DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

March 21, 1990

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Henry Pietraszek
President Takeda-Abbott
Research
& Development
Abbott Park, IL
60064

Notice of Adverse Findings

Dear Mr. Pietraszek:

Please refer to the TAP promotional campaign for Lupron (leuprolide acetate). We have contacted your firm previously in regard to your promotion of unapproved uses of this product.

We have recently received through industry complaints information indicating that your firm has undertaken a deliberate campaign to promote this product for a wide range of unapproved uses. Your promotion of Lupron for unapproved uses misbrands the product under Section 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

Physician-Directed Promotion of Unapproved Uses for Lupron

1. We have been informed that your firm's promotional campaign for Lupron has involved a large number of detail representative visits to obstetricians and gynecologists. Lupron's sole approved use, palliative treatment of advanced prostatic cancer, is not within the usual range of activities undertaken by OB/GYN specialists. However, the unapproved uses of Lupron previously promoted by your firm would be within the usual practice of OB/GYN specialists. These physician visits by your firm strongly suggest promotion of unapproved uses.

2. Independent sources verify numerous OB/GYN visits by your sales force, as well as specific efforts during those visits to promote administration of Lupron for unapproved uses.
3. We have received printed materials further establishing the specific promotion of these unapproved uses by your sales force. We have recently received the business card of one of your firm's sales representatives stamped with the statements "Lupron Depot once-a-month GnRH Agonist" and "NEW TREATMENT FOR: ENDOMETRIOSIS FIBROIDS." Stapled to this card was a printed piece entitled Obstetrical & Gynecological Survey, dated May 1989. This piece constitutes promotional labeling for Lupron, based upon its dissemination by your firm's sales representatives. Your firm is not listed as having funded printing of this publication, but we must assume that TAP funded this publication on the basis of the journal's focus upon unapproved uses of GnRH agonists. In addition, an

article by an employee of your firm discusses various dosage forms of Lupron available and under development at that time.

Presentation of this information in the context of discussions of unapproved uses of your product constitutes promotion of these unapproved uses of your product, particularly when the piece is subject to strict regulation as promotional labeling as disseminated by your sales force. Your firm's dissemination of this piece therefore constitutes promotion of the unapproved uses discussed.

4. We have received a copy of a printed piece entitled "The TAP Difference...Services provided by a TAP Representative." This piece details the extensive services to be provided by a TAP sales representative to facilitate administration of Lupron for gynecologic uses. The name of a TAP representative appears at the bottom of the page, and this name is different from the name on the above business card. This evidence further reflects systematic promotion of gynecologic uses of Lupron by your sales force in their visits to OB/GYN specialists.

5. Representatives of your firm have also been involved in dissemination of numerous printed promotional labeling pieces related to unapproved uses of Lupron, such as a listing of physicians that administer Lupron for unapproved uses. Your firm's detail representatives have also allegedly disseminated reprints discussing unapproved uses of Lupron. Your firm's dissemination of the above promotional labeling pieces constitutes promotion of unapproved uses of Lupron.

6. A brochure entitled "Innovators in GnRH Agonist Research" has been printed and disseminated by your firm. This brochure provides for prominent mention of Lupron, and includes a business reply card which avails the sender of extensive information regarding numerous unapproved uses of Lupron merely by checking appropriate boxes and mailing the card. For your firm to encourage such requests for information regarding unapproved uses by this means constitutes promotion of those unapproved uses.

7. The complainant has provided numerous photos allegedly taken at a physician specialty association meeting during late 1989. Those photos show a TAP Pharmaceuticals exhibit presenting claims not conforming to our agreement of November 8, 1988 regarding such exhibits.

8. Your firm submitted promotional materials for Lupron under the requirements of 21 CFR 314.81 (b)(3) on November 3, 1989. Included in that submission is a promotional labeling piece entitled "The American Fertility Society Revised Classification of Endometriosis," dissemination of which constitutes promotion of unapproved uses for Lupron.

