirely omits all risk information. We note the sponsored link includes the statement "View Important Safety Info & Boxed Warning," however, this statement does not mitigate the misleading omission of risk information. By omitting the risks associated with Contrave, the sponsored link fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the drug's safety.

This misleading presentation is particularly alarming from a public health perspective given that the sponsored link utilizes claims that could appeal to patients who seek assistance with their weight-loss goals, but fails to communicate that Contrave is associated with serious and potentially life-threatening risks, such as those contained in the boxed warning that describes the risk of suicidal thoughts and behaviors.

False or Misleading Claims about Efficacy

Promotional materials misbrand a drug if they are false or misleading with respect to efficacy. 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 sponsored link is misleading because it fails to provide material information from the full FDA-approved indication regarding the use of the drug product as an adjunct to diet and exercise, the minimum initial BMI for which treatment with Contrave is indicated, the requisite presence of weight-related comorbid condition(s) in patients with an initial BMI of greater than or equal to 27 kg/m^2 and the limitations of use. Specifically, the INDICATIONS AND USAGE section of the PI states the following (underlined emphasis original):

> CONTRAVE is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
>
> - 30 kg/m^2 or greater (obese) or
> - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use:

- The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

By failing to disclose this material information from the INDICATIONS AND USAGE section, the sponsored link creates a misleading impression about the FDA-approved indication for Contrave. This is particularly concerning given the claim "Lose 2-4x more weight on average . . ." and the reference to "**CONTRAVE® Weight Loss**" (bolded emphasis original, underlined emphasis added). These broad claims misleadingly imply that patients, no matter their BMI, should expect to achieve the "average" results presented in the sponsored link, when it is not approved for use in patients that do not meet the initial BMI criteria. Furthermore, this presentation is misleading because it omits material information from the full indication about the use as adjunct to diet and exercise. We note the sponsored link states ". . .than with diet and exercise alone!" However, this is not adequate to convey to the viewer that both exercise and diet are necessary in achieving the benefits (weight management) of Contrave as stated in the PI.

In addition, the sponsored link creates a misleading impression regarding the efficacy of Contrave by selectively presenting more favorable data. Specifically, the presentation only references the more favorable co-primary endpoint of percent change from baseline body weight: "Lose 2-4x more weight on average than with diet and exercise alone!" According to the CLINICAL STUDIES section of the PI, the percentage of patients who achieved a treatment response (defined as achieving at least 5 percent weight loss from baseline after 1 year of treatment) ranged from 36 to 57 percent with Contrave compared to 17 to 43 percent with placebo. Without this context, the presentation could be read to suggest that any amount of weight loss (i.e., 2-4x) was considered clinically meaningful for Contrave. The omission of this material information creates a misleading impression regarding the clinically meaningful effect of Contrave.

Conclusion and Requested Action

For the reasons discussed above, the sponsored link misbrands Contrave within the meaning of the 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)(3)(ii); (e)(5).

OPDP requests that Nalpropion immediately cease misbranding Contrave and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before October 7, 2020, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Contrave 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 Contrave. Because the violations described above are serious, 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 516 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 Contrave 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}

Robert Dean
Division Director
Division of Advertising & Promotion Review 2
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/

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