The following are pertinent excerpts from the report prepared by John L. Gueriguian M.D. in a lupron product liability lawsuit. The entire report can be found on PACER or obtained from the court house.

LUPRON AND [PLAINTIFF'S] HEALTH PROBLEMS
A THEMATIC REPORT
John L. Gueriguian, M.D.

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1. Abbreviations

AEs	**Adverse events**
GRH	**Gonadotropin-releasing hormones**
HPh	**Hypophysis**
HTh	**Hypotbalamus**
"L"	**Lupron**
PELI	**patient education booklet & instructions**

2. Introduction

The present report and its accompanying addenda have been prepared for the pharmaceutical liability lawsuit case Klein vs. TAP Pharmaceuticals Products, Inc, et al (case **number 2:08-CV-00681-RLH-RJJ).**

I was asked … to offer my opinions on Lupron (henceforth "L") and how it affected [plaintiff's] health. ….

I am an expert in the following areas of pertinence:

. As a scientist familiar and experienced in the discovery, development and marketing of new drugs;

- As a retired professor of pharmacology familiar with the various ways, beneficial or untoward, that a drug may affect animals and humans;
- As a retired civil servant from the FDA knowledgeable in the ways a pharmaceutical company must interact with drug regulatory agency, to have a drug approved and subsequently monitored;
- As an ex medical officer of the FDA who has been involved with the appraisal of more than 100 new drugs and is therefore adept at estimating their benefit-vs-risk ratios.

...

6. Lupron

6a. General overview

"L" is a hazardous chemotherapeutic drug, which was originally developed and marketed to treat men with advanced prostate cancer. Later TAP aggressively promoted it to gynecologists for the treatment of women with endometriosis. Lupron® is the commercial name for leuprolide acetate, a synthetic analogue of "GRH", a natural hormone that is discharged rhythmically and in short pulses by the "HTh" to stimulate the "HPh." Following each pulse, "GRH" is present in the blood stream for only for a few minutes. "L" and other molecules like it (there are a few on the marketplace) are chemically modified GKH-like molecules that are not quickly destroyed in the blood stream. At first, "L" over-stimulates women's ovaries. Later, it has the opposite effect by inducing a chemical castration, i.e., an artificial menopause. This produces all the signs and symptoms of a natural menopause, i.e., cessation of menstruation, hot flushes, sweats and, singularly and importantly, osteoporosis. Lupron temporarely stops menstruation, but does not eradicate endometriosis long-term. Lupron should only be limited to six injections for the initial treatment, and a retreatment should not exceed six injection. Lupron cannot be given more than twelve injections per life time. Endometriosis can grow back when Lupron treatment is finished.

Lupron affects the autonomic nervous system. Lupron not only affects the gonadal hormones, but is also a powerful modulator of autonomic neural function. The pituitary gland is the "master gland" and is helow the brain in the skull. The pituitary gland affects every physiological process of the body. In addition to the pituitary gland's endocrine functions, the pituitary gland may play a role in the immune response. Lupron suppresses the pituitary-gonadal system. Cancer drugs, such as Lupron, can be highly toxic. The synthetic hormone Lupron is many times more potent than the natural hormone and stays in the blood stream for a prolonged period of time. When injected into humans it displays a biphasic action. In women, during the first days of injections, Lupron stimulates the growth of ovarian tissues and the output of female sex hormones, estradiol and progesterone. During this stimulatory phase, Lupron can induce the growth of ovarian tissue to the extent that cysts are formed. Bleeding can occur in such cysts and they can rupture. In men, receiving Lupron for metastatic prostatic carcinoma, the growth of the cancerous tissue can be activated. This can be dangerous in the event tbat metastases are in the vertebral column since their growth can compress the spinal nerves and cause paralysis.

