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 United States District Court for the District of Nevada
Honorable ROGER L. HUNT, United States District Judge

D.C. No. 2:08-cv-00681-RLH-RJJ

APPELLANT'S OPENING BRIEF

(Corrected)

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JURISDICTIONAL STATEMENT

The United States District Court for the District of Nevada ("district court") had jurisdiction over this diversity action pursuant to 28 U.S.C. § 1332(a). This is an appeal from the district court's final judgment entered on August 25, 2011 (CR 308 [1 ER 2]). This Court has jurisdiction pursuant to 28 U.S.C. § 1291.

ISSUES PRESENTED

I.

Whether the district court abused its discretion in refusing to allow Ms. Klein to introduce evidence of the changes in the Lupron label by showing prior Lupron labels, foreign Lupron labels, and subsequent Lupron labels which essentially admit the association of Lupron with the unlabeled adverse events that Ms. Klein suffered.

II.

Whether the district court abused its discretion in refusing to admit proffered MedWatch adverse events reports that demonstrate that the adverse events that Ms. Klein suffered were also suffered by many other women, and known by the Defendants-Appellees.

III.

Whether the district court abused its discretion in refusing to allow Ms. Klein's counsel to use or refer to scientific journals during her case in chief and

during cross-examination of Defendants-Appellees' expert witnesses that were relevant to establishing Defendants-Appellees' prior knowledge of the risks of adverse events of the kind suffered by Ms. Klein and for which the Lupron 3.75 mg label provided to Ms. Klein did not adequately warn.

IV.

Whether the district court abused its discretion in refusing to allow Ms. Klein's experts to testifying regarding their opinions about the effects of Lupron and in excluding their opinions formulated in their Supplemental Expert Reports.

V.

Whether the magistrate judge and the trial judge erred in their discovery orders.

VI.

Whether the trial judge's bias was so pervasive as to deny Ms. Klein a fair trial.

FEDERAL STATUTES AND RULES

Please refer to Addendum A at the end of this brief.

Appellant's Opening Brief

STATEMENT OF THE CASE

This is a direct appeal from a final judgment (CR 308 [1 ER 2]) entered in favor of defendants-appellees in a pharmaceutical product liability action, following a jury trial and defense verdict (CR 302), including an award of costs taxed in the amount of $17,577.12 (CR 309 [1 ER 1]).

A. Statement of Facts

This appeal arises out of a failure-to-warn, pharmaceutical products liability lawsuit brought by plaintiff-appellant Karin Klein (Ms. Klein) against defendants-appellees TAP Pharmaceutical Products Inc. ("TAP") and Abbott Laboratories ("Abbott") (collectively, "TAP-Abbott").[1] CR 1 at 10-15 (Complaint). The pharmaceutical at issue is Lupron Depot 3.75 mg ("Lupron"). CR 1 at 10-14; CR 136 at 1-2 [2 ER 220-21]. In 1990, the federal Food and Drug Administration ("FDA") approved Lupron for the temporary management of pain in women with endometriosis. CR 136 at 2 [2 ER 221].

Karin Klein was 17 years old when she was prescribed Lupron 3.75 mg by her gynecologist, Gary Wright, M.D. 8/4/2011 AM *Trans.* at 536:25 – 537:1, CR

[1] Defendant Takeda Chemical Industries, Ltd. ("Takeda") was never served with the summons and complaint, made no appearance otherwise, and probably should be removed from the caption in this appeal. *See* CR 136 at 2:4 [2 ER 221].

136 at 2 [2 ER 221]. She received six injections over a six month period, from August 2005 to January 2006. CR 136 at 2 [2 ER 221]. The Lupron injections caused Ms. Klein to suffer very serious side effects, which have left her permanently disabled. *See* 8/3/2011 AM *Trans.* at 282:22-23 [4 ER 661]; 8/3/2011 PM *Trans.* at 493:20 – 494:3 [5 ER 872-73]; 8/2/2011 PM *Trans.* at 169:20 – 171:5 [4 ER 538]; *see also* Plaintiff's Exhibits 29 (records from W. Reid Litchfield, M.D – Desert Endocrinology), 30 (records from James Flowers, M .D. & Dr. Andrew Morovati), and 80 (disability letter – military doctor).

Ms. Klein read the Lupron Depot 3.75 mg packaging label[2] thoroughly after the first injection. 8/4/2011 AM *Trans.* at 539:6-10 [5 ER 918]. However, the label (dated January 2005) provided no warnings for many of the adverse events she has experienced, including but not limited to:

- thyroid disease;
- extreme or permanent bone-density loss;
- bone mass development inhibition;
- neck and back pain;
- long term suffering of warned adverse events.

[2] The January 2005 Lupron Depot 3.75 mg label was admitted at trial as Plaintiff's Exhibit 81 and Defendants' Exhibit 501. *See* CR 306 at 7; 305 at 1. A copy of the unmarked Plaintiff's Exhibit 81 is included in the Addendum to this brief for the convenience of the Court.

See 8/4/2011 AM *Trans.* at 539-40 [5 ER 918-20]; *see also* Plaintiff's Exhibit 81. Moreover, had warning of these risks been adequately communicated to Ms. Klein, she would not have taken the Lupron shots; 8/4/2011 AM *Trans.* at 540:8-18 [5 ER 920].

TAP Pharmaceuticals is a joint venture between Takeda Pharmaceuticals, a Japanese public company, and Abbott, an American public company. TAP was dissolved as an entity with Abbott accepting all of TAP's liability in relation to the Lupron business along with all future revenues.[3] Both Takeda and TAP-Abbott took part in the clinical studies, the manufacture and the marketing of Lupron 3.75 mg.

[3] The parties stipulated to the following statement regarding the status of and relationship between the three named defendants:

> On April 30th, 2008, Abbott and Takeda Pharmaceutical Company concluded their TAP Pharmaceutical Products, Inc./TAP Joint Venture. Abbott exchanged its equity interest in TAP for the assets, liabilities, and employees related to TAP's Lupron business

8/5/2011 PM *Trans.* at 780:25 – 781:4 [6 ER 1159]. *See also* 6/3/2009 *Trans.* at 41:5-10 [1 ER 183] (TAP-Abbott's counsel's representation to the district court that: "Abbott – I think we have to keep in mind that Abbott did not acquire the rights to Lupron until approximately May of 2008 when the entity, former entity known as TAP ceased to exist, so in terms of Abbott personnel being involved directly with Lupron, this didn't happen until May of 2008, after the lawsuit was filed and well after plaintiff received the drug.").

B. Procedural History

1. Ms. Klein's Cause of Action

Ms. Klein filed her complaint in the Eighth Judicial District Court in Clark County, Nevada on February 8, 2008, after which the case was removed to the federal District Court for the District of Nevada (Las Vegas). CR 1 (Notice of Removal).

The complaint alleges three causes of action under Nevada law—strict liability, negligence, and breach of warranty—and seeks compensatory as well as punitive damages. CR 1 at 10-15.

2. The Stipulated Facts

The parties stipulated to several factual matters, as recited in the district court's Joint Pretrial Order:

> The following facts are admitted by the parties and require no proof:
>
> 1. Plaintiff KARIN KLEIN is a resident of the State of Nevada.
>
> 2. In 2005, defendant TAP PHARMACEUTICAL PRODUCTS INC. ("TAP") was a Delaware corporation doing business in the State of Nevada.
>
> 3. In 2005, defendant ABBOTT LABORATORIES ("Abbott") was an Illinois corporation doing business in the State of Nevada.
>
> 4. In October 1990, the FDA approved Lupron Depot 3.75 mg

> for the temporary management of pain associated with endometriosis in women.
>
> 5. Lupron Depot 3.75 mg has been on the market since 1990.
>
> 6. In August 2005, Dr. Gary Wright prescribed Lupron Depot 3.75 mg to plaintiff.
>
> 7. Plaintiff received six (6) treatments of Lupron Depot 3.75 mg—one per month—between August 2005 and January 2006.
>
> 8. Before Dr. Wright prescribed Lupron Depot 3.75 mg to plaintiff, she and her father met with Dr. Wright and discussed different treatment options for plaintiff.

CR 136 at 2-3 [2 ER 221-22]; 8/5/2011 PM *Trans.* at 780:25 – 781:4 [6 ER 1159].

3. Denial of Ms. Klein's Motion to Compel Additional Discovery

On August 6, 2010 the trial judge entered an a discovery-related order (CR 140 [1 ER 112]) overruling Ms. Klein's written objection (CR 138 [2 ER 241]) to a minute order entered by the magistrate judge (CR 135) regarding his orders in response to a motion to compel which Ms. Klein argued effectively denied her the ability to discover internal communications of TAP-Abbott regarding the label of Lupron, the drug they manufactured and sold to Ms. Klein.

4. The Exclusion of Ms. Klein's Proffered Evidence Regarding Prior Labels, Subsequent Labels and Current Foreign Lupron Labels, Relevant Portions of the Physician's Desk Reference, and other Proffered Evidence Regarding Known Lupron Adverse Risks

During trial, Ms. Klein was not allowed to show the jury other Lupron labels, including those in use prior to 2005 that contain warnings about thyroid enlargement and extreme bone density loss. She was also precluded by the trial judge from showing the jury the Danish Lupron label to show that TAP-Abbott knew of the association of Lupron with the known adverse events of enlarged thyroid and extreme bone mineral density loss. Ms. Klein attempted to admit the 2009 and 2010 Lupron labels to show subsequent remedial conduct, but this was also not allowed by the trial judge. *See* CR 285 ("Trial Brief and Offer of Proof Regarding Pre-2005 Lupron Labels and the 2009-2010 Lupron Labels").

Ms. Klein filed a Motion *in Limine* prior to trial in order to address the admissibility of the other Lupron labels. CR 175 at 5:10-6:13 [2 ER 269-70]. The district court erroneously denied the motion *in limine* and ordered that Plaintiff could not mention any Lupron label other than the January 2005 label which Ms. Klein received at the time of her treatment. *See* 7/15/2011 *Trans.* at 13:11-15:6 [1 ER 84-86]. At trial, when the label issue came up again, the district court reaffirmed its ruling on the motion in limine. *See, e.g.*, 8/2/2011 AM *Trans.* (CR 277) at 130:24-25 [1 ER 68].

On direct examination of Ms. Klein's general causation expert, Dr. John L. Gueriguian was not allowed to mention prior labels, Physician's Desk Reference entries (PDR's), or foreign labels. 8/2/2011 AM *Trans.* at 89-93, and 120-131 [1 ER 53-69.

Later, Ms. Klein's specific causation expert, Dr. David Redwine was similarly forbidden from testifying about his 750 patients' experiences with Lupron. 8/3/2011 AM *Trans.* at 310 – 322 [4 ER 689-701]] (objection sustained). Neither was Dr. Redwine allowed to testify regarding the subject Lupron label, or any other labels, on the grounds that Dr. Redwine was not designated as a "labeling expert." 8/3/2011 PM *Trans*. at 403:14 – 405:14 [5 ER 782-84]).[4]

The district court would not allow Ms. Klein's counsel to cross examine Dr. Peck (TAP-Abbott's FDA expert) regarding any other Lupron labels (that is, Lupron labels other that the January 2005 label, which Ms. Klein received). *See* 7/15/2011 *Trans.* at 13:11-15:6 [1 ER 85-86]; 8/8/2011 PM *Trans.* at 1054:6 – 1059 [ER 1434-39]; *see also*, CR 285:2, "Plaintiff's Trial Brief and Offer of Proof Regarding Pre-2005 Lupron Labels and the 2009-2010 Lupron Labels").

[4] The district court later refused to apply the same standard to TAP-Abbott's expert, when it permitted Dr. Blackwell (also not designated as a "labeling expert") to testify on behalf of TAP-Abbott, regarding the Lupron label, over the objection of Ms. Klein's counsel. *See* 8/5/2011 PM *Trans.* at 847:16 – 850:8 [1 ER 25]. At the same time the trial judge allowed TAP-Abbott's expert Dr. Blackwell also to testify specifically about the number of patients he treated with Lupron, the sufficiency of the Lupron label, (beyond his expertise), that it was sufficient; and, that no further warnings were needed other than those that were given.

