II. WAS LUPRON’S INITIAL FDA APPROVAL BASED UPON SAFETY AND EFFICACY?

A – MALES: Initial Approval for Indication of Palliative Treatment of Prostate Cancer

1) Clinical trials involved a comparison of lupron to diethylstilbesterol (DES), and TAP claimed and marketed lupron as having less side-effects than DES – specifically less cardiovascular adverse events. Yet, in the 1984 FDA reviews leading to lupron’s initial approval, the cardiovascular profile of lupron and DES patients was identified as not comparable, since 25% of the DES patients had pre-existing cardiovascular problems verses 15% of the lupron patients. And more serious imbalance is noted in the FDA’s June 25, 1984 and October 5, 1984 FDA ‘Statistical Review and Evaluation’ of the trial data, wherein the FDA reviewer identifies “the willingness of investigators to switch DES patients to lupron” rather than vice versa.

The claim that lupron provided less side effects and a safer cardiovascular profile in comparison to DES were major identified selling points of lupron, and identified as such in Abbott’s Annual Report of 1984. In these 1984 FDA statistical reviews, the “Conclusions to be Conveyed to the Sponsor” were that the early DES dropouts “could be due to adverse reactions and/or physicians’ willingness to let DES patients crossover or drop out sooner than necessary”, identifying that “[t]his practice could also affect the conclusion …” (emphasis added). The reviewer noted that 33 of the 36 lupron patients that crossed over to DES did so because of disease progression versus 14 of the 28 DES patients that crossed over to lupron due to disease progression. “Most of the other half of the crossovers in the DES group did so because of adverse reactions. The willingness of the investigators to switch DES patients to lupron in the early stage of the treatment apparently influenced this result.” (NDA, 1985)

Was lupron shown to have less cardiovascular side effects than DES, a claim that was critical to its approval? The Acting Group Leader of Oncology Drugs provided a Medical Officer Consultation on lupron’s New Drug Application (NDA) in July 1984, and commented on the “biased outcome in favor of L[euprolide]” and the “soft efficacy parameters” used, “particularly as measured in this NDA”. Of note is the following statement within this Leader’s review:

“Since DES has not been shown to improve survival, the rationale for its use is relief of symptoms. If Leuprolide [L] is worse in this regard, this is important. It appears L may be safer regarding cardiovascular adverse events, but L causes an initial temporary flare up of tumor and tumor related symptoms in perhaps 10% of patients. Exact percentage of tumor flare can not be determined from the
submitted reports because some patients may have had more than one category of flare-up. This safety data can not be factored into the approval decision until the efficacy is adequately defined. In cancer drug NDA’s review of the case report forms often shows the reported results are incorrect or not reliable. Unfortunately I can not use the micro fiche. We should request applicant to submit the case report forms (or at least some of them) in hard copy. Recommendations: 1) This NDA is not approvable because it lacks well controlled studies demonstrating substantial evidence of efficacy. … 6) The application mentions “isolated cases of short term worsening” soon after start of Leuprolide. The case report form number for each of these patients should be identified. 7) hard copy of case report forms should be submitted.” (Johnson; NDA 1985). [emphasis added]

On December 24, 1984 Abbott/TAP presented to the FDA Medical Reviewer’s office TAP/Abbott’s “present label” Clinical Safety Update (clinical trial data updates, i.e., adverse reactions) along with a request by TAP/Abbott to the FDA to withhold the updated adverse reactions from lupron’s initial label. The Medical Officer providing this review of lupron, Dr. Schaffenburg, concluded in favor of TAP: “The sponsor’s proposal not to change these [updated adverse reactions] figures for the present label are acceptable.” It is noted in this review that changing these numbers to include these updated numbers “mak[es] them, of course, larger” yet these changes are claimed as “not significantly chang[ing] the differences between the Lurpon [sic] and DES groups.” (emphasis added) This Medical Officer concludes that Drug Experience Reports “(1639s) … will be tabulated at a later date to save time”, and recommends to “Approve label and promotional materials.”

Lupron’s initial label identified that “less than “3%” of pts (3 subjects) reported cardiac arrhythmias and myocardial infarction. However, subsequent labels identify that “ECG changes/ischemia” were reported for 19% of the lupron patients (19 subjects) versus 21% of DES patients (21 subjects) – representing a nearly identical cardiovascular risk. In addition, the initial label revealed no reports of the adverse events cardiac murmur or high blood pressure, and reported just one (1) report of pulmonary emboli. However, subsequent labels identify that there were reports identifying that 3% of lupron patients experienced cardiac murmurs (vs. 8% DES), and 8% of lupron patients developed high blood pressure (vs. 5% DES), and that “less than 5%” of lupron patients developed pulmonary emboli. Is it “acceptable” to grant TAP’s request to withhold the adverse events that were reported to have occurred in the lupron clinical trials from disclosure in the initial approval label – figures which, when tabulated, cast serious doubt upon lupron’s alleged “improved cardiovascular risk profile in comparison to DES”?

