DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Nancy Konnerth
Executive Director
Regulatory Affairs Advertising/Labeling
Harborside Financial Center Plaza 5, Suite 1900
Jersey City, NJ 07311

RE: NDA 022206
RAPAFLO® (silodosin) Capsule for oral use
MA # 242

Dear Ms. Konnerth:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the homepage of a website[1] (webpage) [Part No. 09505] for RAPAFLO® (silodosin) Capsule for oral use (Rapaflo) submitted by Watson Laboratories, Inc., (Watson)[2], now Actavis Laboratories UT, Inc. (Actavis), under cover of Form FDA 2253. The webpage is false or misleading because it makes unsubstantiated claims. Thus, the webpage misbrands Rapaflo 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); 331(a). *See* 21 CFR 202.1(e)(6)(i).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Rapaflo.[3] According to its FDA-approved product labeling (PI):

> RAPAFLO, a selective alpha-1 adrenergic receptor antagonist, is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). RAPAFLO is not indicated for the treatment of hypertension.

Rapaflo is contraindicated in patients with severe renal impairment, severe hepatic impairment, concomitant administration with strong cytochrome P450 3A4 (CYP3A4) inhibitors, or history of hypersensitivity to silodosin or any of the ingredients of Rapaflo. The PI also includes warnings and precautions regarding the risks of orthostatic effects, moderate renal impairment, pharmacodynamic drug-drug interactions, carcinoma of the prostate, intraoperative floppy iris syndrome, and laboratory test interactions. The most common adverse reactions associated with Rapaflo during clinical trials were retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion.

[1] Rapaflo homepage at http://www.rapaflo.com/hcp/default.aspx (last accessed May 19, 2015).
[2] In 2013, Watson Laboratories, Inc., a wholly owned subsidiary of Actavis, plc, officially changed its name to Actavis Laboratories UT, Inc. (Actavis).
[3] 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.

Unsubstantiated Claims

The webpage contains the following claim and presentation (bolded emphasis in original; underlined emphasis added):

- "**BPH SYMPTOM RELIEF THAT <u>WORKS NIGHTS SO HE CAN WORK DAYS</u>**"
- Picture of a man walking to the bathroom from the bed at night.

The claim "works nights so he can work days," along with the picture of a man walking to the bathroom from the bed in the middle of the night, is misleading because the presentation implies that in addition to improving BPH symptoms, Rapaflo has also been shown to improve both sleep disturbance (i.e., quality of sleep) and work productivity. No references were cited in support of this implication. According to the CLINICAL STUDIES section of the PI, the effectiveness of Rapaflo for the treatment of BPH was evaluated in two 12-week, randomized, double-blind, placebo-controlled, multicenter studies. The primary efficacy assessment in these trials was the International Prostate Symptom Score (IPSS), a composite endpoint that evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. These studies did not measure the impact of treatment on *individual* symptoms, such as nocturia. Therefore, efficacy claims and presentations for Rapaflo that suggest improvement in one of the IPSS subscore symptoms (i.e. nocturia) are not supported by substantial evidence. Moreover, the pivotal studies did not evaluate the impact of Rapaflo on quality of sleep or work productivity. Claims and presentations suggesting treatment benefits on nocturia, sleep disturbance, and work productivity must be supported by substantial evidence as demonstrated by adequate and well-controlled studies using well-developed instruments that can validly and reliably measure these specific individual concepts. If you have data to support this presentation, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons described above, the webpage misbrands Rapaflo within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a) & (n); 331(a). *See* 21 CFR 202.1(e)(6)(i).

OPDP requests that Actavis immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before June 2, 2015 stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Rapaflo 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 # 242 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 promotional materials for Rapaflo comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jina Kwak, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Twyla Thompson, Pharm.D., RAC
Acting Deputy Division Director
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINA KWAK
05/19/2015

TWYLA N THOMPSON
05/19/2015