DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Aaron Chesnut
Vice President, Technical Operations
Nalpropion Pharmaceuticals, LLC
155 Franklin Road, Suite 450
Brentwood, TN 37027

RE: NDA 200063
CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets, for oral use
MA 944

Dear Aaron Chesnut:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer (DTC) television broadcast advertisement (TV ad), titled "CONTRAVE TV Spot 60 Sec_v2" (CON- 2306) for CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets, for oral use (Contrave) submitted by Nalpropion Pharmaceuticals LLC (Nalpropion) under cover of Form FDA 2253.[1] FDA has determined that the TV ad is false or misleading. Thus, the TV ad misbrands Contrave and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The TV ad includes claims and presentations that misrepresent the efficacy of Contrave. Specifically, the TV ad begins with a woman at work looking at a bag of chips and putting them away in a closed desk drawer while "smirking defiantly" (Frames 1-9). The TV ad continues with a man looking at a bowl of chocolates, smirking and shaking his head, and then pouring them back in their original bag before placing the chocolates away in a cabinet (Frames 10- 15). The TV ad then presents another woman in between two fighting children who drop a bowl of cereal and milk. While cleaning up the mess, she is seen looking at a box of cookies "for a moment". She is then seen smirking at the cookie box and putting it away in a cookie jar on top of the kitchen counter (Frames 16-19). These presentations are in conjunction with the following claims (in pertinent part, underlined emphasis added):

- **Audio Voice Over (AVO)**: "Lyrics continue: "CONTRAVE <u>helps keep those cravings away</u>."" (Frame 5)

- **AVO:** "Is it hard to lose weight because it can be difficult to <u>control cravings</u>?" (Frames 10-11)

- **AVO:** "It is designed to work in 2 ways to help reduce hunger and <u>control cravings</u>."

[1] The Form FDA 2253 submission included the final produced TV ad video as well as a storyboard annotated with frame numbers. We have referred to those frame numbers in this letter to facilitate communication of our concerns.

- **ON-SCREEN TEXT:** "2 Ways
  Reduce Hunger
  Control Cravings" (Frames 19-20)

These claims and presentations are misleading because they suggest that Contrave's mechanism of action in relation to its therapeutic effect is fully understood when this is not the case. Additionally, these claims and presentations create a misleading impression about the physiology of weight loss, when the contribution of opioid antagonism and dopamine and norepinephrine neuronal reuptake inhibition to weight loss efficacy is not fully understood. According to the CLINICAL PHARMACOLOGY, Mechanism of Action section of the FDA-approved prescribing information (PI) for Contrave (in pertinent part, emphasis added):

> Nonclinical studies suggest that naltrexone and bupropion have effects on two separate areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system). The exact neurochemical effects of CONTRAVE leading to weight loss are not fully understood.

Thus, the impression that Contrave's mechanism of action and neurochemical effects are fully understood is misleading. We acknowledge the following SUPER, "The exact way CONTRAVE works to help people lose weight is not fully understood" (in pertinent part, frames 19-20). However, the comparative emphasis placed on this information undermines its communication. Therefore, the SUPER does not correct or mitigate the overall misleading impression created by the TV ad regarding Contrave's mechanism of action and neurochemical effects.

The TV ad is also misleading because it includes claims and presentations about the uses and benefits of Contrave but fails to include the warning and precaution for activation of mania. Specifically, the major statement does not communicate the following from the "**What are the possible side effects of CONTRAVE?**" section of the Medication Guide (MG) (in pertinent part, underlined emphasis added):

> **CONTRAVE may cause serious side effects, including:**
>
> > **Manic episodes.** One of the ingredients in CONTRAVE, bupropion can cause some people who were manic or depressed in the past to become manic or depressed again.

Additionally, the TV ad includes the following claim, "Call a doctor right away if any unusual changes in mood, behaviors, thoughts, or feelings occur." (Frame 22). This claim includes the recommendation to call a healthcare provider, but fails to communicate the directive to stop taking Contrave. Specifically, the major statement does not communicate the following from the "**What is the most important information I should know about CONTRAVE?**" section of the MG (in pertinent part; underlined emphasis added), "**Stop taking CONTRAVE and call a healthcare provider right away if you** . . . . " Moreover, although the TV ad includes the claim, "Do not take CONTRAVE if you have…history of seizures, ... " (in pertinent part, frame 24) it fails to adequately communicate material risk information that

Contrave can cause seizures as described in the "**What are the possible side effects of CONTRAVE?**" section of the MG.

By omitting these serious risks associated with Contrave and material information pertaining to the risks of Contrave, the TV ad creates a misleading impression of the drug's safety.

Conclusion and Requested Action

For the reasons described above, the TV ad misbrands Contrave and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Nalpropion take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above). Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Contrave that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Contrave.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

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

Please direct your response to 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. Please refer to MA 944 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. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 5432 under NDA 200063.

Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

George Tidmarsh, M.D., Ph.D.
Director
Center for Drug Evaluation and Research

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/

CARTER M BEACH
09/09/2025 05:17:53 PM
On behalf of George Tidmarsh, M.D., Ph.D