The district court also effectively prevented Ms. Klein's counsel from using the other Lupron labels to cross-examine TAP-Abbott's expert, Dr. Richard Blackwell, who testified at trial 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). In fact, the prior labels for Lupron 3.75 mg admitted an association with thyroid disease and extreme bone density loss—as does the current foreign label. Yet, these adverse events had been removed from the current US women's label. *See* CR 281 (offer of proof regarding MedWatch reports); CR 175 (Ms. Klein's motion *in limine* regarding labels with labels attached) at 2-3, 10-14, 16-20, 22-42, 44-53, 55-78 [2 ER 266-67, 274-78, 280-84, 286-306, 308-17, 319-42].[5]

5. The District Court's Exclusion of Ms. Klein's Proffered MedWatch Reports and Other Reports of Lupron Adverse Events

The district court erroneously excluded any testimony from Ms. Klein's FDA expert, Dr. Gueriguian, regarding Lupron's adverse events and MedWatch

[5] Copies of the referenced labels are also attached to this brief. *See* Addendum at B-1, B-2, B-3, B-4.

reports (which contain adverse events reports), which were offered to demonstrate that many other women had reported to the FDA and TAP-Abbott adverse events from Lupron treatment. *See* 8/2/2011 AM *Trans.* at 69:3-24, 70:1-15, 76:20-82 [1 ER 43-51]; *see also* CR 281 (Ms. Klein's Trial Brief submitted as Offer of Proof Regarding Evidence of Certain Adverse Event Reports); CR 209 (Ms. Klein's objection to Defendants' MIL re Adverse Events Reports). The adverse events in these excluded reports were the same or similar to the adverse events suffered by Ms. Klein but were not identified in the January 2005 label she was given.

The district court also prevented cross-examination of TAP-Abbott's expert, Dr. Blackwell, concerning the other labels and MedWatch reports, which would have devastated Dr. Blackwell's credibility and shown the jury that TAP-Abbott had knowledge and notice of the association of Ms. Klein's unwarned adverse events. *See* 8/5/2011 PM *Trans.* at 868:17-870:5 [1 ER 34-36]); s*ee also* CR 169 at 1-5, CR 167 (Ms. Klein's Motion *in Limine* No. 8 regarding admission of MedWatch reports and adverse events) and CR 169 (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]).

6. *The District Court's Refusal to Allow Ms. Klein's Counsel to Use or Refer to Scientific Journal Articles Concerning Known Lupron Risks During Her Case in Chief and During Cross-Examination of TAP-Abbott's Expert Witnesses*

The district court would not allow Ms. Klein's counsel to cross-examine TAP-Abbott's expert, Dr. Richard Blackwell, regarding his knowledge of scientific journal articles which would have confirmed the association of thyroid disorder with Lupron and impeached his credibility. 8/5/2011 PM *Trans.* at 853 – 855 [1 ER 31-33].

The district court also sustained TAP-Abbott's objections when Ms. Klein's counsel tried to cross-examine TAP-Abbott's FDA expert, Dr. Peck, regarding the scientific journal articles that confirmed the association of Lupron with thyroid disorder and extreme bone density loss. *See* 8/8/2011 PM *Trans.* at 1034 – 1037 [1 ER 11-14].

7. *The District Court's Refusal to Allow Ms. Klein's Counsel to Use or Refer to Relevant, Lupron-Related Scientific Journal Articles During Her Case in Chief and During Cross-Examination of TAP-Abbott's' Expert Witnesses*

The district court would not allow Ms. Klein's counsel to cross-examine TAP-Abbott's expert, Dr. Blackwell, regarding his knowledge of scientific journal

articles which confirmed the association of thyroid disorder with Lupron. *See* 8/5/2011 PM *Trans.* at 853 – 855 [1 ER 31-33]; *see also* CR 167 (Ms. Klein's Motion *in Limine* No. 8) and CR 265 (7/15/2011 *Trans.* at 8:20 – 10:10 [1 ER 79-81, 95-96] (denying Motion *in Limine*)).

The district court also sustained TAP-Abbott's objections when Ms. Klein's counsel tried to cross-examine TAP-Abbott's FDA expert, Dr. Peck, regarding the scientific journal articles that confirmed the association of Lupron with thyroid disorder and extreme bone density loss. *See* 8/8/2011 PM *Trans.* at 1034 – 1037 [1 ER 11-14].

8. The Striking of the Supplemental Expert Reports Submitted by Ms. Klein's Experts and the District Court's Exclusion of the Experts' Opinions About the Effects of Lupron, as Set Forth Therein

Just prior to trial, TAP-Abbott successfully moved the district court (CR 231) to strike Ms. Klein's supplemental expert reports and to prevent Ms. Klein's experts from testifying regarding their opinions contained in their Supplemental Reports. *See* 7/15/2011 *Trans.* at 28:6-9 and 36:5 – 37:9) [1 ER 99-107]. The district court made its ruling without the benefit of a written response or any chance to be heard by Ms. Klein, in spite of her counsel's assertion that the supplemental reports were not filed late. When asked if Ms. Klein may have the opportunity to file a timely response, the district court indicated it would not even

consider Ms. Klein's response, but she was free to file it. (*Id.* at 36:5-15). As a result of the district court's ruling, Ms. Klein's experts were prevented from testifying to any subject matter presented in their supplemental reports.

9. The Jury's Verdict

On August 10, 2011, the jury returned a verdict in favor of TAP-Abbott on all claims. CR 302.

10. The District Court's Judgment and the Award of Costs

On August 25, 2011, the district court clerk entered judgment in favor of TAP-Abbott pursuant to the jury's defense verdict. CR 308 [1 ER 2]. Costs were taxed in the amount of $17,577.12 and included in the judgment. CR 309 [1 ER 1].

SUMMARY OF THE ARGUMENT

One of the key elements of a failure to warn case is proving that the drug manufacturer was aware of adverse events associated with their drug of which they failed to warn. The best way to prove knowledge or notice of such an association is to show that a drug manufacturer has already warned of the adverse events, inasmuch as a prior acknowledgement of the association is tantamount to an admission. Ms. Klein was forbidden to mention prior and subsequent Lupron labels, and foreign Lupron labels, in her case in chief. She was also forbidden

from cross-examining TAP-Abbott's experts about their knowledge of the other Lupron labels and the effective admissions contained therein. This was an abuse of discretion and was a denial of due process which guaranteed an erroneous verdict, since the jury never found out about the prior associations of adverse events and that TAP-Abbott previously knew of these associations.

If this failure to disclose is merely a business decision, then U.S. citizens and the general public have a right to know. This is the only acceptable public policy in this regard.

The district court further abused its discretion in refusing to admit proffered MedWatch adverse events reports that also would have demonstrated to the jury that the adverse events suffered by Ms. Klein were known to TAP-Abbott and, in fact, were also suffered by many other women. Similarly, the district court abused its discretion in forbidding Ms. Klein's counsel from using or referring to scientific journals during her case in chief and during cross-examination of TAP-Abbott's' expert witnesses that also were relevant to establishing their prior knowledge of the risks of adverse events suffered by Ms. Klein—but for which there were no adequate warnings on the Lupron 3.75 mg label she was provided.

The district court abused its discretion in striking Ms. Klein's supplemental expert reports prior to trial and in, consequently, forbidding her experts from testifying at trial with regard to the opinions stated in those supplemental reports. Contrary to the district court conclusion, the supplemental reports were not

untimely. They were timely submitted in conformity with the requirements of Fed.R.Civ.P. 26. Moreover, the timing of the supplemental expert reports was largely dictated by the untimely discovery responses provided by TAP-Abbott and the fact that crucial documents sat in the magistrate judge's chambers, undergoing in camera review, for nine months—thus preventing Ms. Klein's counsel (and her experts) from reviewing them.

The district court erred in certain of its discovery-related orders, which had the effect of substantially prejudicing Ms. Klein in the preparation and presentation of her case to the jury. This included the district court's wrongful failure to compel TAP-Abbott to produce documents related to their internal discussions regarding the Lupron labels and why various adverse events, although included in some Lupron labels used elsewhere and at different time, were nevertheless omitted from the label provided with the Lupron administered to Ms. Klein.

Finally, reversal and remand to a new judge is warranted based on the district court judge's pervasive demonstration of bias against Ms. Klein.

ARGUMENT

I.

A NEW TRIAL IS REQUIRED BASED ON THE DISTRICT COURT'S ERRONEOUS EVIDENTIARY RULINGS DURING AND PRIOR TO TRIAL

A. Standard of Review

Evidentiary rulings are reviewed for an abuse of discretion. *See Sprint/United Mgmt. Co. v. Mendelsohn*, 128 S. Ct. 1140, 1145 (2008); *Wicker v. Oregon Bureau of Labor*, 543 F.3d 1168, 1173 (9th Cir. 2008); *see, e.g.*, *Ostad v. Oregon Health Sciences Univ.*, 327 F.3d 876, 885 (9th Cir. 2003) (hearsay); *Geurin v. Winston Indus., Inc.*, 316 F.3d 879, 882 (9th Cir. 2002) (exclusion of evidence); *White v. Ford Motor Co.*, 312 F.3d 998, 1006 (9th Cir. 2002) (admission of expert testimony), *amended by* 335 F.3d 833 (9th Cir. 2003). To reverse on the basis of an erroneous evidentiary ruling, the court must conclude not only that the district court abused its discretion, but also that the error was prejudicial. *See Harper v. City of Los Angeles*, 533 F.3d 1010, 1030 (9th Cir. 2008); *see also Tritchler v. County of Lake*, 358 F.3d 1150, 1155 (9th Cir. 2004); *Geurin*, 316 at 882. Prejudice means that, more probable than not, the lower court's error tainted the verdict. *See Harper*, 533 F.3d at 1030; *McEuin v. Crown Equip. Corp.*, 328 F.3d 1028, 1032 (9th Cir. 2003); *Geurin*, 316 F.3d at 882.

The district court's decision to admit or exclude expert testimony is reviewed for an abuse of discretion. *See Kumho Tire Co. v. Carmichael*, 526 U.S.

137, 152 (1999); *Summers v. Delta Air Lines, Inc.*, 508 F.3d 923, 926 (9th Cir. 2007); *Sullivan v. United States Dep't of Navy*, 365 F.3d 827, 832 (9th Cir. 2004); *see, e.g., Guidroz-Brault v. Missouri Pac. R.R. Co.*, 254 F.3d 825, 830 (9th Cir. 2001) (excluded evidence).

A district court's interpretation of the Federal Rules of Civil Procedure is reviewed de novo. *See Hambleton Bros. Lumber Co. v. Balkin Enterprises, Inc.*, 397 F.3d 1217, 1224 n.5 (9th Cir. 2005) (Fed.R.Civ.P. 30(e)).

The district court's decision to limit the scope and extent of cross-examination is reviewed for an abuse of discretion. *See Dorn v. Burlington N. Santa Fe R.R.*, 397 F.3d 1183, 1192 (9th Cir. 2005); *Robertson v. Burlington N. R.R.*, 32 F.3d 408, 411 (9th Cir. 1994); *see also United States v. Real Property Located at 22 Santa Barbara Dr.*, 264 F.3d 860, 873 (9th Cir. 2001) (applying harmless error review).

A district court's interpretation of state law is reviewed de novo. *See Hauk v. JP Morgan Chase Bank USA*, 552 F.3d 1114, 1118 (9th Cir. 2009).

B. The Court's Erroneous Evidentiary Rulings

1. The district court abused its discretion in precluding Ms. Klein from introducing evidence of prior Lupron labels, subsequent Lupron labels and current foreign Lupron labels which varied from that given to Ms. Klein in certain important respects

In the prior Lupron 3.75 mg labels (the same dosage/milligram that Ms. Klein received), TAP-Abbott warned of "thyroid enlargement," but TAP-Abbott failed to warn of any thyroid disorder in the 2005 label, which Ms. Klein received. Nevertheless, as recounted above, Ms. Klein was precluded by the trial judge introducing evidence and examining and cross-examining witnesses with regard to this 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. Instead, the only label Ms. Klein was allowed to show the jury, or otherwise reference during examination of witnesses, was the 20052005 Lupron label Ms. Klein was given at the time of her treatment. The district court abused its discretion in these

evidentiary rulings related to the admissibility of the other Lupron labels, all of which essentially admit the association of Lupron with the unlabeled adverse events that Ms. Klein suffered.

Moreover, these rulings substantially prejudiced Ms. Klein in the presentation of her case to the jury, both in her case in chief and in her cross-examination of TAP-Abbott's' witnesses. The proffered—but excluded—evidence, testimony, and cross-examination would have allowed Ms. Klein to clearly demonstrate to the jury that TAP-Abbott had already warned of the very adverse events Ms. Klein suffered (and, thus, obviously knew of the associated risks) ***but must have made a conscious business decision to take those warnings out of the 2005 label received by Ms. Klein***. As a result of the district court's erroneous evidentiary rulings, the jury never knew that TAP-Abbott had already admitted the association of Ms. Klein's adverse events to their drug, Lupron, and that there was had no valid reason for removing the warnings of those risks from the January 2005 label received by Ms. Klein.

The Court's rulings were particularly prejudicial with regard to Klein's ability to cross-examine TAP-Abbott's expert, Dr. Richard Blackwell, who testified at trial 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). In fact, the prior labels for Lupron 3.75 mg admitted an association with thyroid disease and extreme bone density loss—as does the current foreign label. Yet, these adverse events had been removed from the current U.S. women's label. *See* CR 281 (offer of proof regarding MedWatch reports); CR 175 (Ms. Klein's motion in limine regarding labels with labels attached) at 2-3, 10-14, 16-20, 22-42, 44-53, 55-78 [2 ER 266-67, 274-78, 280-84, 286-306, 308-17, 319-42].[6] The jury very likely might have reached a different verdict in this case has Ms. Klein's counsel been allowed to ask Dr. Blackwell the logical question: "Then why did TAP-Abbott warn for an association in the former labels, and still warns in the foreign labels?" Unfortunately, the trial judge's ruling on the motions *in limine* precluded this question from being asked.