In the April 1, 1985 Review of Final Printed Label by FDA Medical Officer, Dr. C.A. Schaffenburg, it is stated:

“As fully discussed with the Oncology Advisory Committee … the following possible modifications [were proposed]: 1) Indications and Usages: After the last sentence, add ‘Present findings indicate that DES may present advantages for the treatment of pain due to bone metastases’. … Bioavailability Requirements: I don’t know what the deficiencies are in this area, but it would seem to me that evidence of a full castration effect should be enough to prove the drug’s bioavailability. Recommendations: The label should be approved as is with the addition only of the sentence as above under Indications and Usage.” (Schaffenburg, 1985).
Of note is the fact that this Medical Officer co-authored a book a year prior to lupron’s approval, wherein the collaboration between industry, academia, and the FDA is identified, and it is stated “The FDA was privileged to have been involved early in the developmental process of this class of drugs [GnRHa’s]” (Gueriguian, 1984). In another book written on GnRH analogs in 1981, Dr. Schaffenburg wrote a chapter and was a discussant on “Safety and Secondary Pharmacologic Studies of LHRH [GnRH] Analogs”. In this chapter, Dr. Schaffenburg discusses “concerns about [GnRHa’s] persistent effects after withdrawal”, noting “unfortunately, a paucity of information … particularly in humans”, and identifies “our ignorance of the pulsing LH rhythm in [the brain of] normally menstruating women.” The suggestion for “investigators to undertake studies’ is concluded with the following statement: “The safety of these substances, after long-range and wide application, remains a problem to be solved gradually and with caution.” (Schaffenburg, 1981).

The following 2 quotes illustrate the concerns raised by lupron’s cardiovascular and cerebrovascular effects following its approval:

“… Ischemia [cellular death due to lack of blood supply] resulting from vascular changes may also contribute to the degenerative changes in leiomyomas [fibroids]. … The florid and rapid development of vascular inflammation, fibrinoid deposits, and thrombosis after leuprolide acetate therapy suggest an immune-mediated process. Acute vascular changes are rarely seen in non-leuprolide-treated leiomyomas, even in those showing degenerative changes such as an infarction, suggesting a much more protracted course. Whatever the exact mechanism, these observations are significant and worrisome if such changes affect other organs. Acute myocardial infarction has been reported in a 43 year old woman who received one dose of leuprolide acetate depot … leuprolide acetate has also been linked to other vascular effects, including intraocular venous occlusions and hemorrhage.” (Mesia, Gahr, 1997) (emphasis added)

“… Transient cerebral ischemia (TCI) is one possibility that may explain the symptoms of numbness, headache, paresthesia and paresis [during GnRHa use in IVF]. … This could explain the various neurological symptoms occurring by means of vasospasm of intracerebral blood vessels. Furthermore, a direct effect of potent GnRH-analog on the central nervous system resulting in neurological effects independent of the hypothalamic-pituitary-gonadal axis is possible … it is quite possible that mild cases have escaped notice; thus, the occurrence of this type of complication may be far more common than we realize.” (Ashkenazi, 1990)

TAP/Abbott claimed to the FDA (and continues to reiterate today through physicians and in its product literature) that certain adverse events are “physiological responses to lupron”, yet it is known that “[s]imply classifying a response as expected pharmacology does not satisfy the safety evaluation obligation of the toxicologist”. (Enna, 1998)

2) During the FDA reviews of the initial clinical trials of lupron, a bioavailability study was submitted by Keith G. Tolman, M.D., University of Utah. Keith G. Tolman M.D. is listed at the University of Utah’s website as a consultant for TAP and Abbott, and the University’s Center for Clinical Studies has conducted studies sponsored by Takeda. The FDA found this bioavailability study to be “unacceptable”. It is not clear from the documents released by the FDA whether TAP subsequently requested a deferral for bioavailability study, however FDA memos identify that “deferral of the bioavailability requirements is recommended under CFR 320.22(5)(e) because leuprolide is an important oncologic drug” (Skelly, 1984) (emphasis added). A December 1984 FDA Pharmacokinetics
Evaluation Branch memo states that “after a discussion with [FDA’s] Dr. Sobel … [t]his deferral is granted on the basis of CFR 320.22e because Leuprolide is classified as a 1A drug and it represent [sic] a significant contribution to the area of Oncology.” (Frank, 1984 11/2).

