DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 12 2000

TRANSMITTED VIA FACSIMILE

Binita Kwankin
Senior Regulatory Products Manager
TAP Pharmaceutical Products, Inc.
2355 Waukegan Road
Deerfield, Illinois 60015

RE: NDA #21-118
Uprima (apomorphine HCl tablets) sublingual
MACMIS ID #8899

Dear Ms. Kwankin:

As part of its routine monitoring an surveillance activities, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a press release for Uprima (apomorphine HCl tablets), disseminated by TAP Pharmaceutical Products, Inc. (TAP), that is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and applicable regulations. DDMAC specifically refers to your press release issued on April 10, 2000, entitled "FDA ADVISORY COMMITTEE RECOMMENDS APPROVAL OF UPRIMA (APOMORPHINE HCl TABLETS) SUBLINGUAL FOR THE TREATMENT OF ERECTILE DYSFUNCTION." This press release is considered promotional labeling for Uprima and is in violation of the Act for the following reasons.

Omission of Material Facts

"The most commonly reported side effect was nausea. Of the nausea reported in the NDA clinical studies, most incidences were mild to moderate in severity."

Promotional materials are in violation of the Act if they fail to reveal facts material in light of representations made about the product. The two statements above are represent the full extent of risk information about Uprima in your press release. You fail to disclose, however, material facts relating to significant and potentially life-threatening risks associated with Uprima that were presented at the Advisory Committee meeting. Specifically, syncope and severe hypotension were seen in some patients taking Uprima in clinical trials. These serious adverse events prompted the Committee to voice serious concerns about Uprima's safety profile. For example one Committee member, a cardiologist, stated "There will be some people who will probably lose their lives because they pass out at the top of the stairs or operating a car."

"The committee suggested some cautionary recommendations for labeling. In addition, the committee advised that educational materials be provided to patient at the point of care."

The Committee recommended that the labeling for Uprima include contraindications for use with concomitant ingestion of alcohol and in patients taking nitrate therapy. The Committee also recommended a boxed warning describing vaso-vagal events and the potential for syncope and cardiovascular compromise. These material facts are also omitted from your press release.

Pre-Approval Promotion

"New class of Erectile Dysfunction (ED) therapy may benefit millions of men with ED."

"UPRIMA could offer several benefits for patients suffering from ED....data suggest that UPRIMA is safe and effective in men with varying severities of ED."

"...we feel that UPRIMA would greatly enhance the therapeutic options of millions of men with ED."

Section 21 CFR 312.7 states, among other things, that an investigational new drug may not be promoted as being safe or effective for the uses under investigation. Your press release is violative because it includes claims, representations, and conclusions concerning the safety and efficacy of Uprima, an investigational new drug.

In order to address these objections, DDMAC recommends that TAP take the following actions:

1. Immediately discontinue the use of this, and all other promotional materials and activities for Uprima that contain the same or similar violations.

2. Provide to DDMAC, in writing, your intent to comply with #1 above. Your response should be received by April 26, 2000.

3. This response should include a list of all similarly violative promotional materials and your method for discontinuing their use.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8899 in addition to the NDA number.

Sincerely,

/S/

Mark W. Askine, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

The News

FDA ADVISORY COMMITTEE RECOMMENDS APPROVAL OF UPRIMA® (APOMORPHINE HCl TABLETS) SUBLINGUAL FOR TREATMENMT OF ERECTILE DYSFUNCTION

— New class of Erectile Dysfunction (ED) therapy may benefit millions of men with ED —

Lake Forest, Illinois, April 10, 2000 – TAP Pharmaceutical Products Inc. announced today that the U.S. Food and Drug Administration's Urology Subcommittee of the Advisory Committee for Reproductive Health Drugs recommended approval for UPRIMA® (apomorphine HCl tablets) sublingual for the treatment of erectile dysfunction (ED). The committee's favorable recommendation will be considered by the FDA in its final review of the New Drug Application (NDA) for UPRIMA.

The committee suggested some cautionary recommendations for labeling. In addition, the committee advised that education materials be provided to patients at the point of care.

If approved, UPRIMA will be the first centrally acting oral ED treatment available to patients. "UPRIMA could offer several benefits for patients suffering from ED," says John Mulhall, MD, director of the Center for Male Sexual Health at Loyola University Chicago and an investigator in the UPRIMA clinical trials. "In clinical trials, it worked quickly, in as fast as 10 minutes, with a median response time of 16-19 minutes. With its sublingual route of administration, it is not expected that UPRIMA will interact with food. Finally, data suggest that UPRIMA is safe and effective in men with varying severities of ED."

TAP submitted an NDA for UPRIMA on July 1, 1999, for 2 mg, 3 mg and 4 mg doses. The NDA was based on data from 27 clinical studies in 3,035 men.

"We are extremely encouraged by the recommendation, as we feel that UPRIMA would greatly enhance the therapeutic options of millions of men with ED. Further, UPRIMA will be a significant addition to our product portfolio, allowing us to further build on our experience in urology and primary care," says Thomas Watkins, president of TAP Pharmaceutical Products Inc.

Erectile dysfunction is defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual intercourse. Approximately 30 million American men suffer from some form of erectile dysfunction.

In clinical studies, UPRIMA was administered to men with organic, psychogenic, or mixed etiology erectile dysfunction, and was evaluated for its ability to produce an erection firm enough for intercourse. Initial studies with UPRIMA included patients with controlled hypertension and diabetes (type I and type II). TAP has also evaluated UPRIMA following nerve-sparing radical prostatectomy.

In addition, a unique aspect of TAP's clinical studies was the assessment of patients' partners for satisfaction. This assessment showed corroboration of findings from the patient.

The most commonly reported side effect was nausea. Of the nausea reported in the NDA clinical studies, most incidences were mild to moderate in severity.

Apomorphine HCl tablets sublingual for male erectile dysfunction was licensed from Pentech Pharmaceuticals, Inc. of Buffalo Grove, Illinois.

TAP Pharmaceutical Products Inc. is a joint venture between Abbott Laboratories, headquartered in Abbott Park, Illinois, and Takeda Chemical Industries, Ltd. of Osaka, Japan. Abbott and Takeda will jointly develop and co-market apomorphine in countries outside of the United States and Canada. TAP also markets Lupron Depot® (leuprolide acetate for depot suspension) for the palliative treatment of advanced prostate cancer, management of endometriosis, anemia caused by uterine fibroids in combination with iron, and central precocious puberty, and PREVACID® (lansoprazole) for the treatment of various acid-related disorders including gastroesophageal reflux disease (GERD) and ulcers. TAP has also submitted a NDA to the FDA for the cephalosporin antibiotic SPECTRACEF™ (cefditoren pivoxil).

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