That the district court erred in excluding the other Lupron labels is well established by the case law from other jurisdictions.

In *Shatz v. TEC Technical Adhesives*, 415 A.2d 1188, 1191-92 (N.J. Super., App. Div. 1980), the court held that the trial judge erroneously precluded plaintiff from admitting into evidence a warning label on a container of mastic cement

[6] *See* Addendum to this brief at B-1, B-2, B-3, B-4.

manufactured by defendant that had been changed prior to the date of plaintiff's accident. The court reasoned:

> [W]e perceive of no social policy furthered by allowing a defendant to keep from the jury evidence of remedial conduct undertaken before an accident. Certainly we ought not to presume that defendant would have declined to change its label in apprehension that in claims arising from accidents that had not yet happened the prior label by comparison would be asserted to have given inadequate warnings. Indeed, as a matter of policy the evidence of change should have been admitted.

Id. at 141-42, 415 A.2d 1188.

And, in fact, many courts have approved of the use of earlier versions of labels or warnings to show either the adequacy or inadequacy of present warnings. *See e.g.*, *Tucker v. SmithKline Beecham Corp.*, 596 F.Supp.2d 1225, 1229 (S.D. Ind. 2008) ("[T]he ongoing ability, authority, and responsibility to strengthen a label still rest squarely with the drug manufacturer."); *Felix v. Hoffmann-La Roche Inc.*, 540 So. 2d 103, 103-05 (Fla. 1989); *Higgins v. E.I. DuPont De Nemours & Co.*, 863 F.2d 1162, 1167 n.12 (4th Cir. 1988); *Blasing v. P.R.L. Hardenbergh Co.*, 226 N.W.2d 110, 114 (Minn. 1975). Even in cases where the evidence sought to be admitted is post-accident, courts have admitted such evidence to establish a manufacturer's failure to warn of a known risk or defect. *See e.g. Haran v. Union Carbide Corporation*, 497 N.E.2d 678 (N.Y. App. Div. 1986); *Cover v. Cohen*, 461 N.E.2d 864, 868-69 (N.Y. 1984). Following these authorities, and the reasoning therein, the other Lupron labels used in the United States should have

been recognized by the trial judge in this case as both relevant and admissible, especially when the labels demonstrate (as they do here) an association with the very adverse events that Ms. Klein suffered.

The foreign Lupron labels are similarly relevant and admissible to establish TAP-Abbott's failure to adequately warn of the adverse risks Ms. Klein faced when undergoing her Lupron treatments. For example, in *Delaware [Wyeth] v. Rowatt*, 126 Nev. — , — , 244 P.3d 765, 772-73, 784 (2010), the Nevada Supreme Court, in discussing the history of Wyeth's drug Prempro, cited European studies linking the drug to breast cancer and modifications to the European labels that were not made to the labels used in the United States. Thus, evidence of foreign labels was appropriately admitted to show the jury both the drug company's knowledge of the risks and its conscious failure to warn of these risks within the United States.

Similarly, in the multi-district litigation, *In re Prempro Products Liability Litigation*, the foreign labels were admitted to show the manufacturers knowledge of the risks and their failure to warn users of Prempro in the United States of those same known risks. *See generally In re Prempro Products Liability Litigation*, 586 F.3d 547 (8th Cir. 2009); *See also Woulfe v. Eli Lilly & Co.*, 965 F. Supp. 1478, 1479 (E.D. Okl. 1997) and *Axen v. American Home Prods. Corp.*, 974 P.2d 224, 242 (Or. Ct. App. 1999).

In short, the foreign Lupron labels—like the other American Lupron labels—are relevant and admissible, and the district court abused its discretion in denying their proffered use by Ms. Klein. The foreign labels are relevant to establish that TAP-Abbott knew of the risks of Lupron and that they nevertheless consciously failed to adequately warn their American consumers, including Ms. Klein, of those known risks.

2. The district court abused its discretion in prohibiting Ms. Klein from introducing MedWatch and adverse events reports that would have demonstrated that the adverse events that Ms. Klein suffered, were also suffered by many other women, and the risks were thus well known to TAP-Abbott

The district court erroneously excluded any testimony from Ms. Klein's FDA expert, Dr. Gueriguian, regarding Lupron's adverse events and MedWatch reports (which contain adverse events reports), which would have clearly demonstrated to the jury that many other women had reported to the FDA and TAP-Abbott adverse events. These reports were similar to the adverse events that Ms. Klein suffered, which were not identified in the January 2005 label that was given to Ms. Klein. These excluded adverse events and MedWatch reports were offered to show that TAP-Abbott had knowledge—and, therefore, was on notice—that Lupron was frequently associated with many unwarned adverse events

suffered by Ms. Klein. (*See* 8/2/2011 AM *Trans.* at 69:3-24, 70:1-15, 76:20-82 [1 ER 43-51]; *see also* CR 281 (Ms. Klein's Trial Brief submitted as Offer of Proof Regarding Evidence of Certain Adverse Event Reports).

The district court also prevented cross-examination of TAP-Abbott's expert, Dr. Blackwell, concerning the other labels and MedWatch reports, which would have shown the jury that TAP-Abbott had knowledge and notice of the association of Ms. Klein's unwarned adverse events. *See* 8/5/2011 PM *Trans.* at 868:17-870:5 [1 ER 34-36]); s*ee also* CR 169 at 1-5, CR 167 (Ms. Klein's Motion *in Limine* No. 8 regarding admission of MedWatch reports and adverse events) and CR 169 (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]).

The Supreme Court of Nevada "has recognized that prior and subsequent accidents are admissible in an action based on strict liability." *Robinson v. G.G.C., Inc.*, 107 Nev. 135, 140, 808 P.2d 522, 525 (1991); *Beattie v. Thomas*, 99 Nev. 579, 668 P.2d 268 (1983); *Ginnis v. Mapes Hotel Corp.*, 86 Nev. 408, 470 P.2d 135 (1970). As stated by the Nevada Supreme Court in *Beattie*:

> In strict tort liability cases, evidence of prior or subsequent mishaps similar to the one in issue, involving the same product, are admissible to show faulty design or manufacture or other elements of the strict liability cause of action.

Beattie, 99 Nev. At 585-586, 668 P.2d at 272.

As a general rule, evidence of the occurrence or non-occurrence of prior accidents is admissible for the purpose of showing the dangerous character of an instrumentality and also showing the defendant's knowledge. *Jackson v. Bouton*, 630 So. 2d 1173 (Fla. Ct. App. 1994).

In *Ginnis*, the Plaintiff was injured in an automatic door. The Nevada Supreme Court held that evidence of prior and subsequent repair orders and subsequent accidents involving the same door were admissible to show a defective and dangerous condition and causation. *Ginnis*, 86 Nev. at 413, 470 P.2d at 139 (1970). This evidence is equally important in a negligence cause of action since "[o]ne measure of the duty element of a negligence cause of action is the defendant's actual or implied knowledge of a defect. . . ." *Jackson v. Bouton*, 630 So.2d 1173 (Fla. Ct. App. 1994).

Ms. Klein proffered evidence in the form of MedWatch Reports, Scientific studies and related documents all of which indicated that adverse reactions she experienced with Lupron also occurred in other people and that TAP-Abbott had full knowledge of these adverse effects. All of these incidents go to show whether TAP-Abbott had knowledge of the dangers posed by Lupron Depot and, in particular, knowledge of the risk of certain adverse events posed by Lupron, actually suffered by Ms. Klein, and about which she was not adequately warned. Because this evidence was needed to establish at least one element of Ms. Klein's

causes of action for strict liability, this evidence is relevant and should have been admitted.

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 standard is not a causation standard. 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 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).

Since Ms. Klein's experts were completely forbidden to discuss adverse events reports, and her counsel were blocked from mentioning adverse events reports on cross-examination of defense experts, Ms. Klein was greatly prejudiced in her ability both to present her case to the jury and to rebut TAP-Abbott's defense. Again, had she been able to present a complete case to the jury, including informing the jury of the adverse events and the MedWatch reports (which clearly showed the association of Lupron with the unwarned adverse events that Ms. Klein suffered), Dr. Blackwell, the defense expert on causation would have been severely impeached, and it is likely that the jury would have reached a different result in its deliberations.

3. The district court abused its discretion in refusing to allow Ms. Klein's counsel to use or refer scientific journal articles during her case in chief and during cross-examination of TAP-Abbott's' expert witnesses

The district court would not allow Ms. Klein's counsel to cross-examine TAP-Abbott's expert, Dr. Blackwell, regarding his knowledge of scientific journal articles which confirmed the association of thyroid disorder with Lupron. *See* 8/5/2011 PM *Trans.* at 853 – 855 [1 ER 31-33].

The district court also sustained TAP-Abbott's objections when Ms. Klein's counsel tried to cross-examine TAP-Abbott's FDA expert, Dr. Peck, regarding the scientific journal articles that confirmed the association of Lupron with thyroid disorder and extreme bone density loss. *See* 8/8/2011 PM *Trans.* at 1034 – 1037 [1 ER 11-14].

As stated above, 21 CFR 201.80(e), requires 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***." (Emphasis added). One of the factors to consider, to determine whether or not there is reasonable evidence of an association, are found in 21 U.S.C. § 355-1(b), which includes "information derived from a clinical trial, an adverse event report, a post approval study, or ***peer-reviewed biomedical literature***." (Emphasis added).

In this case, the district court ignored both 21 CFR 201.80(e) and 21 U.S.C. § 355-1(b) and prevented Ms. Klein from using scientific literature in her case in chief, pursuant to the court's decisions on the motions *in Limine*. *See* CR 167 (Ms. Klein's Motion *in Limine* No. 8) and CR 265 (7/15/2011 *Trans.* at 8:20 – 10:10 [1 ER 79-81] (denying Motion *in Limine*)).

The district court also prevented Ms. Klein from using this important evidence during cross-examination of TAP-Abbott's experts. As a result, Ms. Klein was never allowed to show the jury that TAP-Abbott's January 2005 Lupron label was defective because it failed to warn of known adverse events which were clearly associated with use of Lupron in the scientific journals. This error is extremely prejudicial because it goes to the heart of the main elements of Ms. Klein's case (*e.g.*, failure to warn and causation).

4. The district court abused its discretion in refusing to allow Ms. Klein's experts from testifying regarding their opinions about the effects of Lupron, as set forth in their Supplemental Expert Reports submitted prior to trial

Just prior to trial, TAP-Abbott successfully moved the district court (CR 231) to strike Ms. Klein's supplemental expert reports and to prevent Ms. Klein's experts from testifying regarding their opinions contained in their Supplemental Reports. *See* 7/15/2011 *Trans.* at 28:6-9, and 36:5 – 37:9 [1 ER 99-107]). The

district court made its ruling without the benefit of a written response or any chance to be heard by Ms. Klein, in spite of her counsel's assertion that the supplemental reports were not filed late. When asked if Ms. Klein may have the opportunity to file a timely response, the district court indicated it would not even consider Ms. Klein's response, but she was free to file it. (*Id.* at 36:5-15).[7] As a result of the district court's ruling, Ms. Klein's experts were prevented from testifying to any subject matter presented in their supplemental reports.

The supplemental expert reports were not untimely. The district court abused its discretion in striking the reports and in limiting the testimony of Ms. Klein's experts accordingly. Ms. Klein was, again, prejudiced by not being able to present an effective case in support of her claims.

In prematurely granting TAP-Abbott's motion to strike (CR 231), Ms. Klein's counsel engaged in the following colloquy with the trial judge:

> **MR. HUGGINS:** But, your Honor, what we — we didn't really spring any information on them. We are in full compliance with Rule 26 and Rule 26 requires that 30 days prior to trial that you supplement and that's what we did, and that's all we did. And we've got that –
>
> **THE COURT:** You may be in compliance with that rule but

[7] In fact, Ms. Klein did file a response in opposition (CR 258) on July 18, 2011, but this was apparently not considered by the district court, as the district court had warned at the hearing 3 days earlier. On July 15, 2011, the trial judge granted TAP-Abbott's motion (CR 231) to strike Ms. Klein's Supplemental Expert Reports, before the response deadline of July 23, 2011. 7/15/ 2011 *Trans.* at 28:6-9 [1 ER 99-107].

> you're not in compliance with the Court's rule and the Court's order, Counsel.

7/15/2011 *Trans.* at 37:2-9 [1 ER 108].

