No. 11–17250

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

KARIN KLEIN,

Plaintiff–Appellant,

vs.

TAP PHARMACEUTICAL PRODUCTS, INC.; ABBOTT LABORATORIES; TAKEDA CHEMICAL INDUSTRIES, LTD.,,

Defendants–Appellees.

APPEAL

From the U.S. District Court for Nevada (Las Vegas)
Honorable ROGER L. HUNT, United States District Judge
D.C. No. 2:08–cv–00681–RLH–RJJ

APPELLANT'S REPLY BRIEF

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APPELLANT'S REPLY BRIEF

I. The District Court Erroneously Disallowed Evidence of Prior and Subsequent Remedial Measures Regarding the Lupron Label

The only label Ms. Klein was allowed to show the jury, or otherwise reference during examination of witnesses, was the 2005 Lupron label Ms. Klein was given at the time of her treatment.[1] Ms. Klein argued in her Opening Brief (*Brf.* at 17), that the district court abused its discretion when it precluded her from introducing evidence, and examining and cross–examining witnesses, with regard to prior Lupron 3.75 mg labels and various other Lupron labels, including:

(1) Lupron labels in use prior to 2005 that contained warnings about thyroid enlargement and extreme bone density loss;

(2) a Danish Lupron label that also supported Ms. Klein's allegation that TAP–Abbott knew of the association of Lupron with the known adverse events of enlarged thyroid and extreme bone mineral density loss; and

(3) 2009 and 2010 Lupron labels demonstrating TAP–Abbott's subsequent remedial conduct with regard to certain adverse events of the kind suffered by Ms. Klein.

[1] The 2005 Label, inadvertently omitted from the addendum to Ms. Klein's opening brief is included in Abbott's supplemental excerpts of record at 1 SER 173–188 and is attached to this reply brief as Addendum B–5.

In their Answering Brief (*Ans.* at 47), appellees (collectively, "Abbott") argue that the district court properly disallowed evidence of subsequent remedial measures pursuant to Fed. R. Evid. 407. However, Abbott's argument is inconsistent with substantive Nevada law.

Nevada has long recognized that subsequent remedial conduct is admissible in products liability cases, as Klein duly argued to the district court. *See* CR 285 ("Trial Brief and Offer of Proof Regarding Pre–2005 Lupron Labels and the 2009–2010 Lupron Labels").

In *Jeep Corporation, et al v. Owen Patrick Murray*, 101 Nev. 640; 708 P.2d 297 (1985), the Supreme Court of Nevada held that although subsequent remedial conduct is inadmissible in simple negligence cases per NRS § 48.095,[2] these same considerations do not apply in cases of products liability. *Id.*, 101 Nev. at 647–48, 708 P.2d at 302. In the case of mass produced products, the court reasoned, it expected that a manufacturer will make necessary safety improvements to its

[2] NRS § 48.095 provides:

> **1.** When, after an event, measures are taken which, if taken previously, would have made the event less likely to occur, evidence of the subsequent measures is not admissible to prove negligence or culpable conduct in connection with the event.
>
> **2.** This section does not require the exclusion of evidence of subsequent remedial measures when offered for another purpose, such as proving ownership, control, feasibility of precautionary measures, or impeachment.

product regardless of whether doing so might be admitted as evidence:

> In such a case, "it is manifestly unrealistic to suggest that [the] producer will forego making improvements in its product, and risk innumerable additional lawsuits and the attendant adverse effect upon its public image, simply because evidence of ... such improvement may be admitted in an action founded on strict liability for recovery on an injury that preceded the improvement." Accordingly, while decisions on the subject are by no means unanimous, we believe the better rule is to allow admission of post–accident remedial measures in an action based upon strict liability. [Citing illustrative cases from various courts.]

Jeep Corp., 101 Nev. at 647–48, 708 P.2d at 302 (quoting *Ault v. International Harvester Company*, 528 P.2d 1148, 1152 (Cal. 1975)) (citations omitted). Thus, under the applicable substantive law, evidence of Abbott's subsequent remedial conduct—as would have been shown through subsequent and foreign labels of Lupron—was both relevant and admissible, and it was an abuse of discretion, and undisputedly prejudicial, for the district court to exclude this evidence.

II. The District Court Abused its Discretion by Failing to Admit Adverse Events Reported Through MedWatch

One of the elements of a products liability/failure to warn case is proving that the manufacturer ***knew*** of an "association" of its drug with similar adverse events, and still failed to make a proper warning. In this case, Ms. Klein proffered evidence in the form of MedWatch Reports, Scientific studies and related documents—all of which indicated both that certain adverse reactions she

experienced with Lupron had also been experienced by other people and that Abbott had full knowledge of these adverse effects but failed to warn her.[3] There is no "causation" standard here, as the district court mistakenly understood, and as Abbott urges on appeal (*Ans.* at 37). The district court suppressed the adverse events reports in the proffered MedWatch reports on the basis that: Abbott was given no "opportunity to conduct [relevant] discovery on individual reports [such as the reporters'] medical condition, their allergies, *et cetera*, the nature of the diagnosis, the alternative causes for it, who it was that prescribed it, why they prescribed it[.]" 1 ER 81. The district court erroneously held that adverse event reports are "quite frankly, unreliable as to evidence of causation ***or*** notice" *See* 1 ER 95 (emphasis added). To the contrary, there are few better ways to show notice than through adverse events reports, as recognized in *Wyeth v. Levine,* 555 U.S. 555, 129 S.Ct. 1187 (2009). *See id.*, 555 U.S. at 569, 129 S.Ct. at 1197 (noting, with regard to what newly acquired information Wyeth had or should have had about the risks of IV–push administration of Phenergan that Levine presented

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[3] Plaintiff's Tr. Exh. 199–224, 235. *See* 1 SER 132–136 (Plaintiff's Exhibit List).

evidence of at least 20 incidents prior to her injury in which a Phenergan injection resulted in gangrene and an amputation).[4]

The district court erroneously conflates the adverse events with a causation standard. Quite simply, adverse events, even if not admissible to show causation, are still admissible to show notice of an "association." Federal regulations require that drug manufacturers, "shall revise their drug labeling to include a warning as soon as there is ***reasonable evidence of an association*** of a serious hazard with a drug; ***a causal relationship need not have been proved***." 21 CFR § 201.80(e) (emphasis added). The factors to consider, in order to determine whether or not there is reasonable evidence of an association, are found in the definition of "new safety information," which, with respect to a drug, means: "information derived

[4] Indeed, as discussed in Justice Thomas' concurring opinion in (555 U.S. at 592–93, 129 S.Ct. at 1210–11 (THOMAS, J., concurring), drug manufacturers are required to "establish and maintain records and make reports" to the FDA about "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related," after it has received federal approval. 21 CFR § 314.80(a), (c) & (j). In addition, the manufacturer must make periodic reports about "adverse drug experience[s]" associated with its drug and include "a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated)." 21 CFR §§ 314.80(c)(2)(i)–(ii). When such records and reports are not made, the FDA can withdraw its approval of the drug. 21 CFR § 314.80(j); *see also* 21 U.S.C. § 355(e) ("The Secretary may ... withdraw the approval of an application ... if the Secretary finds ... that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports"). The FDA may also determine that a drug is no longer safe for use based on "clinical or other experience, tests, or other scientific data."

from a clinical trial, ***an adverse event report***, a post approval study, or peer reviewed biomedical literature." 21 U.S.C. § 355–1(b) (emphasis added). Yet, the district court refused to allow any evidence of association of Lupron with the unlabeled adverse events that Ms. Klein suffered. *See* 8/2/2011 AM *Trans.* at 69:3–24, 70:1–15, 76:20–82 [1ER 43–51]; *see also* CR 281 [1 RPLY ER 1797] (Ms. Klein's Trial Brief submitted as Offer of Proof Regarding Evidence of Certain Adverse Event Reports). *See also* 8/5/2011 PM *Trans.* at 868:17–870:5 [1 ER 34–36]); s*ee also* CR 167 [1 RPLY ER 1722–26] (Ms. Klein's Motion *in Limine* No. 8 regarding admission of MedWatch reports and adverse events) and CR 169 [1 RPLY ER 1730] (Ms. Klein's Motion in *Limine* No. 10 regarding admission of similar incidents), both of which were denied; 7/15/2011 *Trans.* at 8:20 – 10:10; and 24:9 – 25:8 [1 ER 79–81, 95–96]). *See also* 2 ER 454:5 – 459:24 (where the district court specifically disallowed MedWatches as not relevant). As the district court concluded:

> THE COURT: My ruling on this is not based upon my ruling then, it's based upon the reason for my ruling then is we're not going to get into these specific reports, the number of specific reports, the source of the specific reports or the validity of the specific reports. We don't have the time and it isn't important.

