DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Janet A. Lorenz, D.V.M., Manager
Medical/Regulatory Advertising & Promotion Group
Takeda Pharmaceuticals North America, Inc.
One Takeda Parkway
Deerfield, IL 60015

RE: NDA #21-782
Rozerem™ (ramelteon) Tablets
MACMIS #14700

Dear Dr. Lorenz:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a 10-second direct-to-consumer (DTC) television advertisement (TV ad) for Rozerem (ramelteon) Tablets (Rozerem) disseminated by Takeda Pharmaceuticals North America, Inc. (Takeda). While reminder ads are exempt from the requirement to disclose information relating to risks and effectiveness, for the reasons set forth below, we have determined that your TV ad is not an appropriate reminder ad. As such, the failure of the TV ad to disclose the drug's indication, the failure to include information relating to the major side effects, and the failure to make adequate provision for dissemination of the FDA-approved labeling, as required by 21 C.F.R. §§ 202.1(e)(1) & (3), thus misbrands Rozerem in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(n). In addition, the TV ad was not submitted to FDA under cover of Form 2253, as required by 21 CFR § 314.81(b)(3)(i).

Background

According to the FDA-approved product labeling (PI), "ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset."

The PI also states that Rozerem is associated with several important risks, including the following (in pertinent part):

> **WARNINGS**
> Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM

during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine.

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS (relating to alcohol)
General . . .
Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Drug Interactions
Alcohol: . . . Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

PRECAUTIONS (relating to pediatric use)
Use in Adolescents and Children
ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans.

Pediatric Use
Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

In addition, the Information for Patients section within the Precautions states that patients should consult their health care provider if they experience one of the following reproductive system-related events: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Furthermore, the Adverse Reactions section of the PI states that Rozerem is associated with somnolence, fatigue, and dizziness.

Inappropriate Reminder Ad/Omission of Indication and Risk Information

"Reminder advertisements are those which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product." And, of particular importance here, "reminder advertisements shall contain . . . no representation or suggestion relating to the advertised drug product." See 21 CFR § 202.1(e)(2)(i).

Although the TV ad does not state the drug product's indication or recommended dose, the statements and images suggest that Rozerem is indicated for children. Specifically, the TV ad includes the following statements and corresponding visuals:

> "Rozerem would like to remind you that it's back to school season." (visuals include chalk board, school books, school bus, laptops, school-aged children with backpacks)
>
> Ask your doctor today if Rozerem is right for you." (product logo, collage of visuals noted above, and tagline, "Back to School")

The combination of these statements ("Back to School") and images of school-aged children and school-related objects suggest that Rozerem is indicated for and can be safely used in the pediatric population.

The presentation in the TV ad is especially concerning given that the PI for Rozerem includes the following Precaution regarding pediatric use: "Safety and effectiveness of ROZEREM in pediatric patients have not been established. **Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients**." (emphasis added) Furthermore, the PI for Rozerem includes a Precaution regarding its use in adolescents and children that states "ROZEREM has been associated with an effect on reproductive hormones in adults, e.g., decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans."

Because the ad is not a reminder ad, it must present the indication and information relating to the major side effects, and must make adequate provision for dissemination of the FDA-approved labeling. See 21 C.F.R. §§ 202.1(e)(1) & (3). The TV ad fails to include the specific indication for the drug (namely, treatment of insomnia) and the required risk information. The TV ad also fails to make adequate provision for dissemination of the FDA-approved labeling.

Failure to Submit Under Form 2253

FDA regulations require sponsors to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. See 21 CFR 314.81(b)(3)(i).

You did not submit the TV ad to FDA under cover of Form 2253 as required by 21 CFR § 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the TV ad misbrands Rozerem under section 502(n) of the Act, 21 U.S.C. § 352(n). In addition, the reminder ad was not submitted to FDA under cover of Form 2253, as required by 21 CFR §314.81(b)(3)(i).

DDMAC requests that Takeda immediately cease the dissemination of violative promotional materials for Rozerem such as those described above. Please submit a written response to this letter on or before March 19, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Rozerem 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, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14700 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 Rozerem comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Carrie Newcomer, PharmD
Consumer Promotion Analyst
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/

Carrie Newcomer

3/5/2007 12:31:03 PM