The district court never stated what "Court's rule and the Court's order" were allegedly violated. In any event, there was no violation of any court rule or order. Rather, Ms. Klein timely submitted her initial expert reports in March 2009, but most of TAP-Abbott's discovery documents were not provided to Ms. Klein until March 26, 2010, ten months ***after*** the discovery cutoff date (CR 38 at 22), and after the initial expert reports were due to be exchanged on March 20, 2009 (CR 38 at 23-24). Therefore, any delay in getting the supplemental expert reports was directly and only attributable to TAP-Abbott's delays in producing all the missing adverse events reports and labeling information that had been requested and never produced until after Ms. Klein's motion to compel production.[8]

After defense counsel submitted the adverse events and other materials in camera, they remained in camera and were not disclosed to Ms. Klein ***until more than nine months later***, on or about March 26, 2010, when they were finally released from the Magistrate's chambers. *See* CR 121. During that time, Ms. Klein had virtually no access to most of the adverse events reports concerning

[8] *See* CR 56 (motion to compel) and CR 64 (Minutes of Proceedings), which states: "The motion to compel [56] is GRANTED to the extent that defense counsel is to submit in camera to the Court documents requested in letter exhibit 8 attached to the motion by 6/17/09."

Lupron in TAP-Abbott's possession. Thus, these could not be used by experts or counsel to prepare for trial, summary judgment motions, *Daubert* motions and, of course, the supplemental expert reports.[9]

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[9] Ms. Klein was justified in moving to compel production of adverse events and labeling materials for Lupron, which TAP-Abbott admitted after the fact by their production and by their letter stating that the discovery materials were misplaced in various warehouses due to "collection or filing error or oversight." *See* CR 126 at 11-13).

As a result of TAP-Abbott's delay, Ms. Klein was severely hampered in her preparation for trial. Nevertheless, TAP-Abbott argued in their motion to strike the supplemental expert reports (*see* CR 231) that the supplemental reports were "two years late"—and the district court, to the surprise of Ms. Klein's counsel, agreed. *See* 7/15/2011 *Trans.* at 28:6-9 and 36:5 – 37-9 [1 ER 99-107]).

Due to the blatant unfairness of the Magistrate's discovery orders, which severely restricted Ms. Klein's discovery of all of the adverse events and labeling information, all subsequent reports, motions and trial preparations were likewise severely prejudiced. Ms. Klein objected to the Magistrate's discovery orders (*see* CR 138 [2 ER 241]), hoping to get the remainder of unproduced discovery materials, including undisclosed internal communications regarding the Lupron labeling changes, inter alia, but the Magistrate's discovery orders were affirmed by the district court (CR 140 [1 ER 112]).

Ms. Klein attempted to appeal the interlocutory orders to this Court prior to trial, but the appeal was dismissed on jurisdictional grounds. Accordingly, Ms. Klein was forced to go to trial with incomplete discovery documents and no internal communications showing the motives behind the label changes that lead to the sanitized January 2005 label that Ms. Klein received—the label that lacked warning for several of the known adverse events which she later suffered.

Even those documents that were finally provided on March 26, 2010, had been successfully suppressed as long as possible by TAP-Abbott, who clearly had every intention of not producing the Lupron adverse events and labeling information until they absolutely had to do so by court order. And by the time they were partially provided, they were of little use to Ms. Klein. Essentially, the Magistrate's discovery orders (affirmed by the district judge) relating to Ms. Klein's Motion to Compel were completely ineffective, as they were too little too late, essentially letting TAP-Abbott off the hook for gross discovery abuse.

The district court's order striking Ms. Klein's supplemental expert reports was an abuse of the district court's discretion, and severely prejudiced her case, since the supplemental reports were largely based upon the materials that had to be compelled and were not received until after March 26, 2010.

A party is permitted to supplement an expert report after the close of discovery if the failure to supplement the report in a timely manner is, "substantially justified or harmless." *See* Fed.R.Civ.P. 37(c)(1). In determining whether such a failure is justified or harmless, the Court should consider: (1) the prejudice or surprise to the party against whom the testimony is offered; (2) the ability of the party to cure the prejudice; (3) the extent to which introducing such testimony would disrupt the trial; and (4) the moving party's bad faith or willfulness. *Woodworker's Supply, Inc. v. Principal Mutual Life Ins. Co.*, 170 F.3d 985, 993 (10th Cir. 1999).

Also, "Federal Rule of Civil Procedure 26(a)(2)(B) requires parties to serve expert disclosures containing "a complete statement of all opinions to be expressed and the basis and reasons therefore. . . ." Fed.R.Civ.P. 26(a)(2)(B); *see also Sierra*

Finally, and most importantly, it should be noted that TAP-Abbott ***never*** produced the internal communications regarding Lupron that had been requested since October 20, 2008. *See* CR 56:3-16). Rather, these were flatly rebuffed and never addressed by the Magistrate's erroneous Minute Entry, with no formal order. See CR 56. So, TAP-Abbott's flagrant, bad-faith discovery tactics paid off in spades for TAP-Abbott in what can only be called a complete travesty of justice for Ms. Klein and the general public.

Club v. Cedar Point Oil Co., 73 F.3d 546, 569 (5th Cir. 1996) ("Rule 26(a) requires initial expert disclosures to be complete and detailed). The purpose of this requirement is to "avoid the disclosure of sketchy and vague' expert information." *Id.* (citing Fed.R.Civ.P. 26 advisory committee's note).

Rule 26(e)(1) provides that parties are under a duty to supplement their disclosures or discovery responses when they learn that a prior response was incomplete or incorrect and that the additional corrective information was not otherwise known to the other parties during the discovery process. Fed.R.Civ.P. 26(e)(1). In addition, that subsection provides that with respect to expert reports, any additions or other changes must be disclosed by the parties by the time their Rule 26(a)(3) pretrial disclosures are due (at least 30 days before trial, pursuant to Rule 26(a)(3)(c)).

In this case, Ms. Klein timely provided her initial expert reports by March 20, 2009, per the Scheduling Order (CR 38). Ms. Klein's supplemental expert reports were updated and disclosed ***prior to*** the 30 day deadline, and, thus, they were not late in any way. Further, any delay in updating the expert reports was directly related to the late production of discovery by TAP-Abbott. After discovery documents were finally produced by TAP-Abbott in June 2009, the documents were held in the Magistrate's chambers (for nine months) until March 26, 2010, after which the documents were finally released to Ms. Klein's counsel. It would have been, therefore, impossible for Ms. Klein's counsel to have updated

or supplemented her expert reports prior to the close of discovery. Under the circumstances, the supplemental expert reports submitted by Ms. Klein's experts were timely and it was an abuse of discretion for the district court to rule otherwise. This error, particularly together with the other errors of the district court in its evidentiary rulings, resulted in substantial prejudice to Ms. Klein in the presentation of her case and, therefore, warrants a remand for a new trial.

II.

A NEW TRIAL IS REQUIRED BASED ON THE DISTRICT COURT'S ERRONEOUS DISCOVERY RULINGS

A. Standard of Review

This Court reviews the district court's rulings concerning discovery for an abuse of discretion. *See Preminger v. Peake*, 552 F.3d 757, 768 n.10 (9th Cir. 2008); *Childress v. Darby Lumber, Inc.*, 357 F.3d 1000, 1009 (9th Cir. 2004). "A district court is vested with broad discretion to permit or deny discovery, and a decision to deny discovery will not be disturbed except upon the clearest showing that the denial of discovery results in actual and substantial prejudice to the complaining litigant." *Laub v. United States Dep't of Interior*, 342 F.3d 1080, 1084, 1093 (9th Cir. 2003) (internal quotation marks and citation omitted); *see also Kulas v. Flores*, 255 F.3d 780, 783 (9th Cir. 2001) (the district court's rulings concerning discovery will only be reversed if the ruling more likely than not

affected the verdict); *Blackburn v. United States*, 100 F.3d 1426, 1436 (9th Cir. 1996) (the district court has wide discretion in controlling discovery and the ruling will not be overturned absent a showing of clear abuse of discretion).

B. The Purpose of Discovery

The purpose of discovery is clear. It is to aid a party in the preparation of their case. *See Pacific Fisheries v. U.S.*, 484 F.3d 1103, 1112 (9th Cir. 2007). However, when one party elects to use discovery to thwart the right of another party to prepare its case, it is an appropriate exercise of the Court's discretion to level the playing field and insist upon full and complete answers and the production of all documents which might lead to admissible evidence to which a privilege does not apply.

The Federal Rules of Civil Procedure permit discovery of "any matter, not privileged, that is relevant to the claim or defense of any party." Fed.R.Civ.P. 26(b)(1). Discovery is not limited solely to admissible evidence but encompasses matters which appear reasonably calculated to lead to the discovery of admissible evidence." *Oppenheimer Fund, Inc. v. Sanders*, 437 U.S. 340 (1978). " Relevance is construed broadly and determined in relation to the facts and circumstances of each case." *Hall v. Harleysville Ins. Co.*, 164 F.R.D. 406, 407 (E.D. Pa. 1996).

Federal Civil Procedure Rule 37 contemplates complete and full cooperation in the discovery process coupled with its mechanism to insure that compliance

through motions to compel where a party fails to appropriately respond to discovery propounded. Specifically, Rule 37, in the relevant part, states:

> **Rule 37. Failure to Make Disclosures or to Cooperate in Discovery; Sanctions**
>
> (a) Motion for an Order Compelling Disclosure or Discovery.
>
> A party seeking discovery may move for an order compelling an answer, designation, production, or inspection. This motion may be made if:
>
> (I)
>
> * * *
>
> (iii) a party ***fails to answer an interrogatory*** submitted under Rule 33; or
>
> (iv) a party fails to respond that inspection will be permitted — or fails to permit inspection — as requested under Rule 34.
>
> (4) Evasive or Incomplete Disclosure, Answer, or Response. For purposes of this subdivision (a), ***an evasive or incomplete disclosure, answer, or response must be treated as a failure to disclose, answer, or respond.***

(Emphasis added).

The discovery process should not be a contest of size and resources, but an honest examination of the relevant facts and evidence. Due process requires an element of fundamental fairness, which applies also in the discovery phase of the proceedings.

Many large corporate entities apparently prefer to use evasive, shifty, uncooperative and incomplete answers as a discovery tool, thereby putting undue burden upon the Plaintiff, who has substantially fewer resources. In such a case, judicial intervention is required in order to compel that which should have been provided voluntarily as contemplated by the rules. Such conduct should not be excused or even rewarded by the court by inaction, which would only effect further damages upon the disabled.

Further, information relating to post claim remediation, both in the product itself and in the packaging materials, is relevant. *See* Fed.R.Evid. 407 (Remediation evidence is admissible to prove intent and purpose). As such, the district court should have overruled all objections concerning prior claims of injury or other litigation involving claims of injuries arising from the Lupron Depot product.

TAP-Abbott objected to almost every request for production based on the requested documents being overly broad, unduly burdensome and not reasonably calculated to lead to admissible evidence. Clearly, while the submissions to the FDA may be substantial in volume, such request was not overly broad. These submissions included scientific studies, adverse reactions and other evidence which are clearly relevant to the issues before this Court. In addition, all labeling, package inserts, brochures, printed literature, and other documentation distributed or circulated by TAP-Abbott about Lupron were similarly relevant to the issues

before this Court as these materials are statements by TAP-Abbott about the efficacy of Lupron and its potential uses.

As noted above, the purpose of discovery is clear. It is to aid a party in the preparation of their case. *See Pacific Fisheries*, 484 F.3d at 1112. Unfortunately, in this case the magistrate and the trial judge simply were not willing to go the lengths necessary to assure that the purposes of discovery were fulfilled with regard to the preparation of Ms. Klein's case, as reflected in the following statement made in the context of considering the party's respective motions in limine prior to trial:

> I will say, however, that this trial will not rehash or make an issue of discovery, any failures of discovery, or failures of disclosure, or what have you. We're not going to get involved in discovery debates and issues. I have seen no evidence that – of any intentional failure to disclose things that were not ultimately disclosed and I will not turn this into a discovery issue to try to show that one side or the other is trying to hide things. ***The discovery is what it is.***
>
> You've had plenty of time to bring motions and have brought motions with respect to this and those motions have been, to a certain extent, granted and orders issued for disclosure ***and that's as far as that is going to go***.

7/15/2011 *Trans.* at 25:20 – 26:6 [1 ER 96] (emphasis added).

C. The District Court's Erroneous Discovery Orders Were so Unfair as to Constitute an Abuse of Discretion, and a Violation of Public Policy

As a result of the district court's discovery rulings, Ms. Klein was denied the ability to discover relevant evidence, most especially TAP-Abbott's internal communications regarding the Lupron label and the reasons for the variations in the various Lupron labels used at other times and/or outside of the United States. The district court's discovery orders were an abuse of discretion, caused substantial prejudice to Ms. Klein in the presentation of her case, and, therefore warrant a new trial. Moreover, if the district court's rulings are allowed to stand, to be adopted and followed by other courts, this Court will be opening the door for additional discovery abuses by drug companies in future cases—much to the likely detriment of the general public, who rightly expect to be protected when drug companies fail to adequately warn of the dangers of their drugs present.