2 ER 459:20–25 (*see also* 3 ER 462:9 through 463:25, wherein Ms. Klein's counsel makes verbal offer of proof on MedWatches and states intention to file formal written offer of proof).

. . . .

To illustrate just how important prior adverse events are in proving a failure to warn case we look again to *Wyeth v. Levine,* 555 U.S. 555, 569, 129 S.Ct. 1187, 1197 (2009), wherein the plaintiff therein, Levine, was necessarily allowed to present evidence of 20 prior adverse events.[5] In fact, if Levine had been stopped from proving the manufacturer's knowledge of adverse events through MedWatch reports, the case would have likely resulted in a defense verdict at trial, as did Ms. Klein's case.

The adverse events reports in this case, had they been admitted, would clearly have shown Abbott's knowledge of an association about which it should have warned, but did not. Because, instead, the district court took a prohibitive view of MedWatch reports (just as it did with regard to the prior and foreign labels), Klein was wrongly denied the opportunity to prove Abbott's knowledge of an association with the unlabeled adverse events. In effect, Ms. Klein was foreclosed—from the date of the hearing on the *motions in limine*, where any mention of MedWatch, prior labels, and/or foreign labels was declared verboten by

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[5] As recited by the Supreme Court:

> Levine did, however, present evidence of at least 20 incidents prior to her injury in which a Phenergan injection resulted in gangrene and an amputation. After the first such incident came to Wyeth's attention in 1967, it notified the FDA and worked with the agency to change Phenergan's label.

Wyeth, 555 U.S. at 569, 129 S.Ct. at 1197.

the district court—from any meaningful opportunity of proving her case.[6]

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[6] Moreover, adverse event reports may be probative of causation, even when they are not sufficient by themselves. In such cases, any limitations on the usefulness of the reports is best dealt with on cross–examination—as a credibility issue—rather that a foundational issue warranting their exclusion.

Thus, in *In re Baycol Prods. Litig.*, 532 F. Supp. 1029 (D. Minn. 2007), although the court found that the adverse event reports did not support the plaintiff's expert's opinion that Baycol was more toxic than other similar drugs, the court emphasized that its restriction "is not meant to prevent the admission of AER [adverse event report] evidence at trial. As Plaintiffs point out, the AER data relevant to this case presented a very strong signal concerning Baycol and its association with rhabdomyolysis . . .. It thus follows that Plaintiffs' experts may testify as to the existence of this signal." *Id.* at 1042–43. Similarly, in *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 164 (S.D. N.Y. 2009), the court acknowledged that case reports "should be viewed with caution" but added that a large number of such reports "adds greater weight to the reliability of an opinion on causation" and thus "may be carefully considered in light of other information available." *Id.* at 184. And in *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 1230, 1242 (W.D. Wash. 2003), the court noted that in challenging the admissibility of non–epidemiological evidence of causation such as case reports, as Abbott does here, pharmaceutical defendants "isolate these sources, rather than considering the whole. Non–epidemiological sources are frequently utilized by experts in rendering scientific opinions and, under *Daubert*, should be considered by the court in assessing the reliability of these opinions." *Id.* at 1242.

As the courts have observed, the limitations of adverse event reports will not be hidden from the jury, but may be brought out in cross–examination. In *In re Viagra Prods. Liab. Litig.*, 658 F. Supp. 2d 950 (D. Minn. 2009), the court allowed the plaintiff's expert to testified that 12 adverse event reports "constituted a safety signal," finding that challenges to the expert's "methodologies are better dealt with on cross–examination than in a motion to exclude." *Id.* at 962.

Similarly, in *Smith v. Wyeth–Ayerst Labs.*, 278 F. Supp. 684 (W.D. N.C. 2003), the court allowed the plaintiff's expert to testify that a drug similar in chemical composition to the defendant's was named in case reports of the adverse effect suffered by the plaintiff. The existence of the reports, the court noted, "is a historical fact, or a piece of the puzzle so to speak." *Id.* at 704. The limitations of

(continued)

III. The District Court Abused its Discretion in Suppressing Appellant's Supplemental Expert Reports

Abbott asserts in its Answering Brief (*Ans.* at 49) that Ms. Klein's supplemental expert reports, which she argues were improperly excluded by the district court, were two years too late. As already argued in appellant's Opening

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the reports as proof of a causal connection between the defendant's product and the plaintiff's injury "can be brought out on cross–examination" or by a limiting instruction. *Id.* In any event, the adverse event reports are clearly admissible to show that the defendant was on notice of the potential hazards of its product.

In *Benedi v. McNeil–P.P.C., Inc.*, 66 F.3d 1378 (4th Cir. 1995) the Fourth Circuit ruled that the district court properly admitted case reports known as Drug Experience Reports ("DERs") to show that the defendant had notice that its product could cause the type of injury sustained by the plaintiff. The court noted that adverse reaction reports offered to show the defendant's knowledge of the potential hazard are not hearsay because they are not offered to prove the truth of the matter asserted but rather to show the defendant's state of mind. The court found that the dissimilarities between the plaintiff's situation and those described in the DERs "do not affect the admissibility of the evidence, but rather go to the weight the jury gives to the evidence." *Id.* at 1385. The court also rejected the defendant's contention that the reports were unduly prejudicial and should have been excluded under Fed. R. Evid. Rule 403. The court found that the dissimilarities between the plaintiff's situation and those described in the DERs "do not affect the admissibility of the evidence, but rather go to the weight the jury gives to the evidence." *Id.* at 1386. The court's disposition of the defendant's objection based on Rule 403 is consistent with that of other courts. *See Smith v. Wyeth–Ayers Labs*, 278 F. Supp. at 704 (because the evidence was offered to prove notice and was accompanied by a limiting instruction, "the Court cannot find that the probative value is substantially outweighed by the danger of unfair prejudice to Defendant."); *cf also Matrixx Initiatives, Inc. v. Siracusano*, 131 S.Ct. 1309, 1319 (2011) (holding that failure to disclose adverse event reports can be the basis for a securities fraud claim as courts frequently permit expert testimony on causation based on evidence other than statistical significance).

Brief, (*Brf.* at 27–33), the supplemental reports included information that had to be compelled to be produced to the magistrate's chambers, where they sat for more than nine months—during which time Ms. Klein had ***no access*** to the important adverse events reports that Abbott refused to turn over to Ms. Klein until compelled to do so. Abbott nevertheless argues, in defense, that, it "had long before produced the drug development file which summarized every adverse event reported." *See* 1 SER 99–101. This is incorrect and does not address the fact that Abbott's ***summaries*** of adverse events is not the same thing as the adverse events reports themselves (and are, not surprisingly, of dubious accuracy, and thus utility, from Ms. Klein's perspective). In fact, Abbott's late production of the adverse events reports is not seriously in dispute. Even Abbott's trial counsel (Jeremy Cole) was forced to admit that the adverse events reports were not produced as requested—not, in fact produced until compelled—in his letter to Magistrate Judge Johnston, wherein he asserted that certain boxes of requested information were "misplaced" in a warehouse. 2 ER 262–263.

Abbott's continuing attempt to justify the district court's exclusion of the expert reports on the ground of their being untimely is even harder to reconcile with its own intransigence in producing the adverse events reports given that, regardless of the warehoused documents, it was Abbott's common practice to produce the reports to the FDA ***electronically***, and presumably could just as easily have done so here. *See* 2 ER 257, 259–60. The only reasonable inference is that

the adverse incident reports could easily have been provided to Ms. Klein's counsel electronically, but were not, because they clearly substantiate Ms. Klein's liability claim based on Abbott's failure to warn of a known adverse "association."[7]

Once it was determined that relevant adverse events that could have been easily produced, but were not produced, Ms. Klein's counsel sought to continue the deposition of Mr. Ross until after production of the relevant adverse events, and this again was denied by Abbott's trial counsel (June Ghezzi). *See* 2 ER 256, 260.

