February 26, 1992

Food & Drug Administration Drug
Evaluation & Research Center

5600 Fischers Lane

Rockville, MD. 20857

Dear Drug Evaluation & Research Centers

Recently I contacted the Federal Information Center regarding questions about the use of the drug Lupron (Leuprolide Acetate), and was advised to contact your office.

Shortly after the FDA's approval of Lupron for use in treatment of endometriosis I contacted TAP and received copies of the two clinical trials that were conducted for such FDA approval. With reference to the study published in 'Fertility and Sterility' Vol. 54, No. 3, Sept 1990 I would like to comment on several factors.

Page 425 of this study states "Adverse events were reported by 29 (91%) of the Leuprolide Acetate patients ..." While I realize the definition of "event", I feel this is a significant number of women experiencing a drug induced aberration of normal bodily function. But more importantly, I draw your attention to the statement that "ONLY 7 Leuprolide Acetate patients reported (vasodi1ation)as severe". That figure represents 22% of the Lupron patient population - nearly one quarter of the Lupron patients experienced severe vasodi1ation. I find those numbers very significant. And it is common knowledge that women who go through the menopause have difficulty sleeping because of the interruption of sleep due to the hot flashes - yet insomnia is not mentioned as an "event".

While this clinical trial documents that nearly one quarter of the women experienced severe side effects of vasodilation, it does not appear to be at all clinically significant. How does the FDA view the fact that nearly one quarter of the women prescribed this drug have the potential to experience insomnia from this vasodi1ation, yet it is not c1inically significant?

In addition, to the best of my knowledge, only the depot suspension form of Lupron has been studied and FDA approved. From my own personal experience as well as contacts with many women who have experienced problems with this drug, it appears as if it is not the depot form that is being routinely prescribed, but the daily injections. The explanation that is given by the prescribing MD is universal: " there have been reports of severe side-effects with the depot form and if you should experience these it will take a solid month to eliminate these symptoms from your body therefore you are better off taking the daily injections". Why has only the depot form been approved if this is so, and are there studies done with the daily form of Lupron?

The remainder of my questions deal with the use of Lupron as an

ovulatory adjunct in an IVF *(In* Vitro Fertilization) cycle.

Through phone contact with the Boston FDA office, I have learned that Leuprolide Acetate is not approved for use in an IVF cycle. I do understand that since Lupron is approved by the FDA for use in prostate cancer and endometriosis, this then allows a doctor to prescribe the drug for any reason s/he sees fit. Are there any studies (past, present, or future) on the use of Lupron in an IVF cycle?

Why do IVF clinics not inform women that they are being prescribed and self administering an experimental drug? I understand it's approved for prostate cancer and endometriosis, but since it's not approved for use in an IVF cycle wouldn't it then be considered experimental?

When IVF clinics are asked if Lupron is experimental, the reply is "No". Some patients are required to sign an informed consent form before prescription and some clinics do not require such a form. Can you please explain the discrepancy to me?

Also, I amongst many others have some genuine concerns about the "information" that is being disseminated about the use of Lupron in an IVF cycle. We are told that "Lupron results in better quality and better quantity of eggs". Can the FDA inform me as to where this information might arise from? No one has been able to track down any studies done on the use of Lupron in an IVF cycle.

No one that I am aware of has participated in a clinical trial using Lupron in an IVF cycle, and TAP has informed me that no past, present, or future clinical trials have been done. Therefore, where is this information coming from? If no information has been gathered - how can patients be told a definitive statement if the facts are not known? And lastly, I would like to mention that there are an increasing number of women who are attempting an IVF cycle and are being told they can only cycle if they use Lupron. When there is objection from the patient about using Lupron, the woman is told if she does not use Lupron she will not be allowed to go through the IVF cycle. I know women who have had past successful IVF babies using an established medication protocol who wish to repeat IVF using the exact same drugs - but are denied that option and are told they must use Lupron. Why is this?

If you could please provide me with answers to these questions, I would be very appreciative. Any additional information you might have on this drug also would be helpful.

Thank you very much for your time and attention to this matter.

Sincerely,

Lynne Mi11ican