However, the initial stimulatory phase of Lupron is followed by suppressive action of Lupron on the pituitary gland and consequently on the gonads. In women, ovaries stop making female sex hormones, estrogens in particular, and dosing with Lupron produces an artificial menopause with all its side effects and adverse reactions. The artificial menopause is utilized in the management of endometriosis and for shrinking of myomas since the growth of endometriotic tissue as well as of the

uterine smooth muscle depends on ovarian female sex hormones. It should be stated that after cessation of treatment, when ovaries resume production of female sex hormones, the endometriotic tissue can start growing again and, as a rule, myomas regrow. In men, the suppressive effects of Lupron are equivalent to pharmacological castration since testes stop producing testosterone, the male sex hormone. This is utilized to slow down the growth of prostatic carcinoma and its metastases in those forms of prostate cancer which are sensitive to the male sex hormone. Needless to say, the artificial castration is associated with all side effects typical for surgical castration. Treatment must be continued indefinitely since the cancerous tissue grows back when treatment is interrupted.

In women, Lupron is indicated for the management of endometriosis, including pain relief and reduction of endometriotic foci; and before surgical removal of leiomyomas, concomitantly with iron, for the hematologic improvement of patients with anemia caused by uterine bleeding associated with leiomyomas (tumors of uterine smooth muscle). In men, Lupron is indicated for the palliative management of advanced prostate carcinoma. In children, Lupron is indicated for the treatment of central precocious puberty. Daily Lupron injections are used as an adjunct medication during the in vitro fertilization but have never been approved for this use by the FDA.

6b. Pharmacology & clinical overview

After years of use of "L" in a great number of patients, the evidence is clear that TAP didn't study "L"[1] adequately before marketing. After its introduction into the marketplace, TAP did not perform enough long-term studies to detect potential long-term and irreversible side effects of "L," which has been shown, through independent observations and studies, to be able to cause irreversible side effects and permanent severely disabling health problems. Lupron temporarily stops menstruation, but does not eradicate endometriosis for long-term. Lupron should only be limited to six injections for the initial treatment, and a retreatment should not exceed six injection. Lupron cannot be given more than twelve injections per lifetime.

Endometriosis can grow back when Lupron treatment is finished. When a drug's risks outweigh the drug's benefits, a drug should be banned and pulled from the market

"L" affected the hypothalamus and, indicrectly, the hypophysis through which any number of endocrine functions are affected, including the thyroid. As a result, some patients were shown to develop thyroid abnormalities. Following Lupron treatments, Thyroiditis has been reported to the FDA Adverse Events Reporting System. The independent literature gave a clear signal, beginning in 2000, that such events had been caused by "L"[w]. Despite it all, TAP neglected to perform the necessary studies to adequately study this question and, in the absence of its own studies, failed to warn prescribers and patients of the potential of "L" to cause such toxicities. Another area of unacceptable neglect concerned the use of "L" to treat endometriosis in children (i.e., those less than 18 years old). Though "L" was studied and approved for the treatment of precocious puberty, there was no study to prove the safety and efficacy of "L" in the treatment of underage females affected by endometriosis, a fact admitted by TAP in its labeling,: "Experience with Lupron Depot 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older." TAP's safety signals observed during the precocious puberty studies should have induced it to perform proper studies of underage females treated for endometriosis. It chose not to do so, permissible only if it decided that "L" was contraindicated for the treatment of endometriosis in underage females. It could certainly do that under the "Changes Being Effected" rule of the FDA's regulation. It did not contraindicate the use of "L" in that population.

6c. Adverse events caused by "L"

In 1999, the FDA completed a review of all MedWatch Report Forms for "L". According to a March 1999 FDA memorandum., an FDA official from its Safety Division (Epidemiological Branch) reviewed over 6,000 MedWatch reports received by the FDA and "concluded that there were high prevalence rates for serious side effects" and "requested that the FDA merely reexamine the product label (package insert) to ensure that these events are adequately addressed."[2] In its report, the FDA

listed in rank order the top 35 adverse events for "L" in females, and compared it to the top 35 adverse events for "L" in males. Table 1 lists, side by side, the most frequently experienced adverse events by men and women. It may be observed as (did the FDA) that the nature of the reported adverse events for males and females is quite similar, indicating that the events have occurred more likely due to the drug than to age, gender or underlying disorder. It should also be noted that this 1999 FDA Review indicates that women and men seem equally susceptible to develop depressive states under similar treatment conditions.[3] Side-effects were significant enough to necessitate the use of a concomitant treatment, i.e., the so-called add-back steroidal regimen which decreases some of the symptoms due to Lupron treatment.[4]