Abbott further tries to shift responsibility for the timing of the supplemental expert reports to Ms. Klein by pointing out (*Ans.* at 7) that her counsel only conducted one deposition in this matter. This, of course, begs the question why were more depositions not done? The answer should be obvious: Ms. Klein's

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[7] It is quite obvious in the record that Abbott's trial counsel went to extreme lengths to avoid production of the requested adverse events, and to sideline the issue. For example, Abbott's employee, David C. Ross—who was deposed on the very issue of collection and reporting of adverse events—was essentially hushed up during his deposition, during which Abbott's trial counsel continually obstructed and filibustered honest, direct questions about Abbott's storage and production of adverse events. Only after every attempt was made to steer him away from the issue of production of adverse events, was he finally forced to admit that the adverse events would not be difficult to produce. Thus we have Abbott's insistence that the adverse events were all produced and then its later admission that, in fact, they actually were not all produced because they were "misplaced" in various warehouses due to "collection or filing error or oversight." *See* CR 126 at 11–13. All of which this Court is being asked to ignore in order to accept the assertion that Ms. Klein's supplemental expert reports, concerning the adverse events, were duly excluded as untimely.

practical inability to conduct other depositions (and, indeed, the limited utility of even conducting the single deposition taken) was a direct product of Abbott's intransigence—condoned by the district court—particularly with regard to its delay in producing requested adverse events, but also with regard to the label change information, corporate communications regarding adverse events and label changes (***never produced***), and other materials which were requested and which were needed by Ms. Klein's counsel before any meaningful deposition could be conducted. As previously noted, these materials, (minus the corporate communications) were eventually produced to the magistrate "in camera," but Ms. Klein's counsel had no access to them prior to the time of the discovery cutoff; thus, the crucial documentation supporting liability in this case ***was never available to use for any depositions***. Instead, it sat in the magistrate judge's chambers for nine months. In other words, Ms. Klein may have had the ability to set depositions, but the ability was essentially meaningless; any further depositions would have been an exercise in futility—they, predictably, would have been consumed by the same filibusters and speaking objections that characterized the deposition of David C. Ross.

IV. The District Court Prejudiced Ms. Klein's Case Through a Constant Exhibition of Extreme Animus Directed Against Her and Her Counsel

Although undersigned counsel has the highest respect for the trial judge in this case, the record reflects that manner in which the trial in this matter was conducted before the jury necessarily deprived Ms. Klein of any hope of a fair and impartial resolution of her claims.

For example, the entirety of her counsel's direct examination of her causation expert, Dr. John L. Gueriguian, is replete with more than a dozen instances where the trial judge interrupted the flow of the examination by continually making evidentiary objections and derogatory comments upon the credibility of the witness and the evidence without any objection being lodged by Abbott's counsel. From the very beginning, the clear message sent to the jury was that the judge in charge of the proceedings viewed Ms. Klein, her counsel, and her case with extreme disfavor. *See* 3 ER 449, 452:1–3, 455:14–19, 457 – 459, 462:3, 493:12 – 494:15, 512 – 513, 514 – 518, 515:7–16.

At one point in the Ms. Klein's direct examination of Dr. Gueriguian, the trial judge actually interjects that her counsel is leading the witness, and then actively solicits an objection from defense counsel. ER 519:9–11. In another instance, the trial judge states: "I haven't heard if there is an objection or not, but the court objects to the lack of foundation for the exhibit." ER 519:24 – 520:10.

Although not *per se* improper,[8] this pattern of bias, combined with the many abuses of discretion regarding evidence that was disallowed, sent a clear message to the jurors that Ms. Klein and her counsel should not be believed and that any evidence that they presented must be viewed with suspicion.

V. The District Court's Errors Were Prejudicial and Warrant Reversal

The district court's various errors (as set forth elsewhere in this brief and in Ms. Klein's opening brief) were not harmless and therefore warrant reversal. *See Cassino v. Reichhold Chemicals, Inc.*, 817 F.2d 1338, 1342 (9th Cir. 1987) ("We review evidentiary rulings for abuse of discretion and will not reverse absent some prejudice."); *accord S.E.C. v. Jasper*, 678 F.3d 1116, 1122 (9th Cir. 2012). Ms. Klein presented expert testimony and other evidence showing that she has suffered very serious (in fact, disabling) health problems following treatment with Abbott's drug, that her health problems were in fact caused by Abbott's drug, and that Abbott failed to provide her adequate warning of these problems as potential complications from taking Abbott's drug. The jury could have ruled in Ms. Klein's favor based on the present trial record. However, she was greatly, and improperly, hindered in the effective presentation of her case to the jury, particularly with

[8] *See generally Caperton v. A.T. Massey Coal Co., Inc.*, 556 U.S. 868, 883 (2009); *Aetna Life Ins. Co. v. Lavoie*, 475 U.S. 813, 825 (1986); *Hurles v. Ryan*, 706 F.3d 1021, 1037 (9th Cir. 2013).

regard to her ability to challenge the reliability of the opinions of Abbott's expert Dr. Blackwell and to bolster the opinions of her own experts, Dr. Gueriguian and Dr. Redwine. Had Ms. Klein been able to engage Abbott in a fair battle of the experts, free of the restrictions imposed by the district court's improper rulings, the jury may have reached a different result.

The evidence excluded by the district court (prior labels, subsequent labels, foreign labels, MedWatch reports, *etc.*) and the limitations imposed on Ms. Klein's counsel both during her case in chief and during cross examination of Abbott's experts is abundantly detailed on pages 6 through 12 of the opening brief and need not be repeated here. Nevertheless, in order to rebut the suggestion of lack of prejudice it is perhaps helpful to give a more detailed recital of the conflicting testimony given by the parties' respective experts.

Ms. Klein's general causation expert Dr. Gueriguian[9] testified that the warnings given in the 2005 Lupron Depot 3.75 label were inadequate:

> And Doctor, have you reviewed the label, the Lupron Depot 3.75 label which was the drug that was given to Karin Klein in this case?
>
> A. I have.
>
> Q. Have you reviewed TAP/Abbott's internal studies?
>
> A. I have reviewed whatever we were able to obtain from TAP.

[9] Dr. Gueriguian confirmed that all of his opinions were based on a reasonable degree of scientific/medical certainty. 4 ER 550:6–10.

> Q. Have you been able to compare what was in the internal studies with the label that both Karin's doctor and that Karin saw?
>
> A. Yes. I was able to do that and in addition, I compared it also to the published literature.
>
> Q. And have you reached conclusions as to whether or not the label that went to Karin's doctor and went to Karin was adequate or inadequate?
>
> A. I have reached a conclusion that under main and for specific situations it was inadequate.

2 ER 386:7–22; *see also* 4 ER 632:5–10 (confirming opinion).

Dr. Gueriguian opined specifically, *inter alia*, that the risk warnings in the 2005 label were inadequate with regard to changes in bone density (4 ER 545–548). He discussed thyroid conditions associated with taking Lupron Depot 3.75 and opined that Lupron Depot 3.75 can cause a number of different thyroid–related pathologies, including "Hashimoto's disease."[10] 4 ER 549:3–5. He confirmed that

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[10] Dr. Gueriguian described Hashimoto's autoimmune thyroid disease as follows:

> A. Hashimoto's disease results in hyperthyroidism [*sic*.], that is to say there's not enough Thyroxin in the blood to do what it's supposed to do under normal conditions. But the importance of Hashimoto's disease is that it's an autoimmune disease, which means now the body thinks that some of the elements of its own are foreign to it, it doesn't recognize them, and it makes antibodies to attack and destroy itself. And that is one of the mechanism by which not enough Thyroxin is synthesized because one of the mechanism is to have an antibody that blocks the big blob that produces Thyroxin.
>
> So it's a very severe disease. It is chronic. It can last for a long time.

4 ER 549:6–18.

none of the warnings provided in the 2005 label mentioned "thyroid." 4 ER 550:5. He opined that estrogen levels do not return to normal after taking Lupron Depot 3.75. 4 ER 549:21–23.

Dr. Redwine, Ms. Klein's specific causation expert provided the necessary opinion testimony specifically linking her various health problems to her treatment with Lupron Depot 3.75 and/or low estrogen levels resulting from her treatment with Lupron Depot 3.75, including: bone mineral density loss (5 ER 797:21–25; *see also* 4 ER 759–60); severe neck and back pain (5 ER 798:1–3; *see also* 4 ER 759); and Hashimoto's autoimmune thyroid disease (5 ER 798:4–5). *See also* 5 ER 798:9–12 (attributing Ms. Klein's "long term suffering" to adverse events that are all "a result of chronic low levels of estrogen which in this case would result from the administration of Lupron").[11] Dr. Redwine's testimony was based on his

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[11] The testimony at trial was as follows:

> Q. What is your opinion, Dr. Redwine, with regard to Karin's bone mineral density and the cause thereof?
>
> A. Lupron.
>
> Q. And—
>
> A. Low estrogen state resulting from Lupron.
>
> Q. All right. And, Dr. Redwine, what is your opinion with regard to the cause of Karin Klein's severe neck and back pain?
>
> A. The low estrogen level resulting from Lupron.
>
> Q. And, with regard to Ms. Klein's diagnosis of Hashimoto's?