1. TAP-Abbott's Discovery Abuses

Starting in 2008, Ms. Klein's counsel sent discovery requests to TAP-Abbott's counsel requesting, *inter alia*, internal communications, or any internal documents, that referred or related to Lupron. This was an attempt to track the changes in the Lupron label, which that had formerly warned of "thyroid enlargement" as well as extreme bone density loss. Each of these are adverse events that Ms. Klein suffered—and which were no longer listed among the

warning in the 2005 Lupron label she received. *See* CR 56 at 26:19 – 27:7 (Ms. Klein's Interrogatory No. 3 and TAP-Abbott's Response). As the Response to Interrogatory No. 3 indicates, the internal communications regarding Lupron were completely stonewalled and never produced.[10]

TAP-Abbott's discovery responses were answered on November 24, 2008. TAP-Abbott failed to respond to any interrogatories or any requests for production of documents and, instead, declared that access to the documents would be provided only after a protective order was signed. On or about January 12, 2009, the protective order was agreed to by Ms. Klein's counsel. On February 13, 2009, counsel for Ms. Klein travelled to Chicago to review the documents. Counsel for Ms. Klein was taken to a moot court room that contained 25 boxes. The 25 boxes were not placed in numerical order and were generally disorganized and did not have an index. Counsel reviewed all of the documents in the boxes twice during the review process.

There were over 10,000 pages of documents that were available to view in electronic format. Counsel purchased two 4 GB flash drives to download all of the electronic documents. However, counsel for TAP-Abbott refused to allow Ms.

[10] This apparently was the general approach for all of TAP-Abbott's discovery responses. (For an example of the tone of discovery abuse of TAP-Abbott, refusing to answer virtually any discovery requests in good faith, please refer to Ms. Klein's discovery requests and responses thereto attached to Ms. Klein's motion to compel (CR 56) and in the attachments thereto, CR 56 at 23-74).

Klein's attorney to download the electronic documents so that she could review them upon returning to Las Vegas. Instead, TAP-Abbott demanded another protective order. The electronic documents were received on March 28, 2009, eight days after the expert report deadline on March 20, 2009. This denied Ms. Klein's experts the time to review all the available documents.

All of these issues were raised in Klein's Motion to Compel Discovery (CR 60) and the affidavit of counsel attached thereto.

2. Ms. Klein's Efforts at Obtaining the Discovery She Was Entitled To

Ms. Klein also filed a Motion to Amend/Correct & Extend Discovery Plan & Scheduling Order on June 16, 2009 (*see* CR 66). This Motion was filed due to the fact that the Magistrate had already compelled TAP-Abbott to comply with Ms. Klein's discovery requests. TAP-Abbott admitted when they finally complied that indeed they had not provided all of the documents, just as Ms. Klein had alleged. Further, Ms. Klein was seeking an opportunity for a new Discovery Plan so that her experts could examine the documents that were contained on the computer disks that were received after their initial reports were due on March 20, 2009 and for their experts to review the documents that were being provided pursuant to the motion to compel. The Magistrate denied Ms. Klein's motion to extend discovery nine months later. *See* CR 120 (Order Denying [66] Plaintiff's Motion to Extend and Amend Discovery Plan, *etc.*).

Then on 7/15/2011, the trial judge granted TAP-Abbott's motion to strike Ms. Klein's supplemental expert reports (CR 231) without giving Ms. Klein an opportunity to respond. *See* 7/15/2011 *Trans.* at 28:6, and 36:4 – 37:12 [1 ER 99, 107-08]. This order effectively limited Ms. Klein's expert's testimony to only those opinions and other matters from the expert reports of March 20, 2009—essentially shutting the door on allowing her experts to review and discuss the rest of the discovery which TAP-Abbott had produced late. As argued in the previous section of this brief, this handicapped Ms. Klein's case to the point of cutting off all ability to properly present her case to the jury.

Further, according to TAP-Abbott's designated employee for labeling, David C. Ross, the former Director of Regulatory Affairs for Abbott Laboratories, the Annual Reports containing the MedWatch reports would not have been difficult to obtain because the reports were prepared pursuant to FDA regulations on an annual basis. *See* CR 60-3 (affidavit of counsel). However, these documents were not provided until after Ms. Klein's motion to compel and were kept from Ms. Klein's counsel until after March 26th, 2010. *See* CR 60-3 (including affidavit of counsel). The district court inability, or unwillingness, to assure that Ms. Klein completely—and timely—received the discovery she was rightfully due substantially prejudiced Ms. Klein in her trial preparation and, ultimately, in her ability to present her case to the jury.

3. The Prejudicial Effect of TAP-Abbott's Unremedied Discovery Abuses

The original Proposed Discovery Plan/Scheduling Order was only filed on July 16, 2008. CR 19. And the discovery was to be closed by June of 2009, even though this case involved literally tens of thousands of documents and records. Many of those documents were not received until March 28, 2009 and March of 2010. Each of these dates is beyond the expert report deadline of March 20, 2009. Obviously, this case involved extremely complicated litigation requiring additional time for discovery due to the enormous numbers of documents that must be reviewed and synthesized. Nevertheless, the Magistrate refused to allow an extension of discovery, in spite of the effects of failing to do so on Ms. Klein's ability to litigate her claims. *See* CR 120 (order denying Ms. Klein's motion to extend discovery plan and scheduling order); *see also* CR 66 (motion to extend discovery deadlines).

Ms. Klein was forced to file her Motion to Compel in order to obtain TAP-Abbott's internal communications regarding its label changes, and the adverse events that were reported regarding Lupron. The Motion to Compel was heard before the Magistrate, who ruled via minute entry on 6/9/2009 (CR 64), which granted the Motion to Compel in a very limited way, and only insofar as TAP-Abbott was to produce a list of items requested in Exhibit 8, attached to the motion. However this Order allowed TAP-Abbott to escape production of any of the other materials requested, which had been wholly stonewalled by TAP-Abbott.

This included the all-important internal Lupron documents that Ms. Klein had requested. *See* CR 56-2 at 26:19 – 27:7.

The Magistrate's discovery order (CR 64) and the subsequent order affirming the same (CR 140 [1 ER 112]) were erroneous and not harmless error. The failure to require TAP-Abbott to produce their internal communications was extremely prejudicial to Ms. Klein, and extremely favorable to TAP-Abbott, who never had to disclose their rationale for initially warning for "enlarged thyroid" and extreme bone density loss in their earlier labels, and then removing these warnings from the label that Ms. Klein received. TAP-Abbott was also never required to provide any internal communications regarding why they continue to warn for these removed adverse events in their foreign label. This evidence was of vital importance to Ms. Klein, and the general public, as TAP-Abbott has set forth inconsistent and contradictory positions as to the labeling of adverse events of the kind that Ms. Klein suffered. An inference could be drawn that the only reason why the adverse events were removed from Ms. Klein's label was to increase sales of the Lupron product, even when it was known, as admitted in other Lupron labels, that it is associated with serious adverse events. Ms. Klein was prevented from obtaining this discovery, however.

There is a public interest at stake here as well. Common sense and experience informs that the purposeful under-warning of serious adverse events is likely the result of putting profits over patient safety, as Ms. Klein has alleged in

this case. Unfortunately for Ms. Klein, and the general public, TAP-Abbott was given a free pass to entirely sidestep the issue and never be held accountable for the changes in its label. She is now held to suffer, and the general public will also suffer as a result if this kind of stonewalling is approved in this case and allowed to serve as a precedent for future litigation.

If this matter is remanded, discovery should be re-opened and TAP-Abbott should be required to answer in good faith to the discovery requests, which they were able to unfairly—and improperly—avoid in the proceedings to date.[11]

D. TAP-Abbott's Past Criminal History and its Sanctionable Discovery Abuses in this Case

Defendants-Appellees' criminal histories were raised in Ms. Klein's Motion to Compel (CR 60, 60-2, 60-3) and were tendered to illustrate to the trial court that TAP-Abbott have a history of willfully withholding or manipulating data and breaking the law in a calculated way to the detriment of U.S. Citizens.

Both Abbott and TAP have already pleaded guilty to crimes involving fraudulent marketing of their products, including Medicare and Medicaid fraud,

[11] Moreover, because of TAP-Abbott's purposefully evasive approach to discovery, and the delays which arose therefrom, the district court should have extended the time period for filing expert reports or allowed all such reports to be supplemented by the responses to Interrogatories and documents produced in response to Requests for Production of Documents. To do otherwise was to reward the very discovery abuses that the rules are designed to prevent.

conspiracy and bribery in regards to Lupron. They are infamous manipulators of facts and data. In this matter they used discovery abuse as a tactic to suppress the history of their label changes and the adverse events that are associated with Lupron. TAP-Abbott was never forced to disclose internal communications regarding Lupron, or the reasons for the ever-changing label. The suppression of TAP-Abbott's internal communications rises to the level of spoliation if it is intentional. TAP-Abbott's nondisclosure of internal communications was effectively used as a sword and a shield in the district court. First TAP-Abbott refused to produce timely discovery, and then it moved to strike Ms. Klein's supplemental expert reports that are delayed as a result of TAP-Abbott's discovery delays.

In *Kawamata Farms v. United Agri Products*, 948 P.2d 1055 (Haw. 1997), the Hawaii Supreme Court found that DuPont had intentionally withheld information and documents that it should have produced during discovery, the circuit court sanctioned DuPont by, among other things, (a) ordering DuPont to pay a $1.5 million fine to the State of Hawaii, (b) lifting previous protective orders concerning the confidentiality of DuPont documents, with the exception of those documents that contained trade secrets, and (c) declaring that the circuit court would give the jury remedial instructions

In *Computer Task Group, Inc. v. Brotby*, 364 F.3d 1112 (9th Cir. 2004), the Ninth Circuit noted that Discovery in that case was fought tooth and nail. Brotby

refused to fully respond to CTG's interrogatories. Instead, he gave contradictory answers, made frivolous objections and filed baseless motions, never disclosing all the information CTG sought. He made excuses and changed his story repeatedly, making it impossible for CTG to establish basic facts with any certainty. Brotby also refused to produce key documents. Faced with these roadblocks, CTG filed eight motions to compel discovery. The magistrate judge granted all of the motions and issued five separate orders compelling Brotby's cooperation. The magistrate also imposed two monetary sanctions. Brotby paid one but not the other. In August of 1999 — two years after CTG filed suit — the parties were still mired in discovery. CTG filed a motion for terminating sanctions under Federal Rule of Civil Procedure (b)(2). In February 2000, the Magistrate Judge conducted a three-day hearing on the motion for sanctions. Brotby was given the opportunity to cross-examine CTG's witnesses, call his own witnesses and produce evidence.

After the hearing, the Magistrate Judge issued a report detailing Brotby's discovery abuses and concluded that he "has engaged in a consistent, intentional, and prejudicial practice of obstructing discovery." Based on that finding, the Magistrate recommended that the motion for terminating sanctions be granted. The district court deferred to the Magistrate Judge's credibility determination, *see United States v. Raddatz*, 447 U.S. 667, 676 (1980), but otherwise reviewed the record de novo. The court found that Brotby would not cooperate in discovery, that lesser sanctions had failed to secure his cooperation, and that the only

available alternative was to adopt the magistrate judge's recommendation and dismiss Brotby's counter-claims, strike his answer and enter his default on CTG's claims.

In *Appling v. State Farm Mut. Auto Ins. Co.*, 340 F.3d 769 (9th Cir. 2003), the dissenting judge stated the following regarding pretrial discovery: As the Rules Advisory Committee has explained, Rule 26 explicitly imposes an affirmative duty "to engage in pretrial discovery in a responsible manner that is consistent with the spirit and purposes of Rules 26 through 37," Fed.R.Civ.P. 26, Advisory Committee Notes, 1983 Amendment, Subdivision (g), and Rule 37 (c) permits a district court to sanction a party for making false or misleading discovery disclosures. *See* Fed.R.Civ.P. 37(c). As the Washington Supreme Court has held, the Federal Rules of Civil Procedure explicitly encourage the imposition of sanctions for discovery abuse in part because "a spirit of cooperation and forthrightness during the discovery process is necessary for the proper functioning of modern trials." *Washington State Physicians Ins. Exch. & Ass'n v. Fisons Corp.*, 858 P.2d 1054, 1077 (Wash. 1993). The court noted that although "[f]air and reasoned resistance to discovery is not sanctionable. . . misleading . . . responses [are] . . . contrary to the purposes of discovery and . . . most damaging to the fairness of the litigation process." *Id.* at 1079.

In *Fair Housing of Marin v. Combs*, 285 F.3d 899 (9th Cir. 2002), the district court (N.D. Cal., Jenkins, J.) found that Fair Housing had standing and later

sanctioned Combs for discovery abuses by striking his Answer and entering a Default Judgment against him prior to trial. The district court awarded the plaintiff compensatory damages of $24,377 and punitive damages of $74,400, and adopted the magistrate judge's recommendation, made after a full hearing, of attorney's fees and costs in the amount of $508,606.78.

