DEPARTMENT OF HEALTH AND HUMAN SERVICES

August 21, 2001

Public Health Service
Food and Drug Administration
Rockville MD 20857

The Honorable Sue Tucker
Chair, Human Services and
Elderly Affairs Massachusetts
Senate State House Boston,
Massachusetts 02133-1053

Dear Senator Tucker:

This is in final response to your letter to Melinda K. Plaisier. Associate Commissioner for Legislative Affairs dated May 17, 2001, seeking the comments of the Food and Drug Administration (FDA) on several letters, emails and selected portions of a legal brief submitted by Lynne Millican to multiple parties outside the FDA concerning the drug Lupron and a review of the information provided to you by a Lxx Xxx concerning health problems associated with use of this product.

Requests for information from state and local officials are normally handled outside of the normal FDA-FOIA system and thus, your letter was referred to this office for appropriate follow up and final response.

As I noted in my acknowledgement letter dated June 21st, I had asked the medical staff in FDA's Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER) for their input. I have been provided with the following comments from the two CDER offices who reviewed the issues raised.

I would like to point out initially that the materials submitted dealt with the following issues:

1) Claimed billing fraud related to Lupron, TAP Pharmaceutical and "physicians in several states"
2) Off-label use of Lupron to treat infertility
3) Lack of informed consent regarding the risks of Lupron when used off-label in a clinical practice setting for non-research purposes
4) Redaction procedures by FOIA
5) Claims about postmarketing safety issues related to off-label use of Lupron
6) A lawsuit filed by Ms. Millican in 1992

Several of the above noted issues (#1, #2, #3) are not regulated by the FDA.

The Director, Division of Reproductive & Urologic Drug Products (DRUDP), CDER has provided me with the following comments on issues that were relevant to her office's review jurisdiction.

> Lupron (a gonadotropin-releasing hormone analogue [GnRH-a]) is approved for the treatment of gynecologic disorders including treatment of endometriosis and preoperative hematologic improvement in anemia associated with uterine leiomyomata (uterine

fibroids). Lupron is not approved for the treatment of infertility or in vitro fertilization, and use of the product for this condition is considered off-label use by the FDA. The following comments address specific statements made by Ms. Millican as contained in her correspondences to other parties:

In the letter dated August 18, 2000 from Ms. Millican addressed to the U.S. Attorney's office, the statement is made that, "Published medical reports have noted the occurrence of abnormal pregnancy outcomes associated with the use of Lupron (43.5% in one 1996 study [Fertility and Sterility, Abstract P-34, Program Supplement. April 1996, p. a27]). The "abnormal pregnancy outcomes" reported in the above captioned abstract refer to the outcomes of 10 of 23 patients conceived with Lupron over a period of 3 years. The "abnormal pregnancy outcomes" were 2 tubal pregnancies, 2 chemical pregnancies, and 6 miscarriages. Tubal pregnancies, chemical pregnancies and miscarriages also occur in women who are not taking any drug. Therefore, a causal relationship between the occurrence of the events reported above and Lupron use cannot be definitively established.

The referenced 1999 study (Human Reproduction, 1999, 14(10):2656) is one conducted on the long-term follow-up of children born after inadvertent administration of GnRH-a in early pregnancy. Six children from 6 pregnancies, exposed to a long-acting gonadotropin agonist in early pregnancy were compared to control groups of children born to matched women undergoing in-vitro fertilization and children born after spontaneous pregnancies. One of the infants born after exposure to GnRH-a had a soft cleft palate that was operated successfully at the age of 14 months. Formal psychological examinations were within normal range in all children, both in the study and control groups. However, various neurodevelopmental abnormalities were observed in 4 of the 6 children in the study group compared with one child in the control group. The authors were not familiar with any underlying mechanism that might explain the possible relationship between the exposure to GnRH-a during early pregnancy and late neurodevelopmental abnormalities. As a single, stand-alone study, this study is of limited clinical importance.

Over 340 pregnancies have been reported in the medical literature in association with the administration of GnRH-a. The incidence of abortion and other pregnancy difficulties does not appear to be increased in association with GnRH-a treatment. The prevalence of abnormalities in the neonates is not different from that expected in the general population. There is one case report with a follow-up of 12 months, documenting normal development. An additional case report describes a full-term, healthy neonate with normal development. Another study of 25 cases, all older than 3 years of age, reported normal development in all cases, but this was not validated by either physical or neurological examination, or by appropriate psychological testing.

DRUDP is unaware of any evidence of pituitary adenoma development in humans following exposure to Lupron. Further assessment of this issue should be referred to the Office of Postmarketing Drug Risk Assessment (OPDRA).

Regarding the hormonal profile of a women on Lupron versus that associated with menopause, estradiol levels decline to menopausal levels after several weeks of Lupron therapy causing side effects related to hypoestrogenism, including hot flashes, vaginal dryness, and headaches. These symptoms are the same as those that occur with natural menopause. While pituitary gonadotropins are suppressed after several weeks of Lurpon therapy, such suppression is expected by virtue of the mechanism of action of the drug.

