DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Stefan Antonsson, CEO
Outlook Pharmaceuticals, Inc.
8044 Montgomery Road, Suite 700
Cincinnati, OH 45236

RE: ANDA 040776
PROCENTRA® (dextroamphetamine sulfate) oral solution, CII
MA 60

WARNING LETTER

Dear Mr. Antonsson:

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 PROCENTRA® (dextroamphetamine sulfate) oral solution, CII (ProCentra), a drug distributed by Independence Pharmaceuticals, LLC on behalf of Outlook Pharmaceuticals, Inc. (Outlook).[2] The FDA Bad Ad Program also received complaints regarding this sponsored link on Google. This sponsored link is false or misleading in that it presents information about the benefits of ProCentra, but fails to include **any** risk information about the drug. Thus, the sponsored link misbrands ProCentra 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)(5). These violations are especially concerning from a public health perspective because they create a misleading impression about the safety of ProCentra, a drug that is a schedule II controlled substance used in the vulnerable pediatric patient population, and bears a Boxed Warning that describes the high potential for abuse, that administration of amphetamines for prolonged periods of time may lead to drug dependence, and states that misuse may cause sudden death and serious cardiovascular adverse events. Furthermore, the sponsored link fails to present the required established name, which misbrands ProCentra within the meaning of the Act and makes its distribution violative. 21 U.S.C. 352(e)(1)(B), (n); 331(a). *See* 21 CFR 201.10(g)(1); 202.1(b)(1).

[1] Available at https://www.google.com/search?q=procentra&ei=5PkgXpuDNcXJ5gLLqaVg&start=10&sa=N&ved=2ahUKEwibhdLoqonnAhXFpFkKHctUCQwQ8NMDegQIEBBA&biw=1681&bih=889&dpr=1.03#spf=1579219432220 (Last accessed February 20, 2020).
[2] The ANDA holder for ProCentra is Outlook Pharmaceuticals, Inc. and the U.S. agent is Mikart, LLC.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of ProCentra.[3]

According to the FDA-approved product labeling (PI)[4] (emphasis original, in pertinent part):

> **ProCentra**® (dextroamphetamine sulfate) Oral Solution is indicated in:
> . . .
> **Attention Deficit Disorder with Hyperactivity:** As an integral part of a total treatment program that typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in pediatric patients (ages 3 years to 16 years) with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: Moderate to severe distractibility, short attention span, hyperactivity, emotionally lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

ProCentra is associated with a number of serious risks. According to the PI, ProCentra contains a Boxed Warning that describes the drug's high potential for abuse, that administration of amphetamines for prolonged periods of time may lead to drug dependence, and states that misuse may cause sudden death and serious cardiovascular adverse events.

ProCentra is contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, agitated states, patients with a history of drug abuse, and during or within 14 days following the administration of monoamine oxidase inhibitors.

The PI for ProCentra also includes warnings regarding serious cardiovascular events, including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems, hypertension and other cardiovascular conditions, and the need for assessing cardiovascular status in patients being treated with stimulant medications; psychiatric adverse events in patients with pre-existing psychosis, possible induction of a mixed/manic episode in patients with co-morbid bipolar disorder, and the emergence of new psychotic or manic symptoms, and aggression; long-term suppression of growth; seizures; peripheral vasculopathy, including Raynaud's phenomenon; serotonin syndrome; and visual disturbance. The PI also contains a precaution that healthcare providers should prescribe or dispense the least amount feasible at one time in order to minimize the possibility of overdosage. As described in the approved Medication Guide, the common side effects of ProCentra include fast heartbeat, decreased appetite, tremors, headache, trouble sleeping, dizziness, stomach upset, weight loss, and dry mouth.

[3] 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.
[4] The version of the ProCentra PI referred to in this letter is dated February 2017.

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 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 includes claims and/or representations about the use and/or benefits of ProCentra such as, "Explore Your ADHD Medication Options For Your Child." However, it fails to communicate **any** risk information. By omitting the risks associated with ProCentra, the sponsored link fails to provide material information about the consequences that may result from the use of ProCentra 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 such as, "Liquid Treatment Option" and "Bubblegum Flavor", that could appeal to parents as desirable properties for pediatric administration, but fails to communicate that ProCentra is a schedule II controlled substance associated with serious and potentially life-threatening risks, such as those contained in ProCentra's Boxed Warning that describes the high potential for abuse of the drug and states that misuse may cause sudden death and serious cardiovascular adverse events.

Failure to Use Required Established Name

The established name of a prescription drug must be presented prominently, in direct conjunction with the proprietary name. The sponsored link fails to present the established name for ProCentra (dextroamphetamine sulfate), thereby misbranding the product.

Conclusion and Requested Action

For the reasons discussed above, the sponsored link misbrands ProCentra within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (e)(1)(B), (n); 321(n); 331(a). *See* 21 CFR 201.10(g)(1); 202.1(b)(1); 202.1(e)(5).

OPDP requests that Outlook immediately cease misbranding ProCentra and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before March 6, 2020, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for ProCentra 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 ProCentra. 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 60 in addition to the ANDA 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 ProCentra 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

cc: Michael Kallelis, CEO
Mikart, LLC
Attention: Jason Waldroup, Director, Regulatory Affairs
1750 Chattahoochee Avenue, Atlanta, GA 30318

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
02/21/2020 02:43:57 PM