The documented AEs of "L" can be classified under the following categories: pain & fibromyalgia; 5 climacteric &. other relatively frequent symptoms; 6 decreased in quality of life; 7 musculo-skeletal & articular disorders; 8 memory disorders;[9] nervousness, irritability and sleeplessness;[10] anxiety, depression and other mood disorders; 11 mania, paranoia & other psychotic disorders;[12] and pituitary adenomas & apoplexy. [13]

6d. The "L" label and its deficiencies

During the registration of clinical trials with Lupron for the female indications, and after Lupron had been introduced for general clinical use, various communications by the manufacturer gave the impression that the adverse events result only from suppressed ovarian hormonal function and are identical with those which women experience during the natural menopause, and are therefore physiological. It also has been stated that most of these symptoms are reversible. Similarly, for patients receiving Lupron for prostate carcinoma or for precocious puberty the drug's adverse effects of Lupron are understated. For example, on December 20, 2001, TAP's internet communication 14 states the following with respect to the management of three main indications:

- For endometriosis: "Side effects are generally those related to hypoestrogenism, including vasomotor flushes, headache., and vaginal dryness. For further information, please see the complete prescribing information." [15]

- For prostate carcinoma: "The most common side effect associated with Lupron Depot is hot flashes. Like other treatment options, LH-RH analogs may cause impotence. Symptoms may worsen over the first few weeks of treatment"

. For precocious puberty: "In clinical studies, the most frequent adverse event related to therapy with Lupron Depot-PED was an injection site reaction, seen in 5% of children in the combined studies."

As experience with Lupron has accumulated, it became increasingly evident that for many patients the array of adverse effects has been much broader, and their intensity more severe than those described in the above (or similar) communications. Moreover, a number of symptoms have emerged that are most likely to be drug specific and independent from the pharmacological action of Lupron, e.g., the reduction of gonadal steroidogenesis or reaction on the injection site. TAP did not adequately warn the prescribing physician and their patients about all risks, dangers, long-term and irreversible side effects associated with the use of "L," due to misleading, all-embracing, extremely broad, vague and equivocal terms in the written Lupron warnings. TAP failed to put warnings in the "L" labeling about known adverse events which were reported to the FDA's Adverse Events Reporting System (otherwise known as MedWatcb) and which were known through medical literature and the endometriosis community.

TAP intentionally suppressed knowledge about the real danger associated with the use of Lupron. The 2005 "L" Depot 3.75 mg label stales: "Duration of initial treatment or retreatment should be limited to 6 months," due to the absence of studies investigating the long-term effects of "L," studies judged as essential by recognized experts. [16] Even within these limits, severe "L" toxicities have occurred because, through various means, prescribers and patients were misled.

Though the labeling cites different kinds of side-effects—headacbes, myalgia, joint disorders, small loss of bone density, some of which may not be reversible, ophthalmological disorders, depression, emotional lability, memory disorder—it is incorrect and misleading for the following reasons:

1. It implies that these symptoms are due to an hvpoestrogenism comparable to that experienced by an average menopausal woman;
2. It is incorrect in its statements concerning the severity and/or the reversibility of osteoporosis, e.g., osteoporosis, climacteric effects, and neurological and neuropsychological toxicities;
3. It minimizes the real toxicity of "L" and, in the process, misleads prescribers and patients, flying in the face of the medical literature.[17]

The following analysis of the "L" label (January 2005), the Patient Education Booklet (February 2005), and the Administration Instruction (February 2004) proves its glaring deficiencies

* **Lupron Is a Hazardous Drug: Misleading Instructions on How to Mix And Administer Lupron**—TAP fails to warn about hazards associated with the use of "L". The administration instruction states: "None of the components is hazardous; therefore, no special handling or disposal procedures are needed." This statement of TAP is misleading and false. The National Institutes of Health (NIH) and the Occupational Safety and Health Administration (OSHA) categorize Lupron as "hazardous drug" and that health care workers should only handle Lupron when wearing protective gowns and gloves. They also recommend that health care professionals who intend to conceive or father a child avoid handling Lupron or other such hazardous substances for three months before conception.