(continued)

review of Ms. Klein's medical records and a medical examination of Ms. Klein he conducted personally.[12] 5 ER 796–797.

The testimony of Ms. Klein's medical experts, together with her own testimony, the finding of permanent disability by her treating physician Dr. Flowers,[13] the testimony of her economic damages expert,[14] and other evidence present during her case in chief, was enough to establish a prima facie case of product liability under a failure to warn theory. Thus, the district court denied Abbott's motion for judgment as a matter of law brought at the close of Ms. Klein's case. 6 ER 1173, 1178–1179.

> A. The low estrogen levels associated with Lupron.
>
> Q. And Ms. Klein's diagnosis with regard to positive ANA's?
>
> A. That's not so certain.
>
> Q. Okay. And your opinion with regard to Ms. Klein's long–term suffering of—of the adverse events that she suffers?
>
> A. They're all events that are seen as a result of chronic low levels of estrogen which in this case would result from the administration of Lupron.

5 ER 797–798.

[12] He confirmed that his opinions were based upon a reasonable degree of medical probability. 5 ER 797.

[13] Plaintiff's Exhibit 30, admitted by stipulation (1 RPLY ER 1652–59).

[14] John Brough estimated Ms. Klein's future losses (total present value), depending on whether she entered the workforce with a high school diploma or with a bachelor's degree, at $1,349,759 or $2,338,026, respectively. 4 ER 644, 657:17, 659:12.

In its defense case, Abbott disputed that any of Ms. Klein's medical problems were caused by her treatment with Lupron Depot 3.75 and also disputed that Lupron Depot 3.75 was even capable of causing such medical problems. Its defense was supported, *inter alia*, by the testimony of its medical expert (as discussed in the opening brief at 8), Dr. Blackwell. Dr. Blackwell testified, for example, that it was "biologically impossible" for Lupron to affect the thyroid gland:

> Well, you might say, well, okay. What about the thyroid gland itself? Right? There are no receptors for GnRH. So there is no basic key on the thyroid gland for Lupron. Therefore, it is absolutely biologically impossible for Lupron to affect the thyroid gland. No textbook, no article has ever supported that contention. ***It's simply biologically impossible.***

8/5/2011 PM *Trans.* at 818:5–10 [1 ER 22] (emphasis added). Dr. Blackwell's absolute statement that it was "biologically impossible" for Lupron to affect the thyroid is belied by prior labels and foreign labels, essentially admitting the association, and also by the medical literature, but Ms. Klein's counsel was forbidden to even mention any other labels and was also not allowed to go into the medical literature that made the association. *See Brf* at 20, 31.

The conflicting opinions of the parties' respective experts presented the jury with a classic "battle of the experts." Given this dynamic, it was absolutely crucial that Ms. Klein's counsel be able to attack the reliability of the opinions of Abbott's experts and bolster the credibility of her own experts in the eyes of the jury. Each

of the errors claimed by Ms. Klein in this appeal directly and substantially hindered her ability to do so—by denying her the use of relevant and necessary documents or (with regard to the many incidences of apparent animosity displayed by the trial judge) by directly undermining the credibility of Ms. Klein, her supporting witnesses, and her counsel. The harm, therefore, was substantial, not harmless, and reversal is warranted.

VI. Abbott's Comments on the Evidence are Irrelevant and Misleading

Abbott asserts in its answering brief that "Klein did not produce a single medical record showing a definitive diagnosis of Hashimoto's thyroiditis or confirmatory test results" (*Ans* at 5) and dismisses "enlarged thyroid" as "a condition Klein does not have" (*Ans* at 40). These statements, and other similar statements in Abbott's answering brief, are both misleading and, at this stage of the proceedings, irrelevant.

The statements are irrelevant because Ms. Klein is not arguing that the jury's defense verdict is not supported by substantial evidence. Rather, Ms. Klein is arguing that the district court erred in various evidentiary and pre–trial rulings, that the trial judge exhibited bias in front of the jury, and that, as a result, she was prejudiced in the presentation of her case. To the extent that these statements are intended to imply that there is no evidence in the record to support her claim that she suffers from serious thyroid–related health problems, and that these problems

were caused by her treatment with Lupron Depot 3.7, the statements are directly contradicted by the testimony of her experts. The district court's errors are not prejudicial because the testimony of her experts was undisputed, but because it was disputed—and there is a possibility that, absent the court's errors, the jury would have reached a result in her favor. *See Cassino v. Reichhold Chemicals, Inc.*, *supra*, 817 F.2d at 1342.

The statements are misleading because they are not only contradicted by Ms. Klein's experts (*see* Section V of this *Reply*), but by Ms. Klein's testimony regarding her treatment (5 ER 976, 978, 991) and by the medical records of her treating physicians admitted at trial, which document thyroid and thyroid–related problems, including specifically, Hashimoto's autoimmune thyroid disease.[15] In fact, Ms. Klein's treating physician, Dr. Litchfield, consistently lists "Hashimoto's disease" in the "assessment" portion of his treatment records. 1 RPLY ER 1531–1651 (Plaintiff's Exhibit 29). It is true that Hashimoto's disease is not under a separate heading called "diagnosis" (there is no such heading), but the records, which were admitted by stipulation and without Dr. Litchfield testifying, are more than sufficient to support the interpretation of Ms. Klein's experts. For example:

- In his record for May 13, 2009, Dr. Litchfield writes, under Impressions: "IMPRESSION: autoimmune thyroid disease." 1 RPLY ER 1580 (KK Litchfield –49).

[15] The parties stipulated to the admissibility of all of Ms. Klein's medical records at trial. *See* 4 ER 641; 1 RPLY ER 1827–31.

- From August 19, 2009 to September 2, 2009, He treated Ms. Klein with Synthroid (a synthetic thyroid hormone replacement medication used to treat hypothyroidism). 1 RPLY ER 1589 (KK Litchfield –58).

- In his record for October 5, 2009, he writes, under History of Present Illness: "thyroid minimally enlarged and tender." 1 RPLY ER 1583 (KK Litchfield –52).

- In his record for June 14, 2011, he writes, under Symptoms: "The patient returns for follow–up regarding [her] autoimmune thyroid disease. I've let her know that my primary focus will be to care for her thyroid disease." 1 RPLY ER 1533 (KK Litchfield –2).

CONCLUSION

For the reasons set forth above, it is respectfully requested that this Court grant the relief requested by Ms. Klein in her opening brief.

DATED this 8th day of April, 2013.

RESPECTFULLY SUBMITTED

s/ Beau Sterling

Beau Sterling
Counsel for Appellant

CERTIFICATE OF COMPLIANCE

Pursuant to FRAP 32, the brief's line spacing is double spaced and proportionally spaced. The type face is Time New Roman 14 point and the word count is **5,849**.

DATED this 8th day of April 2013.

s/ Beau Sterling

Beau Sterling
Counsel for Appellant

CERTIFICATE OF SERVICE

Undersigned counsel hereby certifies that on this date, the 8th day of April, 2013, he submitted the foregoing **Appellant's Reply Brief** and **Appellant's Excerpts of Record — REPLY (Volume 1 of 1)** for filing and service via the Court's CM/ECF system. Registered users will automatically receive electronic service.

Undersigned counsel further certifies, based on the Court's electronic service list, that all parties are registered users.

s/ Beau Sterling

Beau Sterling

ADDENDUM

ADDENDUM

B–5

PATIENT INFORMATION ON TREATMENT WITH LUPRON DEPOT 3.75 mg (leuprolide acetate for depot suspension)

LUPRON DEPOT®

3.75 mg

LEUPROLIDE ACETATE
FOR DEPOT SUSPENSION

This is combined labeling. Examples of different colors and fonts appear below.