As this Court has previously recognized:

> There is no point to a lawsuit, if it merely applies law to lies. ***True facts must be the foundation for any just result***. Sometimes, as in *Anheuser-Busch*, a party's discovery violations make it impossible for a court to be confident that the parties will ever have access to the true facts.

Valley Engineers Inc. v. Electric Engineering Co., 158 F.3d 1051, 1058 (9th Cir. 1998) (emphasis added) (referring to *Anheuser-Busch, Inc. v. Natural Beverage Distributors*, 69 F.3d 337, 352 (9th Cir. 1995)).

E. Reversal, and Remand with Specific Instructions to the District Court Regarding Ms. Klein's Right to Obtain Previously Requested Discovery, is Warranted

In this case a key component for Ms. Klein's factual case (and any pharmaceutical case) is the ***Adverse Event Reports, MedWatch Reports, and the ever changing labeling of Defendant TAP-Abbott***, which show remedial behavior that is admissible in a products liability case under Nevada law. It was critically important that Ms. Klein be able to discover and prove to a jury what TAP-Abbott

knew about the lack of safety and effectiveness of the drug Lupron Depot. She was prevented from doing so.

The district court's erroneous discovery orders were harmful errors that prevented Ms. Klein from obtaining relevant facts to prove failure of TAP-Abbott to warn Ms. Klein—and the general public—for adverse events that are admittedly associated with TAP-Abbott's drug, Lupron. Ms. Klein is entitled to a new trial, with reopened discovery, and specific instructions to the district court that will guarantee that she receives the discovery that she is rightly entitled to on remand.

III.

THIS MATTER SHOULD BE REVERSED, AND REMANDED TO A NEW JUDGE, BASED ON THE DISTRICT COURT'S CLEAR DEMONSTRATION OF BIAS AGAINST MS. KLEIN

A. Standard of Review

This Court has recognized that "[f]ederal judges are granted broad discretion in supervising trials, and a judge's behavior during trial justifies reversal only if he abuses that discretion. A judge's participation during trial warrants reversal only if the record shows actual bias or leaves an abiding impression that the jury perceived an appearance of advocacy or partiality." *Price v. Kramer*, 200 F.3d 1237, 1252 (9th Cir. 2000) (internal quotation marks and citation omitted).

B. The District Court's Bias Was So Pervasive as To Deny Ms. Klein Access To Fair Discovery and, Ultimately, to Deny Her a Fair Trial

From the very start of the trial, and even before (for example, at the hearings on Motions *in Limine*), the trial judge exhibited extreme bias against Ms. Klein and her counsel and was so argumentative toward Ms. Klein's case at trial as to completely derail any momentum that would have otherwise been established by Ms. Klein in the proof at trial. Not only did the trial judge rule against Ms. Klein on virtually all of her Motions *in Limine*, but he also ruled for TAP-Abbott on virtually all their Motions *in Limine*. 7/15/11 *Trans.* At trial this prepared the stage for a scenario where every time Ms. Klein's counsel tried to present relevant evidence regarding TAP-Abbott's knowledge of an association between Lupron and the un-warned adverse events that Ms. Klein suffered there was an objection made either by defense counsel or the court, *sua sponte*, resulting in rulings that denied Ms. Klein a fair opportunity to present the elements of her case of failure to warn to the jury.

In addition to the many erroneous evidentiary rulings in favor of the defense, noted above, see also the following excerpts indicative of court bias.

1. The district court objects *sua sponte* and suggests the answer to the witness, and comments on the evidence, and arguing for the defense:

> Q. What risks, sir? That's my point. The risk that the FDA is pointing out to TAP and Abbott is "clinical significance." The risk that TAP and Abbott is telling the public is "not clinically significant." Isn't that accurate?

THE COURT: No, Counsel –

THE WITNESS: No.

THE COURT: — that's a misrepresentation of what that says. One's talking about the overall problem; the part you're reading is talking about for the first six months. The rest of it refers to possible permanent loss.

MR. NEMEROFF: With respect your Honor, I'm on cross-examination.

THE COURT: I understand that. You're just misrepresenting the thing in your question.

MR. NEMEROFF: With respect, your Honor, I don't believe it's the Court's position to tell me or the witness or the jury what I'm doing or not. I'm asking the witness a question. If he thinks I'm misrepresenting, I think it's up to him, not up to the Court, to point that out. And I take umbrage with the fact that you've accused me of misrepresenting anything, which I have not.

8/8/2011 PM *Trans.* at 1069:15 – 1070:10 [7 ER 1449-50]).

2. The district court objects *sua sponte*, and argues for the defense:

Q. So, in 2001, when the medical officer said that the "loss of BMD is the most clinically significant and ... adverse consequence of taking Lupron," that medical officer did so with the entire body of scientific evidence in front of him or her to reach that conclusion; is that correct?

A. Yes.

Q. And, after that conclusion was reached, we have no explanation from anybody in a document that we have seen to explain why the "clinical significance" did not make its way into the label that made its way into Karin Klein's hands; isn't that true?

A. No. I can explain.

Q. I don't want an explanation. I'm asking —

THE COURT: Coun- —

BY MR. NEMEROFF:

Q. — for a document.

THE COURT: — Counsel, he's already explained it and made reference to a document and read you portions of it which he said was an explanation of that language. Doesn't have those two words that you talked about. But his testimony has been that the language that he read from the label and the insert sheet, or both — I'm not sure which he was reading from – he said was an interpretation to explain that. We can go round and round if we want to, Counsel, but he's answered that question.

MR. NEMEROFF: I have to object to the Court's comments as basically the argument of the defendants that they'll be making in this case and I would appreciate, your Honor, if you would not do so. He has not explained it. What he has told me it his interpretation of the label. He has not shown me a document —

BY MR. NEMEROFF:

Q. And I'll ask you again: Is there a document that explains why there is a difference between the 2001 medical officer FDA review language and the label in 2005, something —

THE COURT: And he's —

BY MR. NEMEROFF:

Q. — from that —

THE COURT: — testified there isn't a difference.

MR. REIDY: I object as asked and answered, your Honor.

> THE COURT: It is asked and answered. The objection's sustained.
>
> MR. NEMEROFF: Well, I submit we'll let the jury determine whether that's been asked and answered or — or —
>
> THE COURT: We will indeed.

8/8/2011 PM *Trans.* at 1074:6 – 1075:24 [7 ER 1454-55].

3. The district court unfairly limits cross-examination of TAP-Abbott's FDA expert, Dr. Peck, regarding Lupron labels (8/8/2011 PM *Trans.* at 1054 – 1059 [7 ER 1434-39]).

4. The district court *sua sponte* interjects opinion on lack of bias of TAP-Abbott expert, with no prior objection by defense counsel. (8/8/2011 PM *Trans.* at 1019:7 – 1022:5 [7 ER 1399-1402]).

5. Court does not allow Ms. Klein counsel to cross-examine TAP-Abbott's FDA expert, Dr. Peck, concerning scientific journal articles; and, the district court *sua sponte* negates foundation for Dr. Peck's testimony regarding scientific journals. (8/8/2011 PM *Trans.* at 1034:3 – 1038:2 [7 ER 1414-18]).

6. The district court does not allow cross-examination of Dr. Peck, FDA expert and makes defense objections and comments on evidence *sua sponte*. (8/8/2011 PM *Trans.* at 1038:6 – 1041:22 [7 ER 1418-21]).

7. The district court *sua sponte* interrupts Ms. Klein counsel's cross-examination of Dr. Peck, FDA expert and refuses to allow questioning and begins to argue on behalf of defense and suggesting answer to witness. (8/8/2011 PM *Trans.* at 1048:21 – 1051:12 [7 ER 1428-31]).

8. The district court *sua sponte* objects to questioning of Dr. Peck, FDA expert, and comments on Ms. Klein counsel's questioning as not being legitimate. (8/8/2011 PM *Trans.* at 1052:1-8 [7 ER 1432]).

9. The district court objects *sua sponte*, "counsel you're testifying."

10. The district court lodged multiple objections *sua sponte* for the defense, commented on evidence in favor of defense, and argued for defense.

(8/2/2011 AM *Trans.* at 135:17-25 [3 ER 514]; 8/2/2011 AM *Trans.* at 136:7 – 18 [3 ER 515]; 8/2/2011 AM *Trans.* at 138:1 – 12 [3 ER 517]; 8/2/2011 AM *Trans.* at 139:2 – 19 [3 ER 518]; 8/2/2011 AM *Trans.* at 140:11 [3 ER 519]; 8/2/2011 AM *Trans.* at 140:24 – 141:8 [3 ER 520]);

11. The district court comments on evidence during cross examination of Ms. Klein's FDA expert: (8/2/2011 PM *Trans.* at 183:22 – 184:1 [4 ER 562-63]);

12. The district court *sua sponte* attempts to discredit Ms. Klein's FDA expert and starts to cross-examine witness: (8/2/2011 PM *Trans.* at 192:12- 193:1 [4 ER 571]);

13. The district court *sua sponte* argues with Ms. Klein's FDA expert, Dr. Gueriguian. (8/2/2011 PM *Trans.* at 242:18 243:14 [4 ER 621-22]);

14. The district court refused to allow cross-examination of TAP-Abbott's expert by reference to scientific journal. (8/5/2011 PM *Trans.* at 853:3 – 855:6 [4 ER 631-23]).

Judicial rulings may constitute bias "only in the rarest circumstances. . . [where] they display a deep-seated favoritism or antagonism that would make fair judgment impossible." *Liteky v. United States*, 510 U.S. 540, 555 (1994). The Magistrate and the trial judge in the case exceed the rare standard stated in *Liteky*, starting from their allowing TAP-Abbott to grossly violate the discovery rules from the very beginning, refusal to compel TAP-Abbott to provide answers to discovery, then holding TAP-Abbott's discovery production in chambers for over nine months (requiring Ms. Klein to pay in excess of $4,000.00 "forthwith" in order to receive the "in chambers" production), while Ms. Klein had no access to them during the defense of multiple summary judgment motions, and *Daubert* motions,

which she also needed to confer with her experts for trial preparation and for the drafting of the supplemental expert reports. Judicial bias is also very obvious in multiple rulings on the Motions *in Limine*, which were decided overwhelmingly in favor of TAP-Abbott: the motion to strike Ms. Klein's supplemental expert reports, which was granted without affording Ms. Klein an opportunity to respond; and throughout the trial by making evidentiary rulings that literally tied Ms. Klein's hands and stymied the presentation of her case to the jury. Finally, the trial judge's many statements to the jury as to his opinion of the character of what little evidence was actually adduced completely guaranteed that Ms. Klein would not receive a fair trial.

If this matter is remanded, this court has the power to reassign this matter to another judge based upon the court's statutory power to require such further proceedings to be had as may be just under the circumstances. *See* 28 U.S.C. § 2106; *see also Log Cabin Republicans v. U.S.*, 658 F.3d 1162, 1167 (9th Cir. 2011).

CONCLUSION

For the reasons set forth above, Ms. Klein requests that this Court reverse the judgment of the district court and remand this case for a new trial before a different judge and magistrate, consistent with this Court's disposition of the various evidentiary and discovery issues raised herein. She requests, in particular, that any remand include specific instructions that the district court, *inter alia*, reopen discovery, allow Ms. Klein's experts to supplement their reports, and compel TAP-Abbott to comply with Ms. Klein's outstanding requests—including, but not limited to, those which asked for TAP-Abbott's internal communications regarding the changes to the various Lupron labels and the deletion and addition of certain adverse events therein, and vacate the fees and costs award of $4,074.60 awarded by the district court during discovery.

DATED: June 6, 2012.

Respectfully Submitted,

/s/ Beau Sterling

BEAU STERLING

/s/ Joseph J. Huggins

JOSEPH J. HUGGINS

Attorneys for Appellant

STATEMENT OF RELATED CASES

Counsel is aware of no other related cases pending before this or any other court.

CERTIFICATE OF COMPLIANCE

Pursuant to FRAP 32, the undersigned certifies that the foregoing brief's line spacing is double spaced and proportionally spaced. The type face is Time New Roman 14 point and the word count is **13,214**.

DATED: June 6, 2012.

Respectfully Submitted,

/s/ Beau Sterling

BEAU STERLING
Attorney for Appellant

CERTIFICATE OF SERVICE

I hereby certify that on June 6, 2012, I electronically filed the foregoing **Appellant's Opening Brief (Corrected)** with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system. Participants in the case who are registered CM/ECF users will be served by the appellate CM/ECF system. All parties in this matter are registered users.