Bone Density Loss— The "L" labeling shows minus 3.2% to minus 6.3% bone density loss of the lumbar spine due to a six (6) month Lupron treatment Only 41 patients at week 24 and 29 patients at week 52, were studied for bone density loss. [Plaintiff] suffered osteopenia with 14% bone density loss of her lumbar spine and a 16% bone density loss of her neck, more bone density loss than TAP warned about. I have reviewed a Clinical Summary written by Abbot, entitled Study NO. M86-039., comparing Lupron Depot 3.75 treatments to Danazol treatments (Danazol was an already FDA approved drug for the treatment of endometriosis) in women with endometriosis, which found that in measuring Spinal BMD by QCT, the Lupron Depot group showed a mean BMD decrease of 7.0% (range - 27.8 to + 53.7%) compared to a 6.2% mean increase for the patients (range - 4.5% and + 13.7%). However, one Lupron Depot patient (No. 577/DA) had an unexpected post-treatment increase of 53.7%, which is considered to be a measurement error. If this patient is excluded, the mean change for Lupron Depot patients becomes a decrease of 15.7%. which differs significantly from the 6.2% increase seen in the Danazol patients. Lupron Depot package insert and patient information only warns of a mean bone density loss of 3.2%, which is false and misleading.. I also reviewed an Endometriosis Safety Update No. 43818, which discusses the follow-up on the bone density issue to the M86-039 Clinical Summary, discussed above. This study notes that bone density measurements were performed on 32 patients in the follow-up study. Only 11 of the 32 patients experienced a complete recovery. Thus 21 patients did not have a complete recovery and many showed further decreases.

Alleged "Temporary" Side Effects Associated With Drug-Induced Menopause— Most side effects alleged as "temporary" are, in reality, all-embracing, extremely broad, vague and equivocal; and, according to the Warning section of the label, they should disappear after treatment with "L" is discontinued. The "L" labeling states: "Adverse events occurring in clinical studies with Lupron Depot that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels are stated to be able to return to normal after treatment is discontinued." and "As would be expected with a drug that lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism." The patient education booklet of Lupron states: "What happens after therapy is finished? - Once you have finished your course of treatment with Lupron Depot 3.75 mg

alone or co-treatment with Lupron Depot and norethindrone acetate, your periods will return and the menopausal symptoms you experienced will usually disappear within ten weeks from the day of your last injection. In some patients, thinning of the bone structure may not be completely reversible." Other AEs recognized as "temporary" by TAP include: fibromyalgia, fibromyalgia-like syndromes, mood swings, urticaria (hives), photosensitivity (light sensitivity), hypotension (low blood pressure), peripheral neuropathy (damage to the *peripheral* nervous system), spinal fracture, tenosynovitis-like symptoms (inflammation of the tendon sheath), peripheral neuropathy (damage to the peripheral nervous system)." None of these adverse events are stated as potentially irreversible.