- General Information
- Information on Endometriosis
- Information on Uterine Fibroids

This patient education booklet provides information on the use of LUPRON DEPOT® 3.75 mg (leuprolide acetate for depot suspension) for two different medical conditions:

1. Endometriosis
2. Anemia due to vaginal bleeding from fibroids

Your health care provider will direct you to the section that will discuss your condition.

This booklet is not intended to be a substitute for information provided to you by your health care provider. You should discuss with your health care provider any questions you have about your diagnosis and treatment, and you may ask your health care provider for a copy of the information provided to him or her by TAP Pharmaceuticals Inc.

LUPRON DEPOT 3.75 mg is given to decrease the production of estrogen by your ovaries. The information provided describes the drug's action in the treatment of either condition described in this booklet.

HOW IS LUPRON GIVEN?

LUPRON DEPOT 3.75 mg is a prescription drug that is prescribed by your health care provider. Once a month (approximately every 28 to 33 days), you will receive an injection of LUPRON DEPOT 3.75 mg.

You should get your injections on time. The recommended initial treatment is no more than six injections for endometriosis and up to 3 injections for uterine fibroids. If you need retreatment for endometriosis, it should be limited to 6 months.

WHAT SHOULD I EXPECT?

At first, your estrogen level will increase for one or two weeks. During that time, you may notice an increase in your current symptoms. Then your estrogen level will decline, as it does in menopause.

The common side effects of LUPRON DEPOT 3.75 mg include, but are not limited to, hot flashes, vaginal dryness, headaches, changes in mood, and a decreased interest in sex. You should also know that there is a possibility of the development or worsening of depression and/or the occurrence of forgetfulness.

Your menstrual periods will probably become less regular and the flow may be heavier or lighter. After a few months of therapy your periods may stop completely.

WHAT IS THE MOST IMPORTANT RISK OF TAKING LUPRON?

When you take LUPRON DEPOT 3.75 mg, your estrogen level is decreased to menopausal levels or lower. This low level can result in thinning of the bones, which may not be completely reversible in some patients. There are certain conditions that may increase the possibility of the thinning of your bones when you take a drug such as LUPRON DEPOT 3.75 mg. They are:

- Excessive use of alcohol;
- Smoking;
- Family history of osteoporosis (thinning of the bones with fractures);
- Taking other medications that can cause thinning of the bones.

You should discuss the possibility of osteoporosis or thinning of the bones with your health care provider before starting LUPRON DEPOT 3.75 mg. You should also be aware that repeat treatment with LUPRON DEPOT 3.75 mg alone is not advisable, particularly if you have the above conditions.

WHO SHOULD NOT USE LUPRON DEPOT 3.75 mg?

If you answer YES to any of the following questions, you should **not** use LUPRON DEPOT 3.75 mg.

- Are you pregnant?
- Are you breast-feeding?
- Do you have any abnormal vaginal bleeding that has not been evaluated by your health care provider?
- Have you experienced any type of allergic reaction to a drug like Lupron?

Remember, always ask your health care provider about any concerns you might have regarding this or any medication.

WHAT SHOULD I KNOW IF I AM RECEIVING CO-TREATMENT WITH LUPRON DEPOT 3.75 mg AND NORETHINDRONE ACETATE?

Norethindrone acetate is related to the hormone progesterone and is used in some birth control pills. Your health care provider may recommend co-treatment with LUPRON DEPOT 3.75 mg and norethindrone acetate to reduce the risk of bone loss. This may also reduce some of the menopausal symptoms like hot flashes. To reduce bone loss, norethindrone acetate should be started with the first injection of LUPRON DEPOT 3.75 mg. This drug will not interfere with the desired effects of LUPRON DEPOT 3.75 mg in treating endometriosis.

LUPRON DEPOT 3.75 mg given with norethindrone acetate may lower your HDL-cholesterol level (the "good" cholesterol). Whether this change increases your long-term risk of heart disease is not known. Your health care provider should assess your risk of heart disease prior to starting this co-treatment.

You should not use co-treatment with norethindrone acetate if you have had or have any of the following conditions:

- Blood clots in your legs (phlebitis), heart disease, or stroke;
- Liver disease;
- Breast cancer.

If you have had any of the following conditions or if any of the following apply to you, tell your health care provider before beginning norethindrone acetate co-treatment:

- High levels of cholesterol;
- Migraine headaches;
- Epilepsy;
- Depression;
- Smoking.

After beginning co-treatment, notify your health care provider IMMEDIATELY if sudden loss of vision, double vision, or migraine headaches occur. In addition, you should notify your health care provider if any of the following conditions occur:

- Fluid retention;
- Epilepsy;
- Asthma or worsening asthmatic symptoms;
- Heart or kidney problems.

If your symptoms return after treatment is finished and repeat treatment is desired, you will need co-treatment with LUPRON DEPOT 3.75 mg and norethindrone acetate. Your health care provider should assess your bone density at this time. Be sure to discuss this with your health care provider.

Co-treatment with LUPRON DEPOT 3.75 mg and norethindrone acetate has not been studied for treatment of fibroids.

COULD I GET PREGNANT?

LUPRON DEPOT 3.75 mg is not a method of birth control. Even though you may not have periods, unprotected intercourse could result in pregnancy. Therefore, you should use non-hormonal birth control such as condoms or a diaphragm with contraceptive gel/cream or an IUD. If you think that you may be pregnant while receiving LUPRON DEPOT 3.75 mg, contact your health care provider immediately.

CONDITION DESCRIPTIONS

Endometriosis is a condition in which the endometrium, the tissue that lines the uterus (womb) is found outside of the uterus. Common sites for such "endometrial implants" can be the ovaries, the fallopian tubes, the outer surface of the uterus, and the bowel. Such implants can bleed just like the normal endometrium does during your menstrual cycle, but the blood is trapped so the implants can cause pain and irritation to surrounding tissues. As a reaction to this irritation, the body sometimes forms scar tissue around and near the implants. Scar tissues that bind organs together are called adhesions.

Fibroids are not cancer. They are non-cancerous growths of the body of the uterus and they are very common in women. (They occur in about 20% to 25% of all women and are most common in women aged 30 to 40.) A woman may have only one fibroid or many. They may occur on the outer surface of the uterus, totally within the walls of the uterus, or on the inside surface. Many women who have fibroids are not aware of them because they do not cause problems.

Fibroids can cause problems due to their size, number and location, but a major problem is excessive menstrual bleeding. LUPRON DEPOT 3.75 mg is used with iron for the improvement of anemia due to heavy menstrual bleeding because of fibroids. Like any growth, fibroids should be checked by a health care provider. Fibroids are also called myomas or leiomyomas.

SIGNS AND SYMPTOMS

Endometriosis can be the cause of severe menstrual cramps just before or during your menstrual cycle as well as pelvic pain or pressure and/or pain during intercourse.

Fibroids may cause you to have unusually heavy menstrual periods, bleeding between periods, sudden or long-lasting pain or a feeling of pressure in the lower abdomen. Excessive bleeding may lead to anemia from a shortage of iron in the blood and can make you feel tired or sick.

HOW DOES LUPRON DEPOT 3.75 mg WORK?

LUPRON DEPOT 3.75 mg interrupts the normal menstrual cycle and the production of estrogen and this may slow the growth of endometrial implants. As a result, pain and other symptoms resulting from endometriosis can be eased during treatment. In about 50% to 60% of the women treated during clinical studies, LUPRON DEPOT 3.75 mg afforded relief from symptoms. Some of the symptoms were more responsive to treatment than others. The list below shows the percent of patients with specific symptoms who found relief at the end of treatment.

Menstrual pain/cramping	96%
Pelvic pain	53%
Pain with intercourse	56%
Pelvic tenderness	66%
Thickening of pelvic tissue	71%

Many of the original patients were followed up to 1 year after treatment with LUPRON DEPOT 3.75 mg was stopped to determine when symptoms of endometriosis recurred. In these patients, some of the symptoms reappeared faster than others.

Fibroids that do not cause symptoms or occur in women nearing menopause often will not require treatment. However, if you have heavy bleeding as a result of your fibroids, you may also be anemic. LUPRON DEPOT 3.75 mg together with iron may stop the bleeding and allow your blood count to build up to a normal level. The uterine and fibroid volume will decrease and you may also experience relief from abdominal bloating, pelvic pain and pressure if you have suffered from these symptoms because of your fibroids.

Your health care provider may consider a one month trial of iron alone as some patients' anemia will improve with iron alone.

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.

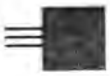
CAN I GET PREGNANT AFTER THERAPY IS FINISHED?