/s/ Beau Sterling

BEAU STERLING

ADDENDUM

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ADDENDUM

A

ADDENDUM

A-1

21 U.S.C. § 355-1. Risk evaluation and mitigation strategies

(b) Definitions

For purposes of this section:

(1) Adverse drug experience

The term "adverse drug experience" means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including--

(A) an adverse event occurring in the course of the use of the drug in professional practice;

(B) an adverse event occurring from an overdose of the drug, whether accidental or intentional;

(C) an adverse event occurring from abuse of the drug;

(D) an adverse event occurring from withdrawal of the drug; and

(E) any failure of expected pharmacological action of the drug.

(2) Covered application

The term "covered application" means an application referred to in section 355(p)(1)(A) of this title.

(3) New safety information

The term "new safety information", with respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 355(o)(3) of this title), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific data deemed appropriate by the Secretary about--

(A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

(4) Serious adverse drug experience

The term "serious adverse drug experience" is an adverse drug experience that--

(A) results in--

(i) death;

(ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);

(iii) inpatient hospitalization or prolongation of existing hospitalization;

(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

(v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

(5) Serious risk

The term "serious risk" means a risk of a serious adverse drug experience.

(6) Signal of a serious risk

The term "signal of a serious risk" means information related to a serious adverse drug experience associated with use of a drug and derived from--

(A) a clinical trial;

(B) adverse event reports;

(C) a postapproval study, including a study under section 355(o)(3) of this title;

(D) peer-reviewed biomedical literature;

(E) data derived from the postmarket risk identification and analysis system under section 355(k)(4) of this title; or

(F) other scientific data deemed appropriate by the Secretary.

(7) Responsible person

The term "responsible person" means the person submitting a covered application or the holder of the approved such application.

(8) Unexpected serious risk

The term "unexpected serious risk" means a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically and pathophysiologically related to an adverse drug experience identified in the labeling, but differs from such adverse drug experience because of greater severity, specificity, or prevalence.

CREDIT(S)

(June 25, 1938, c. 675, § 505-1, as added Sept. 27, 2007, Pub.L. 110-85, Title IX, § 901(b), 121 Stat. 926.)

ADDENDUM

A-2

28 U.S.C. § 2106. Determination

The Supreme Court or any other court of appellate jurisdiction may affirm, modify, vacate, set aside or reverse any judgment, decree, or order of a court lawfully brought before it for review, and may remand the cause and direct the entry of such appropriate judgment, decree, or order, or require such further proceedings to be had as may be just under the circumstances.

CREDIT(S)

(June 25, 1948, c. 646, 62 Stat. 963.)

ADDENDUM

A-3

Federal Rules of Civil Procedure Rule 26

Rule 26. Duty to Disclose; General Provisions Governing Discovery

(a) Required Disclosures.

(1) ***Initial Disclosure.***

(A) *In General.* Except as exempted by Rule 26(a)(1)(B) or as otherwise stipulated or ordered by the court, a party must, without awaiting a discovery request, provide to the other parties:

(i) the name and, if known, the address and telephone number of each individual likely to have discoverable information--along with the subjects of that information--that the disclosing party may use to support its claims or defenses, unless the use would be solely for impeachment;

(ii) a copy--or a description by category and location--of all documents, electronically stored information, and tangible things that the disclosing party has in its possession, custody, or control and may use to support its claims or defenses, unless the use would be solely for impeachment;

(iii) a computation of each category of damages claimed by the disclosing party--who must also make available for inspection and copying as under Rule 34 the documents or other evidentiary material, unless privileged or protected from disclosure, on which each computation is based, including materials bearing on the nature and extent of injuries suffered; and

(iv) for inspection and copying as under Rule 34, any insurance agreement under which an insurance business may be liable to satisfy all or part of a possible judgment in the action or to indemnify or reimburse for payments made to satisfy the judgment.

(B) *Proceedings Exempt from Initial Disclosure.* The following proceedings are exempt from initial disclosure:

(i) an action for review on an administrative record;

(ii) a forfeiture action in rem arising from a federal statute;

(iii) a petition for habeas corpus or any other proceeding to challenge a criminal conviction or sentence;

(iv) an action brought without an attorney by a person in the custody of the United States, a state, or a state subdivision;

(v) an action to enforce or quash an administrative summons or subpoena;

(vi) an action by the United States to recover benefit payments;

(vii) an action by the United States to collect on a student loan guaranteed by the United States;

(viii) a proceeding ancillary to a proceeding in another court; and

(ix) an action to enforce an arbitration award.

(C) *Time for Initial Disclosures--In General.* A party must make the initial disclosures at or within 14 days after the parties' Rule 26(f) conference unless a different time is set by stipulation or court order, or unless a party objects during the conference that initial disclosures are not appropriate in this action and states the objection in the proposed discovery plan. In ruling on the objection, the court must determine what disclosures, if any, are to be made and must set the time for disclosure.

(D) *Time for Initial Disclosures--For Parties Served or Joined Later.* A party that is first served or otherwise joined after the Rule 26(f) conference must make the initial disclosures within 30 days after being served or joined, unless a different time is set by stipulation or court order.

(E) *Basis for Initial Disclosure; Unacceptable Excuses.* A party must make its initial disclosures based on the information then reasonably available to it. A party is not excused from making its disclosures because it has not fully investigated the case or because it challenges the sufficiency of another party's disclosures or because another party has not made its disclosures.

(2) ***Disclosure of Expert Testimony*****.**

(A) *In General*. In addition to the disclosures required by Rule 26(a)(1), a party must disclose to the other parties the identity of any witness it may use at trial to present evidence under Federal Rule of Evidence 702, 703, or 705.

(B) *Witnesses Who Must Provide a Written Report*. Unless otherwise stipulated or ordered by the court, this disclosure must be accompanied by a written report--prepared and signed by the witness--if the witness is one retained or specially employed to provide expert testimony in the case or one whose duties as the party's employee regularly involve giving expert testimony. The report must contain:

(i) a complete statement of all opinions the witness will express and the basis and reasons for them;

(ii) the facts or data considered by the witness in forming them;

(iii) any exhibits that will be used to summarize or support them;

(iv) the witness's qualifications, including a list of all publications authored in the previous 10 years;

(v) a list of all other cases in which, during the previous 4 years, the witness testified as an expert at trial or by deposition; and

(vi) a statement of the compensation to be paid for the study and testimony in the case.

(C) *Witnesses Who Do Not Provide a Written Report*. Unless otherwise stipulated or ordered by the court, if the witness is not required to provide a written report, this disclosure must state:

(i) the subject matter on which the witness is expected to present evidence under Federal Rule of Evidence 702, 703, or 705; and

(ii) a summary of the facts and opinions to which the witness is expected to testify.

(D) *Time to Disclose Expert Testimony*. A party must make these disclosures at the times and in the sequence that the court orders. Absent a stipulation or a court order, the disclosures must be made:

(i) at least 90 days before the date set for trial or for the case to be ready for trial; or

(ii) if the evidence is intended solely to contradict or rebut evidence on the same subject matter identified by another party under Rule 26(a)(2)(B) or (C), within 30 days after the other party's disclosure.

(E) *Supplementing the Disclosure*. The parties must supplement these disclosures when required under Rule 26(e).

(3) ***Pretrial Disclosures.***

(A) *In General.* In addition to the disclosures required by Rule 26(a)(1) and (2), a party must provide to the other parties and promptly file the following information about the evidence that it may present at trial other than solely for impeachment:

(i) the name and, if not previously provided, the address and telephone number of each witness--separately identifying those the party expects to present and those it may call if the need arises;

(ii) the designation of those witnesses whose testimony the party expects to present by deposition and, if not taken stenographically, a transcript of the pertinent parts of the deposition; and

(iii) an identification of each document or other exhibit, including summaries of other evidence--separately identifying those items the party expects to offer and those it may offer if the need arises.

(B) *Time for Pretrial Disclosures; Objections.* Unless the court orders otherwise, these disclosures must be made at least 30 days before trial. Within 14 days after they are made, unless the court sets a different time, a party may serve and promptly file a list of the following objections: any objections to the use under Rule 32(a) of a deposition designated by another party under Rule 26(a)(3)(A)(ii); and any objection, together with the grounds for it, that may be made to the admissibility of materials identified under Rule 26(a)(3)(A)(iii). An objection not so made--except for one under Federal Rule of Evidence 402 or 403--is waived unless excused by the court for good cause.

(4) ***Form of Disclosures.*** Unless the court orders otherwise, all disclosures under Rule 26(a) must be in writing, signed, and served.

* * *

(e) Supplementing Disclosures and Responses.

(1) ***In General.*** A party who has made a disclosure under Rule 26(a)--or who has responded to an interrogatory, request for production, or request for admission--must supplement or correct its disclosure or response:

(A) in a timely manner if the party learns that in some material respect the disclosure or response is incomplete or incorrect, and if the additional or corrective information has not otherwise been made known to the other parties during the discovery process or in writing; or

(B) as ordered by the court.

(2) ***Expert Witness.*** For an expert whose report must be disclosed under Rule 26(a)(2)(B), the party's duty to supplement extends both to information included in the report and to information given during the expert's deposition. Any additions or changes to this information must be disclosed by the time the party's pretrial disclosures under Rule 26(a)(3) are due.

* * *

CREDIT(S)

(Amended December 27, 1946, effective March 19, 1948; January 21, 1963, effective July 1, 1963; February 28, 1966, effective July 1, 1966; March 30, 1970, effective July 1, 1970; April 29, 1980, effective August 1, 1980; April 28, 1983, effective August 1, 1983; March 2, 1987, effective August 1, 1987; April 22, 1993, effective December 1, 1993; April 17, 2000, effective December 1, 2000; April 12, 2006, effective December 1, 2006; April 30, 2007, effective December 1, 2007; April 28, 2010, effective December 1, 2010.)

ADVISORY COMMITTEE NOTES
1983 Amendment

* * *

Subdivision (g); Signing of Discovery Requests, Responses, and Objections. Rule 26(g) imposes an affirmative duty to engage in pretrial discovery in a responsible manner that is consistent with the spirit and purposes of Rules 26 through 37. In addition, Rule 26(g) is designed to curb discovery abuse by explicitly encouraging the imposition of sanctions. The subdivision provides a deterrent to both excessive discovery and evasion by imposing a certification requirement that obliges each attorney to stop and think about the legitimacy of a discovery request, a response thereto, or an objection. The term "response" includes answers to interrogatories and to requests to admit as well as responses to production requests.

If primary responsibility for conducting discovery is to continue to rest with the litigants, they must be obliged to act responsibly and avoid abuse. With this in mind, Rule 26(g), which parallels the amendments to Rule 11, requires an attorney or unrepresented party to sign each discovery request, response, or objection. Motions relating to discovery are governed by Rule 11. However, since a discovery request, response, or objection usually deals with more specific subject matter than motions or papers, the elements that must be certified in connection with the former are spelled out more completely. The signature is a certification of the elements set forth in Rule 26(g).

Although the certification duty requires the lawyer to pause and consider the reasonableness of his request, response, or objection, it is not meant to discourage or restrict necessary and legitimate discovery. The rule simply requires that the attorney make a reasonable inquiry into the factual basis of his response, request, or objection.

The duty to make a "reasonable inquiry" is satisfied if the investigation undertaken by the attorney and the conclusions drawn therefrom are reasonable under the circumstances. It is an objective standard similar to the one imposed by Rule 11. See the Advisory Committee Note to Rule 11. See also *Kinee v. Abraham Lincoln Fed. Sav. & Loan Ass'n,* 365 F.Supp. 975 (E.D.Pa.1973). In making the inquiry, the attorney may rely on assertions by the client and on communications with other counsel in the case as long as that reliance is appropriate under the circumstances. Ultimately, what is reasonable is a matter for the court to decide on the totality of the circumstances.

Rule 26(g) does not require the signing attorney to certify the truthfulness of the client's factual responses to a discovery request. Rather, the signature certifies that the lawyer has made a reasonable effort to assure that the client has provided all the information and documents available to him that are responsive to the discovery demand. Thus, the lawyer's certification under Rule 26(g) should be distinguished from other signature requirements in the rules, such as those in Rules 30(e) and 33.

Nor does the rule require a party or an attorney to disclose privileged communications or work product in order to show that a discovery request, response, or objection is substantially justified. The provisions of Rule 26(c), including appropriate orders after *in camera* inspection by the court, remain available to protect a party claiming privilege or work product protection.

The signing requirement means that every discovery request, response, or objection should be grounded on a theory that is reasonable under the precedents or a good faith belief as to what should be the law. This standard is heavily dependent on the circumstances of each case. The certification speaks as of the time it is made. The duty to supplement discovery responses continues to be governed by Rule 26(e).

Concern about discovery abuse has led to widespread recognition that there is a need for more aggressive judicial control and supervision. *ACF Industries, Inc. v. EEOC,* 439 U.S. 1081 (1979) (certiorari denied) (Powell, J., dissenting). Sanctions to deter discovery abuse would be more effective if they were diligently applied "not merely to penalize those whose conduct may be deemed to warrant such a sanction, but to deter those who might be tempted to such conduct in the absence of such a deterrent." *National Hockey League v. Metropolitan Hockey Club,* 427 U.S. 639, 643 (1976). See also Note, *The Emerging Deterrence Orientation in the Imposition of Discovery Sanctions,* 91 Harv.L.Rev. 1033 (1978). Thus the premise of Rule 26(g) is that imposing sanctions on attorneys who fail to meet the rule's standards will significantly reduce abuse by imposing disadvantages therefor.

