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U.S. Attorney's Office
Health Care Fraud Division
U.S. Court House
One Court House Way
Suite 9200
Boston, MA. 02210

Dear Health Care Fraud Division,

It is my understanding, based upon reports published in the Boston Globe on 4/12/00 and the Chicago Tribune on 4/26/00, that your office is investigating billing fraud involving the drug lupron (leuprolide acetate), lupron's manufacturer (Takeda-Abbott Pharmaceuticals [TAP]), and physicians in several states. I am writing to request an opportunity to meet with you to discuss serious matters involved in the marketing of lupron for the off-label use in fertility treatment, the detrimental effects of fetal exposure to lupron as reported in published medical literature, and other alarming issues involving lupron.

Briefly: the original patent for lupron was for "induc[ing] ovulation" (Patent # 3,914,412, 10/25/75), and Abbott Annual Reports for the years 1988 through 1992 state that "clinical trials for lupron's efficacy in infertility treatment and IVF [in vitro fertilization] are currently underway". However, while lupron has become "widely and routinely used in fertility treatment", the clinical trials which the manufacturer conducted for at least 5 years "have been discontinued" - and lupron has not gained and does not have FDA approval for the indication of fertility treatment and/or IVF. It is proprietary information as to whether these clinical trials were discontinued because of efficacy reasons, or safety reasons, or both reasons, or for other reasons.

Considered by the FDA as a pregnancy Category X drug (fetal risk outweighs benefit, and any woman who is or who may become pregnant should not take), lupron is being prescribed to hundreds of thousands of women attempting to conceive (without informed consent of its risks). 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]), and numerous reports raise the issue of a need for a registry to monitor the long-term effects of children conceived during or before exposure to lupron (a gonadotrophin-releasing hormone analogue [GnRHa]) and other GnRHa's.

Lupron, according to medical literature, is the most frequently prescribed GnRHa in fertility treatment, and has been used in gynecology and reproductive endocrinology for well over a decade. FDA documents from the prostate cancer approval, as well as published medical literature, evidence that the effects of daily and depot (monthly) lupron continue *weeks* and *months*, respectively, beyond the discontinuation of lupron. Since lupron is classified by the National Institutes of Health (NIH) and the Occupational Safety and Health Administration

(OSHA) as a "hazardous drug", why is this hazardous, pregnancy Category X drug marketed and prescribed for fertility treatment - which involves injecting lupron the month prior to and continuing up to within days of egg retrieval, embryo transfer, and implantation?

In 1999, the first study was conducted on the *long-term* follow-up of children born after inadvertent administration of GnRHa in early (undetected) pregnancy. In the six children studied, a major congenital malformation and four neurodevelopmental abnormalities, including epileptic disorder, attention deficit hyperactivity disorder, motor difficulties and speech difficulties, were seen. The conclusion was that "[t]his observation of neurodevelopmental abnormalities in four of six children in the study group justifies the need for long-term follow-up of more children previously exposed to GnRHa." (Human Reproduction, 1999;14(10):2656). In addition, a follow up letter published in response to this article stated that "[t]he need for long term follow-up possibly sponsored by GnRH-analogue producing pharmaceutical companies echoes the intuition of many clinicians." (Human Reproduction, 1999,15(6):1421).

According to published scientific, governmental, medical and/or pharmaceutical literature: lupron is classified as an "antineoplastic/*other*" yet is promoted as a "hormone" or "antineoplastic/hormone"; lupron was approved out of the FDA's Division of Biologics and *not* out of the FDA's Division of Drugs; lupron is classified by the California Environmental Protection Agency as a "reproductive toxicant" and a "developmental toxicant"; lupron is a "probe"; lupron is a teratogen; and lupron is a toxin. Healthcare professionals handling any hazardous drug, including lupron, who intend to conceive or father a child, are advised to *avoid handling* the hazardous drug (lupron) for a recommended 3 months *prior to conception* (American Hospital Formulary System, 1999 Revised Guidelines for the Handling of Hazardous and Cytotoxic Drugs). Yet healthy young fertility patients handle lupron and self-inject lupron *daily* into their bodies up to within days of conception, uninformed of any of the latter information. And these healthy young women are injecting lupron at a dose that far *exceeds* that used in the palliative treatment of terminal prostate cancer: terminal older men with cancer use 7.5 mg/month ... young healthy women use as much as 1 mg or more *per day*, for up to and beyond one *month*, for *each* fertility 'cycle'.