Once you have finished your course of treatment with LUPRON DEPOT 3.75 mg, your health care provider may schedule you for surgery. You may be able to get pregnant after your surgery if only your fibroids are removed. You will not be able to get pregnant if your uterus is removed during surgery. Fibroids may develop again even after their removal. If they do, 20% to 40% of patients may require more surgery. Your health care provider will help you to make decisions about any need for more surgery.

This patient education brochure is not intended to be a substitute for information provided to you by your health care provider or provided to your health care provider by TAP Pharmaceuticals Inc.

You should discuss with your health care provider any questions you have about the diagnosis and treatment of your condition.

This information is provided as a service of TAP Pharmaceuticals Inc.



GLOSSARY

Adhesions – scar tissue.

Anemia – low blood count.

Aygestin® - brand name of norethindrone acetate.

Diaphragm – barrier type birth control device that covers the cervical opening between the vagina and the uterus.

Estrogen – female hormone produced by the ovaries.

Fallopian tube – a tube that transports eggs from each ovary to the uterus.

Fibroids – non-cancerous growths of the body of the uterus.

Implants – endometrial tissue that fixes itself outside the uterine cavity.

IUD – birth control device temporarily implanted in the uterus.

Menopause – the end of a woman's reproductive years.

Norethindrone acetate - a drug related to the hormone progesterone.

Osteoporosis – a thinning of the bone structure that is most often found in women after menopause.

Progesterone - female hormone produced by the ovaries.

Uterus – the womb; muscular organ in which a fertilized egg embeds and is nourished.

TAP Pharmaceuticals Inc.
Lake Forest, IL 60045

(No. 3641)
03-5337-R10; Revised: Febuary, 2004

ADDITIONAL INFORMATION

- None of the components is hazardous; therefore, no special handling or disposal procedures are needed.
- Dispose of the syringe according to local regulations/procedures.

LuproLoc™
U.S. Patent Nos. 5,823,997 and 5,980,488.
Other patents pending.

INSTRUCTIONS ON HOW TO MIX AND ADMINISTER

If you have any questions regarding the drug or the mixing/administration procedure, please call
1-800-622-2011
for further assistance.

TAP Pharmaceuticals Inc.
Lake Forest, IL 60045

035254

NOTE: **LUPRON** DEPOT® and **LUPRON** DEPOT-PED® must be administered under the supervision of a physician.

LUPRON DEPOT®
LUPRON DEPOT-PED®

PREFILLED DUAL-CHAMBER SYRINGE

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

(Nos. 2108, 2282, 2440, 3346, 3641, 3642, 3663, 3683)
03-5254-R6; Revised: March, 2003
TM-Trademark
®-Registered Trademark

KK JAN 2005 LABEL
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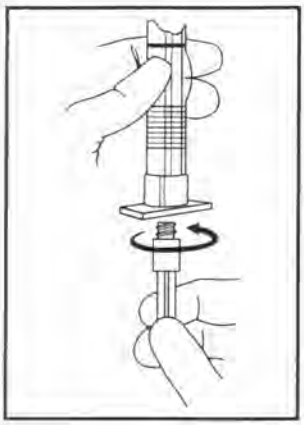
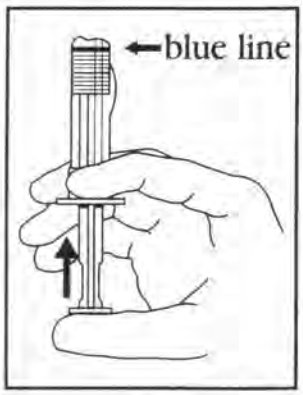
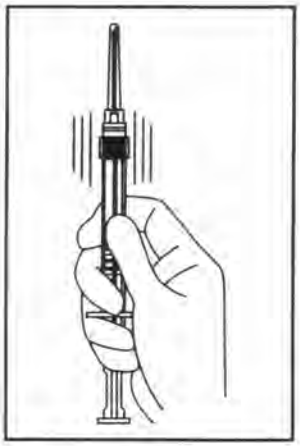
For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:



1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



2. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.

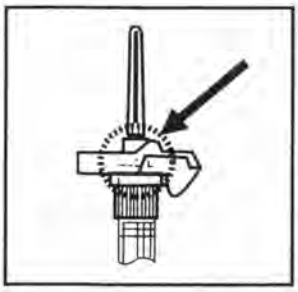


3. Keep the syringe UPRIGHT. Gently mix the microspheres (particles) thoroughly to form a uniform suspension. The suspension will appear milky.

4. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

5. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.

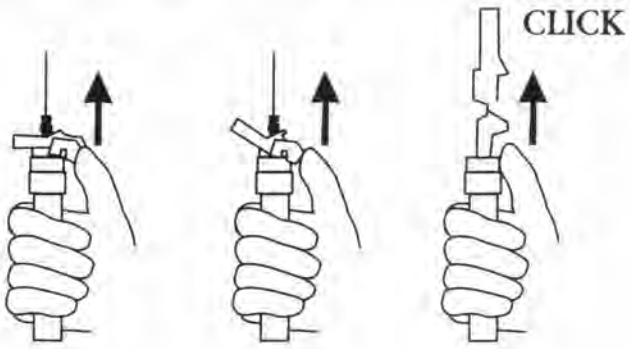
6. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.



NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc™ safety device.

AFTER INJECTION

7. Withdraw the needle. Immediately activate the LuproLoc™ safety device by pushing the arrow forward with the thumb or finger, as illustrated, until the device is fully extended and a CLICK is heard or felt.



KK JAN 2005 LABEL
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HOW SUPPLIED

LUPRON DEPOT 3.75 mg is packaged as follows:
Kit with prefilled dual-chamber syringe NDC 0300-3641-01

Each syringe contains sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT 3.75 mg is administered as a single monthly IM injection.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

U.S. Patent Nos. 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; 5,330,767; 5,476,663; 5,575,987; 5,631,020; 5,631,021; 5,716,640; 5,823,997; 5,980,488; and 6,036,976. Other patents pending.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, IL 60045, U.S.A.
by Takeda Pharmaceutical Company Limited
Osaka, JAPAN 540-8645

(No. 3641)

03-5412-R19; Revised: January, 2005

035412

This is combined labeling. Examples of different fonts and colors appear below.

- General information
- Information on endometriosis
- Information on uterine fibroids

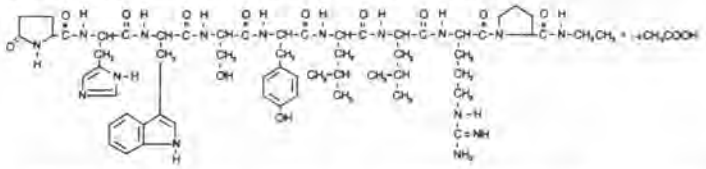
LUPRON DEPOT® 3.75 mg

(leuprolide acetate for depot suspension)

℞ only

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON DEPOT is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a monthly intramuscular injection.

The front chamber of LUPRON DEPOT 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 3.75 mg, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long-acting GnRH analog. A single monthly injection of LUPRON DEPOT 3.75 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally. Intramuscular injection of the depot formulation provides plasma concentrations of leuprolide over a period of one month.

Pharmacokinetics

Absorption A single dose of LUPRON DEPOT 3.75 mg was administered by intramuscular injection to healthy female volunteers. The absorption of leuprolide was characterized by an initial increase in plasma concentration, with peak concentration ranging from 4.6 to 10.2 ng/mL at four hours postdosing. However, intact leuprolide and an inactive metabolite could not be distinguished by the assay used in the study. Following the initial rise, leuprolide concentrations started to plateau within two days after dosing and remained relatively stable for about four to five weeks with plasma concentrations of about 0.30 ng/mL.

Distribution The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism In healthy male volunteers, 4 major metabolites of leuprolide

administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Special Populations The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

Drug Interactions No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

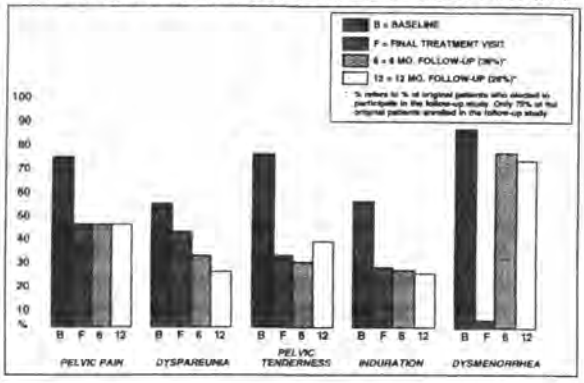
CLINICAL STUDIES

Endometriosis: In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of patients, respectively, excluding those who became pregnant.

Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during two controlled clinical studies. This included all patients at end of treatment and those who elected to participate in the follow-up period. This might provide a slight bias in the results at follow-up as 75% of the original patients entered the follow-up study, and 36% were evaluated at 6 months and 26% at 12 months.

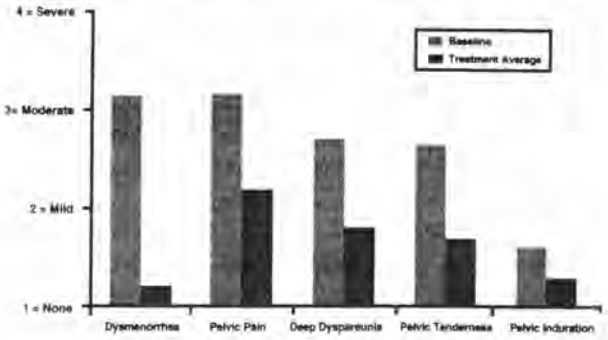
FIGURE 1–PERCENT OF PATIENTS WITH SIGN/SYMPTOMS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP



Hormonal replacement therapy: Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with LUPRON DEPOT alone and 55 women treated with LUPRON plus norethindrone acetate 5 mg daily. The second study was an open label study in which 136 women were treated with LUPRON plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 illustrates the mean pain scores for the LD/N group from the controlled study.

Figure 2
Treatment Period Mean Pain Scores for LD/N* Patients



* LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily

Uterine Leiomyomata (Fibroids): In controlled clinical trials, administration of LUPRON DEPOT 3.75 mg for a period of three or six months was shown to decrease uterine and fibroid volume, thus allowing for relief of clinical symptoms (abdominal bloating, pelvic pain, and pressure). Excessive vaginal bleeding (menorrhagia and menometrorrhagia) decreased, resulting in improvement in hematologic parameters.

In three clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Benefit occurred by three months of therapy, but additional gain was observed with an additional three months of LUPRON DEPOT 3.75 mg. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

Post-treatment follow-up was carried out for a small percentage of LUPRON DEPOT 3.75 mg patients among the 77% who demonstrated a $\geq$ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

In another controlled clinical study, enrollment was based on hematocrit $\leq$ 30% and/or hemoglobin $\leq$ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of $\geq$ 6% hematocrit and $\geq$ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of $\geq$ 36% and hemoglobin of $\geq$ 12 g/dL, thus allowing for autologous blood donation prior to

surgery. At three months, 75% of patients met this criterion.

At three months, 80% of patients experienced relief from either menorrhagia or menometrorrhagia. As with the previous studies, episodes of spotting and menstrual-like bleeding were noted in some patients.

In this same study, a decrease of ≥ 25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT 3.75 mg.

INDICATIONS AND USAGE

Endometriosis:

LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for WARNINGS, PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 6 months.

Uterine Leiomyomata (Fibroids):

LUPRON DEPOT 3.75 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. (See Table 1.) LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to** three months.

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older.

Table 1
PERCENT OF PATIENTS ACHIEVING HEMOGLOBIN ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
LUPRON DEPOT 3.75 mg with Iron	41*	71**	79*
Iron Alone	17	40	56

* P-Value < 0.01
** P-Value < 0.001

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. 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. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **Pregnancy** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
4. Use in women who are breast-feeding. (See **Nursing Mothers** section.)
5. Norethindrone acetate is contraindicated in women with the following conditions:
   – Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions
   – Markedly impaired liver function or liver disease
   – Known or suspected carcinoma of the breast

WARNINGS

Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.

When used monthly at the recommended dose, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT. Therefore, patients should use non-hormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.

The following applies to co-treatment with LUPRON and norethindrone acetate:

Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

PRECAUTIONS

Information for Patients An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation usually stops with effective doses of LUPRON DEPOT, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT may experience breakthrough bleeding.
2. Patients should not use LUPRON DEPOT if they are pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.
3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a non-hormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
4. 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 returned to normal after treatment was discontinued.

5. Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6. The induced hypoestrogenic state **also** results in a loss in bone density over the course of treatment, some of which may not be reversible. For a period up to six months, this bone loss should not be clinically significant. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.) (See ***Changes in Bone Density*** section).
7. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Retreatment with LUPRON DEPOT alone is not recommended.
8. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.
9. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
10. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.

Laboratory Tests See **ADVERSE REACTIONS** section.

Drug Interactions See **CLINICAL PHARMACOLOGY, Pharmacokinetics**.

Drug/Laboratory Test Interactions Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery.

Pregnancy, Teratogenic Effects Pregnancy Category X. (See **CONTRAINDICATIONS** section.) When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, LUPRON DEPOT produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

Nursing Mothers It is not known whether LUPRON DEPOT is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of LUPRON DEPOT on lactation and/or the breast-fed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

Pediatric Use Experience with LUPRON DEPOT 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older. See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

Geriatric Use This product has not been studied in women over 65 years of age and is not indicated in this population.

ADVERSE REACTIONS

Clinical Trials

Estradiol levels may increase during the first weeks following the initial injection of LUPRON, but then decline to menopausal levels. This transient increase in estradiol can be associated with a temporary worsening of signs and symptoms. (See **WARNINGS** section.)

As would be expected with a drug that lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

The **monthly formulation of LUPRON DEPOT 3.75 mg** was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in ≥5% of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

Table 2

ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN ≥5% OF PATIENTS

	Endometriosis (2 Studies)						Uterine Fibroids (4 Studies)			
	LUPRON DEPOT 3.75 mg N=166		Danazol N=136		Placebo N=31		LUPRON DEPOT 3.75 mg N=166		Placebo N=163	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body as a Whole										
Asthenia	5	(3)	9	(7)	0	(0)	14	(8.4)	8	(4.9)
General pain	31	(19)	22	(16)	1	(3)	14	(8.4)	10	(6.1)
Headache*	53	(32)	30	(22)	2	(6)	43	(25.9)	29	(17.8)
Cardiovascular System										
Hot flashes/sweats*	139	(84)	77	(57)	9	(29)	121	(72.9)	29	(17.8)
Gastrointestinal System										
Nausea/vomiting	21	(13)	17	(13)	1	(3)	8	(4.8)	6	(3.7)
GI disturbances*	11	(7)	8	(6)	1	(3)	5	(3.0)	2	(1.2)
Metabolic and Nutritional Disorders										
Edema	12	(7)	17	(13)	1	(3)	9	(5.4)	2	(1.2)
Weight gain/loss	22	(13)	36	(26)	0	(0)	5	(3.0)	2	(1.2)
Endocrine System										
Acne	17	(10)	27	(20)	0	(0)	0	(0)	0	(0)
Hirsutism	2	(1)	9	(7)	1	(3)	1	(0.6)	0	(0)
Musculoskeletal System										
Joint disorder*	14	(8)	11	(8)	0	(0)	13	(7.8)	5	(3.1)
Myalgia*	1	(1)	7	(5)	0	(0)	1	(0.6)	0	(0)
Nervous System										
Decreased libido*	19	(11)	6	(4)	0	(0)	3	(1.8)	0	(0)
Depression/emotional lability*	36	(22)	27	(20)	1	(3)	18	(10.8)	7	(4.3)
Dizziness	19	(11)	4	(3)	0	(0)	3	(1.8)	6	(3.7)
Nervousness*	8	(5)	11	(8)	0	(0)	8	(4.8)	1	(0.6)
Neuromuscular disorders*	11	(7)	17	(13)	0	(0)	3	(1.8)	0	(0)
Paresthesias	12	(7)	11	(8)	0	(0)	2	(1.2)	1	(0.6)
Skin and Appendages										
Skin reactions	17	(10)	20	(15)	1	(3)	5	(3.0)	2	(1.2)
Urogenital System										
Breast changes/tenderness/pain*	10	(6)	12	(9)	0	(0)	3	(1.8)	7	(4.3)
Vaginitis*	46	(28)	23	(17)	0	(0)	19	(11.4)	3	(1.8)

In these same studies, symptoms reported in <5% of patients included: *Body as a Whole* - Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* - Palpitations, Syncope, Tachycardia; *Digestive System* - Appetite changes, Dry mouth, Thirst; *Endocrine System* - Androgen-like effects; *Hemic and Lymphatic System* - Ecchymosis, Lymphadenopathy; *Nervous System* - Anxiety*, Insomnia/Sleep disorders*, Delusions, Memory disorder, Personality disorder; *Respiratory System* - Rhinitis; *Skin and Appendages* - Alopecia, Hair disorder, Nail disorder; *Special Senses* - Conjunctivitis, Ophthalmologic disorders*, Taste perversion; *Urogenital System* - Dysuria*, Lactation, Menstrual disorders.