The OPDRA at the FDA monitors post-marketing reports of adverse events following use of approved drug products. If an increase in reporting of specific adverse events is found, the review division is notified. DRUDP has received no such notification *from* OPDRA regarding an increase in abnormal pregnancy outcomes following Lupron exposure.

DRUDP has performed an evaluation of all postmarketirig spontaneous reports of adverse events associated with Lupron and at this point there is not a signal related to the concerns expressed in the letters contained in the consult (i.e., documents accompanying incoming request from Senator Tucker)..

The Office of Postmarketing Drug Risk Assessment (OPDRA), CDER has also reviewed the

materials submitted and have provided me with the following comments:

DRUG TRADE NAME: Lupron Depot 3.75 mg., Lupron 11.25 ing. 3-month Drug (Est): Leuprolide Acetate NDA #20-011, 20-708, 19-943

SPONSOR: Tap Pharmaceutics

EVENT: Abnormal Pregnancy Outcomes

RELEVANT PRODUCT LABELING: The CONTRAINDICATIONS Section of Lupron states the following ... Lupron Depot is contraindicated in women who are or may become pregnant while receiving the drug. Lupron Depot may cause fetal harm when administered to a pregnant woman.

The PRECAUTIONS, Pregnancy, Teratogenic Effects Section lists Lupron as a pregnancy Category *X* drug. The FDA defines Pregnancy Category X drugs as those that: "Studies in animals or humans demonstrate fetal abnormalities or adverse reaction reports indicate evidence of fetal risk. The risk of use in a pregnant woman clearly outweighs any possible benefit."

Search Results: Of all of the leuprolide acetate reports received via the MedWatch system since 1985 (date of approval of the first leuprolide acetate NDA), approximately 0.3% of the reports were for the adverse event terms "complications of maternal exposure So therapeutic drugs" and "congenital abnormality." With the exception of the term "abortion NOS" (0.67%), these two terms represent the highest number of reports received for leuprolide acetate under the "Pregnancy, Puerperium, & Perinatal Conditions" and "Congenital and Familial/Genetic Disorders" search categories. The Adverse Event Reporting System (AERS) search included all reports received by the FDA up through August 16, 2001 and represents all reports received for the drug (i.e., for approved indications and off label use). It should be noted that these percentages may include duplicate and follow-up reports. Therefore, the actual number of cases received for these two terms may in fact be less than 0.3%.

Summary: MedWatch reports have been received for both the approved indications (prostate cancer and endometriosis) and the off label use of leuprolide acetate. Although leuprolide acetate is a Pregnancy Category X drug, it is currently being used off label for *in vitro* fertilization (1VF). Several reasons make it difficult to ascertain causality between the off label use of leuprolide acetate and abnormal pregnancy outcomes.

- Patients experiencing 1VF treatment frequently receive combination drug therapy. These other drugs may be confounding factors in the determination of causality.

- Factors that may contribute to congenital anomaly outcomes such as obstetrical history and family genetic history are usually not captured on the MedWatch form. Maternal age may also be a factor. The MedWatch form requests the age of the patient; however, when the congenital anomaly reports have the infant's age, they often do not report the mother's age.

^ Prior and/or pertinent adverse maternal reproductive history is usually not reported. For example, a history of spontaneous abortions and/or miscarriages may be a contributing factor in a patient who has experienced a similar pregnancy outcome while being treated with leuprolide acetate for IVF.

^ Most reports associated with the off label IVF use of leuprolide acetate will come from patients or their respective agents (e.g., family members, lawyers, etc). These "direct reports" are the smallest number of reports received by the FDA.

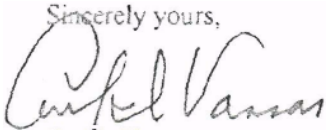
Additionally, the limitations of a spontaneous reporting system may also contribute to the difficulty in ascertaining causality. The Adverse Event Reporting System (AERS) contains over 2 million records of adverse events for marketed products. These data have been captured since 1969. The main utility of a spontaneous reporting system (such as AERS) is to provide signals of potential drug safety issues. Reporting of adverse events is a voluntary process for health care professionals in the U.S. Some factors that influence whether or not an event will be reported include recognition of the event as a possible adverse drug event, the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. Manufacturers are required by regulation to report to the FDA any adverse events obtained or otherwise received from any source (21 CFR 310.305, 314.80, 314.98). Currently, manufacturers submit over 90% of reports in AERS, and the remainder is submitted directly to the FDA via the MedWatch program. Manufacturers are also required to submit foreign adverse event cases that meet the regulatory criteria of "serious" and "'unexpected". A causality assessment is not a requirement to submit these reports to the FDA, so it should not be assumed that the drugs involved caused the reported events.

It should be noted that one report might contain more than one adverse event term. Additionally, these numbers may include some duplicate reporting and thus may not always be counts of unique patient cases.

Conclusion: OPDRA continues to monitor all adverse event reports received for leuprolide acetate. However, at this time the available postmarketing data do not provide a signal that "abnormal pregnancy outcome" reports have increased.

If you have any further questions on this issue, please let me know on (301) 827-2898,

Sincerely yours,



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