> Adverse Events Reported To Be Causally Related to Drug — Warnings in the "L" labeling identify the following AEs as causally related to "L": asthenia (physical weakness & loss of strength), body odor, flu syndrome, general pain, migraine, pain, palpitations, tachycardia (abnormal beating of the heart), syncope, altered bowel function, changes in appetite, nausea/vomiting, androgen-like effects (like increased body hair growth), hirsutism (increased body hair growth), ecchymosis (easy bruising), lymphadenopathy (inflammation of the lymph nodes), weight gain/loss, dizziness/vertigo, memory disorder, paresthesias (feeling of "pins and needles" / limb feeling "asleep"), rhinitis, alopecia/ hair disorder, skin reactions, skin/mucous membrane reaction, conjunctivitis (eye inflammation), menstrual disorders." The adverse events of Lupron are written under "Adverse Events Reported To Be Causally Related to Drug" and "Treatment-Related Adverse Events". Warning is also given the following adverse events should disappear after discontinuation of Lupron therapy: headache, hot flashes/sweats, GI disturbances, joint disorder, myalgia, anxiety, decreased libido, depression/emotional lability, insomnia/sleep disorders, nervousness, neuromuscular disorders, ophthalmologic disorders, breast changes/tenderness/pain, dysuria, vaginitis. The patient education booklet states the following: "You should also know that there is a possibility of the development or worsening of depression and/or the occurrence of forgetfulness." Due to the terms "causally related to drug " and "treatment related" the mind of a fair and reasonable person believes that these "adverse events", side effects, would disappear when the Lupron therapy is finished. The warnings did not state that these adverse events could be long-term or irreversible side effects. In fact "L" causes *irreversible damage to the human body* and the development of chronic disabling diseases. The side effects were not "temporary" as alleged by TAP. The irreversible adverse events appear more to be symptoms of chronic diseases, than just "temporary" side effects. Due to inadequate warnings, no physician nor patient could ever expect that a Lupron patient could suffer permanent, chronic, severe health problems and life destroying disabilities.

7. The FDA and TAP

7a. General handling of safety issues

After the approval of a drug, the FDA receives, through its MedWatch system, reports of AEs for that drug. It should be immediately emphasized that "reported" AEs represent only a fraction of the "actual" number of AEs. According to expert epidemiologists only 5-10% of AEs are reported. Also, the FDA has been shown totally unable to affect any of the marketing practices of an approved drug

(from changes in labeling to the withdrawal of the drug) against the firm opposition of the manufacturers to such actions. It is well known that the FDA, throughout its recent history, has never been able to withdraw a drug without the approval of its manufacturer.

7b. TAP'S relied upon false clinical data provided Dr. Andrew Friedman, M.D.

Between 1992 and 1995, Dr. Andrew Friedman falsified and fabricated information,[18] altering permanent patient medical records and notes by changing dates, changing and adding text, and jotting down notes for clinical visits that did not occur. Dr. Friedman admitted that he had falsified and fabricated approximately 80 percent of the data in published research reports [19]
regarding Lupron Depot that were later retracted, TAP Pharmeutical relied upon falsified and fabricated articles to promote the "add back" therapy for endometriosis, which assisted TAP in under-reporting the risks associates with bone density loss.

7c. TAP's **sales practices**

TAP sales practice [20] were investigated when Douglas Durand, a former TAP VP of sales, alleged that TAP marketers gave doctors free samples of Lupron and coached them to profit from the gifts by billing Medicare and Medicaid at $500 per dose. In turn, Dr. Joseph Gerstein told prosecutors that he was approached by a TAP representative who asked why he had replaced, in his practice, the use of "L" with its competitor Zoladex. The representative then offered him $25,000 if he would agree to switch back to prescribing "L".

The American Urology Association then told TAP to stop providing free samples to doctors because doing so was placjng doctors in jeopardy of being prosecuted for taking and biling for free samples. Notwithstanding that warning, TAP continued to give each of its sales representatives samples worth about $40,000 per year and they continued to provide these samples to urologists expecting that those doctors would bill the samples to their patients. Four doctors have pleaded guilty in connection with this investigation.

TAP officials did admit that the company provided free samples of Lupron to a number of physicians, primarily in the early to mid-1990s, with the knowledge that those physicians would seek and receive reimbursement. As a result, on or about October 15, 2001 TAP Pharmaceuticals, Inc., agreed to pay $875 million in order to settle claims that it paid kickbacks to doctors to promote Lupron, which is covered by Medicare and Medicaid. TAP has also pleaded guilty to a criminal charge of violating the Federal Prescription Drug Marketing Act. Prescription drugs are typically not covered by Medicare, however, Lupron, which is injected in the doctor's office, is covered under Medicare as a cancer treatment . The $875 million settlement comprises $290 million for violating the Prescription Drug Marketing Act, $559.5 million to settle federal fraud charges for overcharging Medicare, and a $255 million reimbursement to 50 stales and Washington, D.C., for filing false claims with the states' Medicaid programs.