In addition, nurses working in various areas who administer the lupron depot injections for male and female approved and unapproved indications are *unaware* that, according to NIH and OSHA guidelines, the recommendations for healthcare workers handling and administering lupron involve the use of protective gear, including but not limited to, two pairs of chemotherapy gloves and a chemotherapy gown. The manufacturer of lupron advises that "no special handling or disposal precautions are necessary."

Moreover, FDA documents for the initial FDA approval for palliative treatment of prostate cancer contain a frightening and unacceptable level of redacted information (words, sentences, paragraphs, and pages [19 pages in just one instance]), including "toxicology data", among others. One sentence that was not redacted concerned the effects of lupron on rats, whereby all rats - at all doses - developed pituitary adenomas (tumors): the FDA documents state: "[t]here is no obvious reason to suggest that the same process [pituitary tumors] could not occur in humans." In addition, there are also serious problems within the alleged studies and data for the

indication of endometriosis. As just one example, TAP markets lupron as a "drug" that induces a "menopausal" state, and that lupron "reduces these hormones ["LH (leutenizing hormone) and FSH (follicle stimulating hormone)"] to the very low levels found after menopause" ... yet menopause is historically characterized and diagnosed by *high* levels of LH and FSH. The hormonal profile of a woman on lupron does not match the hormonal profile of menopause, but rather matches the hormonal profile of pituitary-hypothalamic disease. Medical literature refers to lupron as an "agent" that induces a "hypophysectomy" (excision or destruction of the pituitary), yet the patient is told it is a "hormone" that "causes menopause". And likewise, there are also problems within the approval for the indication of "anemia associated with fibroids". The lead investigator involved with the fibroid studies, Dr. Friedman, was subsequently found guilty of scientific misconduct for falsifying and fabricating 80% of data in 2 published lupron studies. In March 1995, in written testimony in support of MA. House 3477 (which proposes to mandate informed consent of risks of fertility treatment and lupron, among others), I cited Dr. Friedman's "manipulated figures" in yet a third published study.

Based upon years of researching the involved literature and relevant documents, I believe that the matters I wish to discuss with you involve issues affecting public safety as well as crimes against society. It is my understanding that the U.S. Attorneys Offices are investigating the fraudulent billing involved with lupron (and I can provide a little information here as well), but I am hoping that this investigation could also examine these other issues as well. While the focus of my concern involves matters other than "billing fraud", I hope to convey the pertinence of the fact that insurers, including Medicare, are bearing the financial cost of serious, acute and chronic, consequential medical problems as a direct result of the fraudulent misrepresentation of the alleged safety and mechanism(s) of action of this hazardous, biologic agent. That there is a National Lupron Victims Network and several lupron internet forums -- comprising ***thousands and thousands*** of women (and men), many disabled, experiencing serious medical problems (and death) during and/or since exposure to lupron -- begs for investigation. TAP has settled numerous product liability lawsuits involving lupron; and court records for a pending medical malpractice case involving lupron and Dr. Friedman reveals the plaintiff's medical expert (who opines her stroke and seizures during and since lupron is due to causes other than lupron) is an Abbott consultant for 13 years and counting.

There is so much that I could say that I hardly know where to begin. Hopefully, these brief comments can lead to a meeting with your office and the opportunity to elaborate further on these issues. In any event, I would respectfully request that your office endeavor to (1) obtain unredacted copies of the FDA's Summary Basis of Approvals for all approved and denied indications of lupron, especially the initial approval for the indication of prostate cancer, and (2) obtain the conclusions and data from the discontinued 'clinical trials conducted to determine the efficacy of lupron in treating infertility and in IVF'. Clues to the etiology of 'lupron disease', shared by *thousands* of lupron victims, likely reside in the redacted and proprietary materials mentioned above - which remain beyond the reach of consumers and victims. It is my hope that your office will be compelled to obtain this information, and allow for scrutiny of this data.

In addition, if possible, I would like to request the names and addresses of other U.S. Attorneys Offices in the country who are also conducting grand juries concerning lupron, as I'd

like to share similar information with those offices as well.

Thank you for your time and consideration.

Sincerely,

Lynne Millican