DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

John Driscoll
Senior Manager, Regulatory Affairs
Forest Laboratories, Inc.
Harborside Financial Center Plaza 5, 24th Floor
Jersey City, NJ 07311

RE: NDA # 022256
Savella (milnacipran HCl) Tablets
MACMIS # 19038

Dear Mr. Driscoll,

This letter notifies Forest Laboratories, Inc. (Forest) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by a Forest sales representative on May 12, 2010, to a healthcare professional, regarding its drug, Savella (milnacipran HCl) Tablets (Savella), submitted on September 10, 2010 as a complaint to the DDMAC Bad Ad Program. The sales representative's statements are false or misleading because they promote unapproved uses for Savella, make unsubstantiated superiority and mechanism of action claims about the drug, and minimize the serious risks associated with Savella. Thus, this promotional activity misbrands Savella in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(f)(1) & (n), and FDA implementing regulations. *See* 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(i); & (e)(6)(i), (ii) & (vii).

Background

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI)[1] for Savella:

> Savella is indicated for the management of fibromyalgia.
> Savella is not approved for use in pediatric patients.

The PI for Savella includes a Boxed Warning regarding the increased risk of suicidality. Savella is also associated with a number of other serious risks, as reflected in its PI. Savella is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) due to serious and sometimes fatal reactions, and in patients with uncontrolled narrow-angle glaucoma. Warnings and Precautions associated with the use of Savella include the following: serotonin

[1] At the time of this violative action, the approved PI (and the version referred to within this letter) for Savella was the version dated February 1, 2010. Although not relevant to the issues cited in this letter, the most recent version of the Savella PI was approved on May 17, 2010.

syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, effects on blood pressure and heart rate, seizures, hepatotoxicity, withdrawal symptoms following discontinuation, hyponatremia, abnormal bleeding, activation of mania, effects on urethral resistance and micturation, use in patients with controlled narrow-angle glaucoma, and concomitant use with alcohol. The PI for Savella also includes information regarding several clinically important interactions with other drugs and use in pregnancy. In the placebo-controlled fibromyalgia patient trials the most frequently occurring adverse reaction in clinical trials was nausea. The most common adverse reactions (incidence ≥ 5% and twice placebo) in patients treated with Savella were constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension.

In addition, the Clinical Pharmacology section of the Savella PI states, "The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown."

Promotion of Unapproved Uses

On Wednesday, May 12, 2010, at approximately 1:15 p.m., a sales representative from Forest made an unsolicited sales call to a physician at his office. During this sales call, the sales representative stated that Savella is approved for fibromyalgia. The sales representative further stated that Savella is useful in back pain and mood disorder, because it concurrently elevates mood and relieves depression. The sales representative also pointed out that Savella is approved for depression in Europe. These representations were not made in response to a request for such information by the physician.

FDA is not aware of any substantial evidence or substantial clinical experience supporting the use of Savella for back pain, mood disorder, or depression. According to its PI, Savella is only indicated for the management of fibromyalgia. Therefore, the oral statements made by the sales representative misleadingly suggest new "intended uses" for Savella. Because the PI for Savella lacks adequate directions for these uses, the drug is therefore misbranded.

Unsubstantiated Superiority Claims/Minimization of Risk

During the May 12, 2010, sales call, the sales representative stated that Savella has a 3:1 affinity for norepinephrine reuptake inhibition and it is this action that makes it a better analgesic than Cymbalta. Although, we acknowledge that Savella inhibits norepinephrine uptake with approximately 3-fold higher potency in vitro than serotonin, this claim is misleading because it implies that Savella is clinically superior (i.e., more effective) to Cymbalta because of its increased affinity for norepinephrine reuptake inhibition in vitro. Pre-clinical in vitro data demonstrating Savella's increased affinity for norepinephrine reuptake inhibition does not constitute substantial evidence to support claims implying that Savella is more effective that Cymbalta.

The sales representative also stated that Savella is less sedating and does not result in peripheral edema and/or as much weight gain compared to Lyrica. This claim is misleading because it implies that Savella is clinically superior (i.e., safer) to Lyrica. DDMAC is not aware of **any** adequate and well-controlled, head-to-head trials comparing the incidence of

sedation, peripheral edema, or weight gain of Savella versus Lyrica. If you have any evidence to support such claims, please submit them to FDA for review.

Furthermore, the overall impression of the presentation minimizes the serious risks associated with Savella. Specifically, the sales representative's statement comparing the safety of Savella versus Lyrica and complete failure to mention **any** of the most serious and most common risks associated with the use of Savella suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. The presentation is particularly concerning given that the PI for Savella includes a number of serious risks, including a Boxed Warning regarding suicidality.

Unsubstantiated Mechanism of Action Claim

The sales representative also stated that, the increase in spinal cord norepinephrine provides analgesia for Savella and this is the mechanism of action that should be targeted as the goal for use of centrally acting analgesics. This statement is misleading because it implies a greater degree of certainty about the mechanism of action of Savella than is supported by substantial evidence or substantial clinical experience. As noted in the background section, the exact mechanism of the central pain inhibitory action of Savella and its ability to improve the symptoms of fibromyalgia in humans are unknown.

Conclusion and Requested Action

For the reasons discussed above, the oral statements made by the Forest representative misbrand Savella in violation of the Act, 21 U.S.C. 352(f)(1) & (n), and FDA implementing regulations. *See* 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(i); & (e)(6)(i), (ii) & (vii).

DDMAC requests that Forest immediately cease violative promotional activities for Savella such as those described above. Please submit a written response to this letter on or before May 12, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Savella that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444.

In all future correspondence regarding this matter, please refer to MACMIS #19038 in addition to the NDA number. We remind 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 Savella comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Mathilda Fienkeng, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

MATHILDA K FIENKENG
04/28/2011