7d. TAP's promotional activities

TAP aggressively promoted "L" to doctors and bribed physicians. TAP engaged in illegal kickbacks and fraud. They pleaded guilty to criminal charges of violating the Federal Prescription Drug Marketing Act. TAP agreed to pay $875 million in order to settle claims that it paid kickbacks to doctors to promote Lupron, which is covered by Medicare and Medicaid. Dr. Andrew Friedman, associated with TAP, admitted that he had falsified and fabricated 80 percent of the data in leuprolide acetate research reports.

In May 29, 1997, the FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) asserted that TAP was in violation of the Federal Food, Drug and Cosmetic Act in making fraudulent claims. These included misinformation, that Lupron given to men with prostate carcinoma suppresses testosterone levels more efficiently than Zoladex, (a GRH analog) and that "L" had a lower

incidence of testosterone escapes and a better adverse event profile than the competitive congener Zoladex. Other misleading claims implied superiority of Lupron over Zoladex wben used for gynecological indications, specifically endometriosis.

> TAP has been warned repeatedly by the FDA for undertaking a deliberate campaign promoting Lupron for a wide range of unapproved uses. This claim is to be further investigated, in as much as the promotion by any manufacturer of off-label (i.e., unapproved) uses is currently forbidden by statutes and regulations, e.g., the use of "L" in *in vitro* infertility clinics.[21]
>
> **7e. Official sanction of the above activities**
>
> All these activities were eventually sanctioned by the courts after the FDA concluded that some of them were in violation of the Federal Food, Drug and Cosmetic Act in making fraudulent claims implying superiority of Lupron over its competitor's drug when used for gynecological indications, specifically endometriosis. Its reporting of adverse events to the FDA in the 1997-2001 periods suggests that it may have railed to report all known adverse events to the FDA. . All these events, taken together, strongly suggest that TAP did not, directly or indirectly, adequately wam physicians and consumers about the real nature of the long-term risks of Lupron Depot.

8. [Plaintiff's] health condition

8.3 Her post-treatment evolution & disabilities

… Following her regimen of "L" injections, [plaintiff] presented with chronic disabling health problems. In addition, she showed signs of precocious ageing …Thus, "L" had wrought debilitating adverse events and had caused chronic and apparently permanent health problems …

9. Conclusions

My opinions rendered in this matter are the product of reliable principles and methods, which are generally accepted within the medical and scientific community. In preparation for rendering my professional opinion herein I have reviewed the following facts and data:

a. [Plaintiff's] medical records …

b. All discovery materials provided to date by TAP, including Medwatch reports, summaries of clinical studies and information provided in TAP'S NDA (new drug application); and, discovery disc provided by TAP, containing pdf documents, Bates numbered TAP-KK000001 - TAP-KK00836.

c. Criminal conviction in United States of America vs. TAP Pharmaceuticals, Case No. 1:01 -10354-001-WGY, wherein TAP Pharmaceuticals was ordered to pay a $290,000,000.00 fine and was placed on probation for five years.

d. Order granting preliminary approval of settlement in In re: Lupron marketing and sales practices litigation, MDL No. 1430, Master file no. 01-CV-10861-RGS.

e. All studies., journals and other data referenced in the footnotes hereto.

It is my opinion to a reasonable degree of medical probability, that Lupron caused all of [plaintiff's] adverse symptoms.