However, inexplicably, lupron is NOT classified by the FDA as a Type “1A” drug, but rather lupron is classified by the FDA as a Type “1B” drug (FDC Reports, 2/23/87), and the important distinction will be addressed below. The Code of Federal Regulations (320.22) state that the FDA may defer bioavailability requirements if:

(5): The drug product contains the same active drug ingredient or therapeutic moiety and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both drug products meet an appropriate in vitro test that has been approved by the Food and Drug Administration.

(e): The Food and Drug Administration, for good cause, may defer or waive a requirement for the submission of evidence of in vivo bioavailability if deferral or waiver is compatible with the protection of the public health.

Therefore, it is baffling how the FDA could proffer or accept this criteria in light of (1) the thousands of lupron victims within the National Lupron Victims Network alone, and (2) the FDA’s own classification of lupron as being a Type “1B” category ‘drug’ (FDC Reports, May 27, 1985). The following are the pertinent FDA’s definition for the FDA’s drug classification system:

“Type 1: New molecular entity: An active ingredient that has never been marketed in this country. … A drug for which the active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) has not been previously approved or marketed in the United States for use in a drug product, either as a single ingredient or as part of a combination product or as part of a mixture of stereoisomers.”

“Type B: Modest therapeutic gain, i.e., drug has a modest, but real, potential advantage over other available marketed drugs, for example, greater patient convenience, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, useful in specific subpopulation of those with disease (e.g., those allergic to other available drugs), etc.” (FDA Consumer, 1988) [emphasis added]

Note that while lupron is described as an “important” oncologic drug in the FDA memo favoring a deferral of bioavailability studies, Type B drugs actually provide only a “modest” gain. Type “A” drugs, however, are designated by the FDA as those drugs that provide an “important” therapeutic gain. Why do FDA memos explain away the need for minimal testing prior to FDA approval based upon lupron being a Type “1A” drug – when, in fact, the FDA’s classification of and for lupron is in a lesser, ‘not so important’, “modest gain” category? Moreover, lupron was a new molecular entity”, and therefore was, in fact, new; and when approved by the FDA in 1985, lupron became the first GnRH analog to be approved in the United States. Therefore, how did lupron come to qualify for a deferral based upon CFR 320.22(5)(e)?

Two years after lupron’s approval, in the 1987 Proceedings of Conference, entitled ‘Biotechnologically Derived Medical Agents: The Scientific Basis of Their Regulation’, Dr. Sobel and others from the FDA discussed proteins with a “chemically modified N-terminus” (i.e. lupron) and wrote in regards to the purity of the final product that:

“… impurities are derived from or structurally related to the active drug substance. … These contaminants often have reduced biological activity, and may be antigenic. Eliminating all of these
impurities to ppm level is costly and impractical. It is common for a purified drug to contain up to 3 – 5% of these impurities all together.” (Chiu, 1987)

And in the same 1987 Proceedings, Alex Jordan, who provided the FDA toxicology review for lupron’s initial approval in 1985, wrote:

“… As was stated above, certain synthetic peptides or their analogues may have untoward effects when injected systemically. Whenever one gives larger than physiological doses or introduces even a human peptide into an ‘unnatural’ body compartment, there is a chance that nonphysiological receptors may be activated.” (Jordan, 1987, p. 57)

3) The simplest way to answer the question of whether lupron was approved based upon demonstration of safety is through citation of the 1998 ‘Current Protocols in Pharmacology’:

“It must be recognized that rDNA [recombinant DNA] products containing amino acid sequences purposefully altered to increase potency, duration of action, solubility, etc., relative to the native protein will require a more comprehensive toxicology profile. This situation was apparent with the [1994] FDA recommendations for nonclinical safety studies with analogs of GnRH. … GnRH analogs had originally been developed for the treatment of prostate cancer, and were accordingly subjected to a less rigorous toxicology program than the standard. The current focus with these agents on less serious conditions such as fertility disorders, and the modifications in the structure of the native compound have made it necessary to examine them in a more traditional way (Table 10.3.11)”. The latter table identifies the ‘acute toxicology, subchronic and chronic toxicology, genetic toxicology, carcinogenicity, and special studies, including antigenicity studies’ that were recommended by the FDA. (Enna, 1998)

These 1994 recommendations “only pertain to GnRH analogues and should not be considered as guidance for the testing of any other drug classes”. The authors of these 1994 FDA recommendations also participated as FDA officers in either the review of lupron’s data for the approvals of prostate cancer and/or endometriosis. In the 1994 FDA recommendations, in which it is acknowledged that “unpublished work” from TAP Pharmaceuticals was used, Alexander Jordan writes:

“[Rat] tests showed various degrees of testicular degeneration which were detectable within 2 days. The severity of the lesions were greater in testes of rats sacrificed 7 days after cessation of treatment indicating that the effects continued after drug withdrawal [emphasis added]. … There are other inconsistent effects of Leuprolide in the various toxicity studies but potentially the most serious effect of Leuprolide, in my view, is its effect on spinal column bone marrow. This increased fat deposition and subsequent hypocellularity was explained as a physiological response to the drug. The sponsor states that
there was no alteration in the type or number of hematopoietic cells in the peripheral circulation. … The only other consistent adverse effect of Leuprolide was the increased erythrocyte, hematocrit and hemoglobin values in female rats. … Leuprolide administration produced a dose-related increase in pituitary adenomas in rats. There was approximately a two-fold increase in pituitary adenomas in both male and females at the low dose (600 ug/kg) with no no-effect dose demonstrated. The sponsor’s explanation is that Leuprolide acts as a constant stimulator of gonadotroph function resulting in hyperplasia and ultimately, production of tumors. However, in the method and dose employed, Leuprolide does not stimulate but actually inhibits pituitary gonadotropin synthesis and secretion. Nevertheless, the possibility exists that Leuprolide at the same time may be acting as a stimulator of other cell functions which could result in pituitary adenomas. There is no obvious reason to suggest that the same process could not occur in humans. … Other tumors which were significantly increased by Lupron treatment included pancreatic islet-cell adenoma and testicular interstitial-cell adenoma. [end of discussion redacted]” (Jordan, March 1984)

4) In April 1984, another FDA reviewer performing a ‘Statistical Review and Evaluation’ of these studies noted that once treatment failed to curb disease progression or when adverse reactions developed, “[a]ccording to the sponsor, there were indications that the investigators were less reluctant to take a patient off treatment with DES than leuprolide.” This FDA reviewer identified that “[i]t should be commented that Subjective Response did not always agree with the Objective Response in [the M81-017] study. In about 10% of the patients the Subjective Response rating was in the opposite direction from the Objective Response.”

Documents released by the FDA of it’s reviews of the 2 human studies involved with the prostatic cancer approvals (Study M81-107 and M80-036) clearly identify biases amongst the study investigators – investigator/physicians who were “supported in part by TAP Pharmaceuticals/Abbott Laboratories” – and at least two of these investigators have numerous patents related to lupron. The FDA reviews also clearly identify methodological weaknesses and statistical flaws, as well as clearly state that efficacy and safety had not been demonstrated. What is not clear is why lupron was approved in the first place.

5) After less than sixteen (16) months under FDA review (FDC, 1987), lupron was approved – not by the Division of Drugs, or by the Division of Oncologic Drugs – but by the FDA’s Office of Biologics, on April 9, 1985. (Lupron’s label did not contain, among others, the patient advisory that “DES may present advantages for the treatment of pain due to bone metastases”.) This initial approval of the daily lupron injections, for the palliative treatment of terminal cancer, thus allowed the prescription of lupron for any and all indications, many of which remain unapproved by the FDA some 15 years later (i.e. ovulation induction, fertility treatment, breast cancer, contraception). It would be a solid decade after this initial lupron approval before changes in FDA policy were instituted to reduce the ‘infamously tardy and protracted FDA dug-approval process’.

6) By the summer of 1989, prior to any approved female used for lupron, Senator Kennedy had written to Abbott/TAP asking about advertising, marketing and promotional activities, and their “possible effects on the prescribing practices of physicians”, as well as requesting specific information on any gifts, reminder items, and dispensed samples of products, including the number of dispensed product and the
method of delivery (Conlan, 1990). Following congressional hearings on this industry-wide problem:

“Kennedy was angry that individual drug firms chose not to appear: “Less than a week after receiving a warning from FDA against symposia on unapproved uses for Lupron, why did Abbott sponsor an all-expenses-paid symposium at Disney World for doctors and spouses devoted entirely to unapproved uses?” Abbott did not respond specifically to the Lupron charge; in a statement issued after the hearing, it said marketing activities “are planned and executed to maintain the high ethical and scientific standards required to assist physicians with the practice of good medicine.” (Anonymous, 1991)

It is clear that lupron was quickly facilitated through the approval process with minimal scrutiny, due to its professed ‘importance’ for terminally ill men – all the while an orchestrated and aggressive attempt was underway for the broad application in women. Before any female approval was granted, FDC Reports identified that “Lupron is ‘already being popularized’” for gynecological indications (FDC, 10/30/89). But even though the earliest studies of lupron centered on ovulation induction, it was approval for prostate cancer that was gained – and then the pharmaceutical literature headlines proclaimed “Cancer drug reborn as fertility treatment” (Starr, 1988). Yet neither the daily nor depot lupron has ever been able to gain FDA approval for the indication of fertility treatment, while both continue to enjoy widespread use for this off-label use.