Patient-Directed Promotion of Unapproved Uses of Lupron

In your firm's November 30, 1989 letter, you informed us that you would comply with our request that you halt distribution of patient information brochures discussing unapproved uses of Lupron. These brochures were prepared by Reproductive Education and Choices for Health (REACH) on behalf of your firm. On December 12, 1989, a

representative of your firm met with our division to discuss these scientific/educational activities for Lupron.

As you were informed in that meeting, we described any involvement of a firm in public discussions of unapproved uses of their products as an extremely sensitive issue that must be approached with utmost concern for the quality, objectivity, and balance of those discussions. Activities should not be unduly devoted to superiority or unapproved uses of the sponsor's products, and any such discussions should clearly avoid encouraging administration of the sponsor's products for those unapproved uses. We also discussed agency consideration of factors such as the degree and nature of direct industry (particularly sales and marketing) participation, quality of the medium of the activity, and peer review.

Your firm described your efforts to ensure the quality of materials generated under the REACH program, but acknowledged that those efforts did not succeed in that regard.

In our meeting, we offered numerous objections to them:

1. They claim that Lupron is safe and effective, and actively promote its administration in a range of indications for which Lupron is not approved and apparently has not been adequately demonstrated to be safe and effective.

2. The brochures do not acknowledge the potential for discovery of significant hazards or efficacy limitations as you continue to characterize Lupron’s possible usefulness for these indications.

3. They focus upon administration of Lupron for these unapproved uses to an excessive degree, rather than uniformly covering the array of available treatment options for these medical conditions.

4. The materials were directed to consumers. We are strongly opposed to any involvement of a firm in creation, dissemination, or funding of promotional/scientific/ educational activities directed to consumers when those activities involve discussion of unapproved uses of the firm's products. We are even more concerned when the activity overtly promotes administration of the sponsor's product for the unapproved use, as in this case.

5. We were also concerned by the direct dissemination of the brochures by patient groups as well as by physicians who had elected to administer the drug for these unapproved uses. A patient-directed brochure discussing an unapproved use is objectionable when disseminated by a physician, because of the potential that it may encourage the physician to administer the drug for that unapproved use. If the brochure is disseminated directly by a patient group outside of the physician-patient relationship, it only creates demand for an unproven therapy. You were thus advised at that time to redirect your scientific/educational efforts (if any) to appropriate physician-directed activities.

6. We informed you that we had received complaints regarding this

program.

Your firm was involved in direct promotion of these unapproved uses to physicians at the time of our meeting, but elected not to inform us of such activities at that time. We have since been informed that your firm has continued to promote these unapproved uses to physicians on an ongoing basis.

We request the following actions of your firm:

1. Immediately suspend all public activities (promotional, scientific/educational, or otherwise) by or on behalf of your firm that promote or discuss administration) of Lupron or GnRH agonists for unapproved uses.

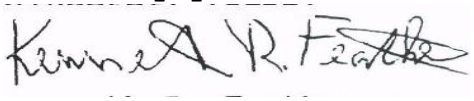
2. Provide a statement of your agreement to provide for agency preclearance of all promotional activities for Lupron until further notice.

3. Provide a written agreement to submit to this office a summary of information regarding any future scientific/ educational activities for Lupron until further notice. This submission should be received by the Division of Drug Advertising and Labeling not less than five (5) working days before those activities occur or are disseminated. We will be prepared to prohibit these activities, regardless of the resources devoted to them by your firm, if they discuss administration of Lupron or GnRH agonists for unapproved uses.

4. Provide a written description of your firm's direct or indirect participation in, or funding of, all previous presentations of unapproved uses of Lupron, including traditional promotional activities, press releases, media appearances, formulary-related activities, and sole-sponsored publications, and/or any other consumer or physician-directed activities.

Please inform us, in writing, of steps taken as requested above. Your response within ten (10) working days of your receipt of this letter is requested. If you do not comply with these requests, we are prepared to recommend initiation of adverse regulatory action against your firm.

Sincerely yours,



Kenneth R. Feather
Acting Director
Division of Drug Advertising
and Labeling Office of
Drug Standards

cc: Dean P. Sundberg
Director, Regulatory Affairs