It is my opinion to a reasonable degree of medical probability that Lupron aggravated some of [plaintiff's] pre-existing conditions, …

It is my opinion to a reasonable degree of medical probability that TAP Pharmaceutical failed to adequately warn doctors and their patients, like [plaintiff], about the foreseeable risks of harm posed by Lupon Depot 3.75, which could have been reduced or avoided by reasonable warnings, and that TAP Pharmaceuticals also failed to adequately warn concerning the adverse events, including, but not limited to, the decrease in bone density caused by Lupron, which was known to them by virtue of their own studies, including Abbot Study No. M86-039 and other medical literature referenced through this report. It also my opinion to a reasonable degree of medical probability that Lupron Depot is both ineffective and unsafe, **based** upon Abbot Study No. M86-039, which showed that Lupron Depot caused a mean bone density decrease of more than 15% vs. Danazol, which caused a mean increase in bone density of more than 6%. This study also showed that participants reported being worse after Lupron Depot therapy, compared to Danazol. Also, 10.3% of Lupron participants reported "back pain" while 0% of Danazol participants reported back pain. In addition, 27.6% of Lupron participants reported "headache" while only 6.7% of Danazol participants reported headache. It should be noted that in the Abbot study, under "Concurrent Medications" the participants were allowed to take Advil, Motrin, Anaprox, Extra Strength Tylenol, Excedrin and Marijuana for pain relief thereby obscuring the data related to TAP's claims that Lupron relieves pain. …

It is my opinion to a reasonable degree of medical probability that TAP Pharmaceutical failed to provide an adequate warning of the risks to doctors and their patients, like [plaintiff], that many of the side-effects of Lupron therapy were long term and/or irreversible.

It is my opinion to a reasonable degree of medical probability that TAP Pharmaceutical failed to adequately warn of irreversible, adverse side-effects, and in doing so, fell below the standard of care, i.e., what a reasonably prudent manufacturer would have warned about and that these risks were reasonably foreseeable.

My expert opinions are also predicated on the chronology (symptoms most detected within a short period after Lupron administration), the statements on the 2005 Lupron Depot 3.75 labeling, and on the published medical literature beginning in 1992, and the fact that [plaintiff] is far from being the only one suffering from said symptoms. A great number of individuals have come forth to describe the same or similar problems and the published medical literature now supports their claims. I have also referenced hundreds of Med Watch Reports which detail adverse events and reactions just like [plaintiff's]. These documents are contained in TAP-KK000001- TAPKK008436.

It is my opinion to a reasonable degree of medical probability that TAP Pharmaceuticals, Inc. did not supply in its labeling sufficient information (as to the nature, frequency, and gravity of the various long-term adverse events that could be expected following Lupron Depot administration). Further, lupron appears to be more toxic than other GRH-analogs. 24 When I extrapolate from "reported" events to estimate "actual" events, Lupron appears to be twice as toxic as its congener Zoladex. TAP misled prescribers and patients as to the degree and the severity of Lupron 's toxicities by falsely implying that the drug was no more dangerous than an average menopausal climacteric, while the published medical literature stated that Lupron was more toxic than other GRH analogs.

I have relied on facts and data from Federal Court filings showing that TAP also engaged in illegal and unethical activities that were eventually sanctioned by the courts: directing its representatives to pay kickbacks to prescribers, thus defrauding Medicare and Medicaid. Other questionable activities also occurred: falsifying clinical data and patients' records, engaging in unapproved promotional activities, engaging in unfair competitive practices, encouraging or (at least) tolerating revenue-producing off-label uses of Lupron.

It is my opinion to a reasonable degree of medical probability an objective analysis of all the available evidence supports the conclusion that proper clinical testing was not performed in a timely

fashion to fully assess the benefit vs. risk profile of Lupron. Further, TAP'S sales practices would have forced certain physicians to administer Lupron Depot to patients who didn't need this therapy, or in whom the therapy would not be indicated because of its unacceptable benefit vs. risk ratio.

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[24] **The FDA's Adverse Events Reporting System shows that L.upron has a reported *2.26 %* frequency of "depression NOS," as opposed to a 1 . 12 % fcequency of the same event for Zoladex which is a pharmacological congener of** Lupron; QED, personal communications