*=Possible effect of decreased estrogen.

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRON DEPOT. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included glossitis, hypesthesia, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

Table 3 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group during the first 6 months of treatment in the add-back clinical studies.

In the controlled clinical trial, 50 of 51 (98%) patients in the LD group and 48 of 55 (87%) patients in the LD/N group reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes. The mean number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups, respectively.

Table 3
TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS

	Controlled Study				Open Label Study	
	LD - Only[1] N=51		LD/N[2] N=55		LD/N[2] N=136	
Adverse Events	N	(%)	N	(%)	N	(%)
Any Adverse Event	50	(98)	53	(96)	126	(93)
Body as a Whole						
Asthenia	9	(18)	10	(18)	15	(11)
Headache/Migraine	33	(65)	28	(51)	63	(46)
Injection Site Reaction	1	(2)	5	(9)	4	(3)
Pain	12	(24)	16	(29)	29	(21)
Cardiovascular System						
Hot flashes/sweats	50	(98)	48	(87)	78	(57)
Digestive System						
Altered Bowel Function	7	(14)	8	(15)	14	(10)
Changes in Appetite	2	(4)	0	(0)	8	(6)
GI Disturbance	2	(4)	4	(7)	6	(4)
Nausea/Vomiting	13	(25)	16	(29)	17	(13)
Metabolic and Nutritional Disorders						
Edema	0	(0)	5	(9)	9	(7)
Weight Changes	6	(12)	7	(13)	6	(4)
Nervous System						
Anxiety	3	(6)	0	(0)	11	(8)
Depression/Emotional Lability	16	(31)	15	(27)	46	(34)
Dizziness/Vertigo	8	(16)	6	(11)	10	(7)
Insomnia/Sleep Disorder	16	(31)	7	(13)	20	(15)
Libido Changes	5	(10)	2	(4)	10	(7)
Memory Disorder	3	(6)	1	(2)	6	(4)
Nervousness	4	(8)	2	(4)	15	(11)
Neuromuscular Disorder	1	(2)	5	(9)	4	(3)
Skin and Appendages						
Alopecia	0	(0)	5	(9)	4	(3)
Androgen-Like Effects	2	(4)	3	(5)	24	(18)
Skin/Mucous Membrane Reaction	2	(4)	5	(9)	15	(11)
Urogenital System						
Breast Changes/Pain/Tenderness	3	(6)	7	(13)	11	(8)
Menstrual Disorders	1	(2)	0	(0)	7	(5)
Vaginitis	10	(20)	8	(15)	11	(8)

[1] LD-Only = LUPRON DEPOT 3.75 mg
[2] LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg

Changes in Bone Density

In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) and calcium supplementation is effective in significantly reducing the loss of bone mineral density that occurs with LUPRON treatment, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis.

LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data of the lumbar spine from these two studies are presented in Table 4.

Table 4
MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE

	LUPRON DEPOT 3.75 mg		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change	N	Change	N	Change
Week 24[1]	41	-3.2%	42	-0.3%	115	-0.2%
Week 52[2]	29	-6.3%	32	-1.0%	84	-1.1%

[1] Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.
[2] Includes on-treatment measurements >252 days after the first day of treatment.

When LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LUPRON DEPOT for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended.**

Changes in Laboratory Values During Treatment

Plasma Enzymes

Endometriosis: During early clinical trials with LUPRON DEPOT 3.75 mg, regular laboratory monitoring revealed that AST levels were more than twice the upper limit of normal in only one patient. There was no clinical or other laboratory evidence of abnormal liver function.

In two other clinical trials, 6 of 191 patients receiving LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Five of the 6 increases were observed beyond 6 months of treatment. None were associated with elevated bilirubin concentration.

Uterine Leiomyomata (Fibroids): In clinical trials with LUPRON DEPOT 3.75 mg, five (3%) patients had a post-treatment transaminase value that was at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

Lipids

Endometriosis: In earlier clinical studies, 4% of the LUPRON DEPOT 3.75 mg patients and 1% of the danazol patients had total cholesterol values above the normal range at enrollment. These patients also had cholesterol values above the normal range at the end of treatment.

Of those patients whose pretreatment cholesterol values were in the normal range, 7% of the LUPRON DEPOT 3.75 mg patients and 9% of the danazol patients had post-treatment values above the normal range.

The mean (±SEM) pretreatment values for total cholesterol from all patients were 178.8 (2.9) mg/dL in the LUPRON DEPOT 3.75 mg groups and 175.3 (3.0) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 193.3 mg/dL in the LUPRON DEPOT 3.75 mg group and 194.4 mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.03$) in both groups.

Triglycerides were increased above the upper limit of normal in 12% of the patients who received LUPRON DEPOT 3.75 mg and in 6% of the patients who received danazol.

At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT 3.75 mg patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT 3.75 mg compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT 3.75 mg but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables below.

Table 5
SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24

	LUPRON		LUPRON plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change	Baseline Value*	Wk 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0**	5.0%	2.1**	43.4%	2.3**	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%

* mg/dL
** ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data returned to pretreatment values.

Table 6
PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE

	LUPRON		LUPRON plus norethindrone acetate 5 mg daily			
	Controlled Study (n=39)		Controlled Study (n=41)		Open Label Study (n=117)	
	Wk 0	Wk 24*	Wk 0	Wk 24*	Wk 0	Wk 24*
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%

* Includes all patients regardless of baseline value.

Low HDL-cholesterol (<40 mg/dL) and elevated LDL-cholesterol (>160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with LUPRON and norethindrone acetate.

Uterine Leiomyomata (Fibroids): In patients receiving LUPRON DEPOT 3.75 mg, mean changes in cholesterol (+11 mg/dL to +29 mg/dL), LDL cholesterol (+8 mg/dL to +22 mg/dL), HDL cholesterol (0 to +6 mg/dL), and the LDL/HDL ratio (-0.1 to +0.5) were observed across studies. In the one study in which triglycerides were determined, the mean increase from baseline was 32 mg/dL.

Other Changes

Endometriosis: The following changes were seen in approximately 5% to 8% of patients. In the earlier comparative studies,

LUPRON DEPOT 3.75 mg was associated with elevations of LDH and phosphorus, and decreases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH. In the hormonal add-back studies LUPRON DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT.

Uterine Leiomyomata (Fibroids):

Hematology: (See **CLINICAL STUDIES** section.) In LUPRON DEPOT 3.75 mg treated patients, although there were statistically significant mean decreases in platelet counts from baseline to final visit, the last mean platelet counts were within the normal range. Decreases in total WBC count and neutrophils were observed, but were not clinically significant.

Chemistry: Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant.

Postmarketing

During postmarketing surveillance, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported. There have been rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of development or worsening of depression during treatment with LUPRON.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection. Symptoms consistent with fibromyalgia (eg: joint and muscle pain, headaches, sleep disorder, gastrointestinal distress, and shortness of breath) have been reported individually and collectively. Other events reported are:

Cardiovascular System - Hypotension, Pulmonary embolism; *Hemic and Lymphatic System* - Decreased WBC; *Central/Peripheral Nervous System* - Peripheral neuropathy, Spinal fracture/paralysis; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Urogenital System* - Prostate pain.

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in different patient populations.

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.

Endometriosis: The recommended duration of treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate is six months. The choice of LUPRON DEPOT alone or LUPRON DEPOT plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to LUPRON DEPOT alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT monthly and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. LUPRON DEPOT alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.

An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with LUPRON DEPOT and norethindrone acetate.

Uterine Leiomyomata (Fibroids): Recommended duration of therapy with LUPRON DEPOT 3.75 mg is up to 3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

The recommended dose of LUPRON DEPOT is 3.75 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection. *For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:*

1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc™ safety device.

AFTER INJECTION

8. Withdraw the needle. Immediately activate the LuproLoc™ safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

Since the product does not contain a preservative, the suspension should be discarded if not used immediately.

As with other drugs administered by injection, the injection site should be varied periodically.