DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Howard B. Rosen
President
Alza Corporation
1900 Charleston Rd.
Mountain View, CA 94039-7210

Re: NDA # 21-088
Viadur® (leuprolide acetate implant)
MACMIS ID # 12538

WARNING LETTER

Dear Mr. Rosen:

This letter notifies Alza Corporation (Alza), and, by copy, Johnson & Johnson Pharmaceuticals, the parent company of Alza, and Bayer Pharmaceuticals Corporation (Bayer), the distributor and marketer of Viadur® (leuprolide acetate implant) on behalf of Alza, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a "patient disc puzzle" (VV0911103) for Viadur submitted by Bayer under cover of Form FDA 2253 that is false or misleading because it omits material risk information about Viadur, and thus misbrands the drug in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n). In addition, it appears that the FDA-approved product labeling (PI) for Viadur did not accompany the patient disc puzzle, in violation of 21 CFR § 201.100(d). The patient disc puzzle thus suggests that Viadur, which is indicated for the palliative treatment of advanced prostate cancer, is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the PI for the drug, "Viadur® (leuprolide acetate implant) is a sterile nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate . . . ." The Indications and Usage section of the PI for Viadur states:

> Viadur® is indicated in the palliative treatment of advanced prostate cancer.

The Contraindications section of the PI states:

> 1. Viadur® is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs, or any of the components in Viadur®. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.

> 2. Viadur® is contraindicated in women and in pediatric patients and was not studied in women or children. Moreover, leuprolide acetate can cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

The Warnings section of the PI states:

> Viadur®, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction (see PRECAUTIONS).
>
> Cases of ureteral obstruction and spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LH-RH agonists.
>
> If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

Viadur is also associated with many other risks, as described in the Adverse Reactions section of the PI. The following possibly or probably related systemic adverse events were reported with the use of Viadur in clinical trials: vasodilation (hot flashes) (67.9%), asthenia (7.6%), gynecomastia/breast enlargement (6.9%), depression (5.3%), and sweating (5.3%). According to the Adverse Reactions section: "Local reactions after initial insertion of a single implant included bruising (34.6%) and burning (5.6%)."

Omission of Risk Information

The patient disc puzzle includes the brand name for Viadur and states:

- "For the treatment of symptoms of advanced prostate cancer"
- "Hey, you got a choice 3, 4, or 12 injections a year or a 1-year implant"
- "The only once-a-year hormone therapy for advanced prostate cancer"

The patient disc puzzle includes none of the risk information discussed above. The statement "Please see patient safety information at viadur.com or call 1-866-2VIADUR" which appears on the patient disc puzzle, is not sufficient to disclose information on the risks associated with Viadur.

Failure to Provide Adequate Directions for Use

It appears that the PI was not included with the patient disc puzzle. The statement "Please see patient safety information at viadur.com or call 1-866-2VIADUR" does not substitute for the PI.

Conclusion and Requested Action

The patient disc puzzle is false or misleading because it omits material risk information for Viadur, and thus misbrands the drug in violation of the Act. 21 U.S.C. §§ 352(a) and 321(n). In addition, it appears that Viadur is misbranded under 21 U.S.C. § 352(f) because the PI for Viadur did not accompany the patient disc puzzle, as required by 21 CFR § 201.100(d).

DDMAC requests that Alza and its distributor Bayer immediately cease the dissemination of violative promotional materials for Viadur such as those described above. Please submit a written response to this letter on or before October 5, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Viadur such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8-B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12538 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 Viadur comply with each applicable requirement of the 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}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

cc: Johnson & Johnson Pharmaceuticals
Attention: William C. Weldon
CEO

Bayer Pharmaceuticals Corporation
Attention: Attila Molnar
President and CEO

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

/s/

Thomas Abrams

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