Because of the asserted reluctance to impose sanctions on attorneys who abuse the discovery rules, see Brazil, *Civil Discovery: Lawyers' Views of its Effectiveness, Principal Problems and Abuses,* American Bar Foundation (1980); Ellington, *A Study of Sanctions for Discovery Abuse,* Department of Justice (1979), Rule 26(g) makes explicit the authority judges now have to impose appropriate sanctions and requires them to use it. This authority derives from Rule 37, 28 U.S.C. § 1927, and the court's inherent power. See *Roadway Express, Inc. v. Piper,* 447 U.S. 752 (1980); *Martin v. Bell Helicopter Co.,* 85 F.R.D. 654, 661-62 (D.Col.1980); Note, *Sanctions Imposed by Courts on Attorneys Who Abuse the Judicial Process,* 44 U.Chi.L.Rev. 619 (1977). The new rule mandates that sanctions be imposed on attorneys who fail to meet the standards established in the first portion of Rule

26(g). The nature of the sanction is a matter of judicial discretion to be exercised in light of the particular circumstances. The court may take into account any failure by the party seeking sanctions to invoke protection under Rule 26(c) at an early stage in the litigation.

The sanctioning process must comport with due process requirements. The kind of notice and hearing required will depend on the facts of the case and the severity of the sanction being considered. To prevent the proliferation of the sanction procedure and to avoid multiple hearings, discovery in any sanction proceeding normally should be permitted only when it is clearly required by the interests of justice. In most cases the court will be aware of the circumstances and only a brief hearing should be necessary.

ADDENDUM

A-4

Federal Rules of Civil Procedure Rule 37

Rule 37. Failure to Make Disclosures or to Cooperate in Discovery; Sanctions

(a) Motion for an Order Compelling Disclosure or Discovery.

(1) ***In General.*** On notice to other parties and all affected persons, a party may move for an order compelling disclosure or discovery. The motion must include a certification that the movant has in good faith conferred or attempted to confer with the person or party failing to make disclosure or discovery in an effort to obtain it without court action.

(2) ***Appropriate Court.*** A motion for an order to a party must be made in the court where the action is pending. A motion for an order to a nonparty must be made in the court where the discovery is or will be taken.

(3) ***Specific Motions.***

(A) *To Compel Disclosure.* If a party fails to make a disclosure required by Rule 26(a), any other party may move to compel disclosure and for appropriate sanctions.

(B) *To Compel a Discovery Response.* A party seeking discovery may move for an order compelling an answer, designation, production, or inspection. This motion may be made if:

(i) a deponent fails to answer a question asked under Rule 30 or 31;

(ii) a corporation or other entity fails to make a designation under Rule 30(b)(6) or 31(a)(4);

(iii) a party fails to answer an interrogatory submitted under Rule 33; or

(iv) a party fails to respond that inspection will be permitted--or fails to permit inspection--as requested under Rule 34.

(C) *Related to a Deposition.* When taking an oral deposition, the party asking a question may complete or adjourn the examination before moving for an order.

(4) ***Evasive or Incomplete Disclosure, Answer, or Response.*** For purposes of this subdivision (a), an evasive or incomplete disclosure, answer, or response must be treated as a failure to disclose, answer, or respond.

(5) ***Payment of Expenses; Protective Orders.***

(A) *If the Motion Is Granted (or Disclosure or Discovery Is Provided After Filing).* If the motion is granted--or if the disclosure or requested discovery is provided after the motion was filed--the court must, after giving an opportunity to be heard, require the party or deponent whose conduct necessitated the motion, the party or attorney advising that conduct, or both to pay the movant's reasonable expenses incurred in making the motion, including attorney's fees. But the court must not order this payment if:

(i) the movant filed the motion before attempting in good faith to obtain the disclosure or discovery without court action;

(ii) the opposing party's nondisclosure, response, or objection was substantially justified; or

(iii) other circumstances make an award of expenses unjust.

(B) *If the Motion Is Denied.* If the motion is denied, the court may issue any protective order authorized under Rule 26(c) and must, after giving an opportunity to be heard, require the movant, the attorney filing the motion, or both to pay the party or deponent who opposed the motion its reasonable expenses incurred in opposing the motion, including attorney's fees. But the court must not order this payment if the motion was substantially justified or other circumstances make an award of expenses unjust.

(C) *If the Motion Is Granted in Part and Denied in Part.* If the motion is granted in part and denied in part, the court may issue any protective order authorized under Rule 26(c) and may, after giving an opportunity to be heard, apportion the reasonable expenses for the motion.

(b) Failure to Comply with a Court Order.

(1) ***Sanctions in the District Where the Deposition Is Taken.*** If the court where the discovery is taken orders a deponent to be sworn or to answer a question and the deponent fails to obey, the failure may be treated as contempt of court.

(2) ***Sanctions in the District Where the Action Is Pending.***

(A) *For Not Obeying a Discovery Order.* If a party or a party's officer, director, or managing agent--or a witness designated under Rule 30(b)(6) or 31(a)(4)--fails to obey an order to provide or permit discovery, including an order under Rule 26(f), 35, or 37(a), the court where the action is pending may issue further just orders. They may include the following:

(i) directing that the matters embraced in the order or other designated facts be taken as established for purposes of the action, as the prevailing party claims;

(ii) prohibiting the disobedient party from supporting or opposing designated claims or defenses, or from introducing designated matters in evidence;

(iii) striking pleadings in whole or in part;

(iv) staying further proceedings until the order is obeyed;

(v) dismissing the action or proceeding in whole or in part;

(vi) rendering a default judgment against the disobedient party; or

(vii) treating as contempt of court the failure to obey any order except an order to submit to a physical or mental examination.

(B) *For Not Producing a Person for Examination.* If a party fails to comply with an order under Rule 35(a) requiring it to produce another person for examination, the court may issue any of the orders listed in Rule 37(b)(2)(A)(i)-(vi), unless the disobedient party shows that it cannot produce the other person.

(C) *Payment of Expenses.* Instead of or in addition to the orders above, the court must order the disobedient party, the attorney advising that party, or both to pay the reasonable expenses, including attorney's fees, caused by the failure, unless the failure was substantially justified or other circumstances make an award of expenses unjust.

(c) Failure to Disclose, to Supplement an Earlier Response, or to Admit.

(1) ***Failure to Disclose or Supplement.*** If a party fails to provide information or identify a witness as required by Rule 26(a) or (e), the party is not allowed to use that information or witness to supply evidence on a motion, at a hearing, or at a trial, unless the failure was substantially justified or is harmless. In addition to or instead of this sanction, the court, on motion and after giving an opportunity to be heard:

(A) may order payment of the reasonable expenses, including attorney's fees, caused by the failure;

(B) may inform the jury of the party's failure; and

(C) may impose other appropriate sanctions, including any of the orders listed in Rule 37(b)(2)(A)(i)-(vi).

(2) ***Failure to Admit.*** If a party fails to admit what is requested under Rule 36 and if the requesting party later proves a document to be genuine or the matter true, the requesting party may move that the party who failed to admit pay the reasonable expenses, including attorney's fees, incurred in making that proof. The court must so order unless:

(A) the request was held objectionable under Rule 36(a);

(B) the admission sought was of no substantial importance;

(C) the party failing to admit had a reasonable ground to believe that it might prevail on the matter; or

(D) there was other good reason for the failure to admit.

(d) Party's Failure to Attend Its Own Deposition, Serve Answers to Interrogatories, or Respond to a Request for Inspection.

(1) ***In General.***

(A) *Motion; Grounds for Sanctions.* The court where the action is pending may, on motion, order sanctions if:

(i) a party or a party's officer, director, or managing agent--or a person designated under Rule 30(b)(6) or 31(a)(4)--fails, after being served with proper notice, to appear for that person's deposition; or

(ii) a party, after being properly served with interrogatories under Rule 33 or a request for inspection under Rule 34, fails to serve its answers, objections, or written response.

(B) *Certification.* A motion for sanctions for failing to answer or respond must include a certification that the movant has in good faith conferred or attempted to confer with the party failing to act in an effort to obtain the answer or response without court action.

(2) ***Unacceptable Excuse for Failing to Act.*** A failure described in Rule 37(d)(1)(A) is not excused on the ground that the discovery sought was objectionable, unless the party failing to act has a pending motion for a protective order under Rule 26(c).

(3) ***Types of Sanctions.*** Sanctions may include any of the orders listed in Rule 37(b)(2)(A)(i)-(vi). Instead of or in addition to these sanctions, the court must require the party failing to act, the attorney advising that party, or both to pay the reasonable

expenses, including attorney's fees, caused by the failure, unless the failure was substantially justified or other circumstances make an award of expenses unjust.

(e) Failure to Provide Electronically Stored Information. Absent exceptional circumstances, a court may not impose sanctions under these rules on a party for failing to provide electronically stored information lost as a result of the routine, good-faith operation of an electronic information system.

(f) Failure to Participate in Framing a Discovery Plan. If a party or its attorney fails to participate in good faith in developing and submitting a proposed discovery plan as required by Rule 26(f), the court may, after giving an opportunity to be heard, require that party or attorney to pay to any other party the reasonable expenses, including attorney's fees, caused by the failure.

CREDIT(S)

(Amended December 29, 1948, effective October 20, 1949; March 30, 1970, effective July 1, 1970; April 29, 1980, effective August 1, 1980; amended by Pub.L. 96-481, Title II, § 205(a), October 21, 1980, 94 Stat. 2330, effective October 1, 1981; amended March 2, 1987, effective August 1, 1987; April 22, 1993, effective December 1, 1993; April 17, 2000, effective December 1, 2000; April 12, 2006, effective December 1, 2006; April 30, 2007, effective December 1, 2007.)

ADDENDUM

A-5

Federal Rules of Evidence Rule 407

Rule 407. Subsequent Remedial Measures

When measures are taken that would have made an earlier injury or harm less likely to occur, evidence of the subsequent measures is not admissible to prove:

- negligence;
- culpable conduct;
- a defect in a product or its design; or
- a need for a warning or instruction.

But the court may admit this evidence for another purpose, such as impeachment or--if disputed--proving ownership, control, or the feasibility of precautionary measures.

CREDIT(S)

(Pub.L. 93-595, § 1, Jan. 2, 1975, 88 Stat. 1932; Apr. 11, 1997, eff. Dec. 1, 1997; Apr. 26, 2011, eff. Dec. 1, 2011.)

ADDENDUM

A-6

Code of Federal Regulations (C.F.R.) Title 21: Food and Drugs
PART 201—LABELING
Subpart C—Labeling Requirements for Over-the-Counter Drugs

§ 201.80 Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in §201.56(b)(1).

Each section heading listed in §201.56(d), if not omitted under §201.56(d)(3), shall contain the following information in the following order:

* * *

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised 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. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

ADDENDUM

B

ADDENDUM

B-1

PDR® 49 EDITION 1995

PHYSICIANS' DESK REFERENCE®

ISBN: 1-56363-087-7

tion; *Endocrine System*—Libido increase; *Hemic and Lymphatic System*—Decreased WBC, Hemoptysis; *Musculoskeletal System*—Ankylosing spondylosis, Pelvic fibrosis; *Central/Peripheral Nervous System*—Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System*—Pulmonary infiltrate, Respiratory disorders; Integumentary System—Hair growth; *Urogenital System*—Penile swelling, Prostate pain; *Miscellaneous*—Hypoproteinemia, Hard nodule in throat, Weight gain, Increased uric acid.

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 at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate 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

The recommended dose is 1 mg (0.2 ml) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically.
NOTE: As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON (leuprolide acetate) Injection is a sterile solution supplied in a 2.8 ml multiple-dose vial, **NDC** 0300-3626-28. Refrigerate until dispensed. Patient may store unrefrigerated below 86°F. Avoid freezing. Protect from light—store vial in carton until use.
Each 0.2 ml contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.
Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.
Revised: August, 1993.
U.S. Patent Nos. 4,005,063 and 4,005,194.

Reference: 1. MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48 (3):500–502.

INFORMATION FOR PATIENTS

NOTE: Be sure to consult your physician with any questions you may have or for information about LUPRON (leuprolide acetate) Injection and its use.

WHAT IS LUPRON?

LUPRON (leuprolide acetate) Injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH), a hormone which occurs naturally in your body.
Normally, your body releases small amounts of LH-RH, and this leads to events which stimulate the production of sex hormones.
However, when you inject LUPRON Injection, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.
LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.
If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LUPRON

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the .2 or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the .2 or 20 unit mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the .2 or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

SOME SPECIAL ADVICE

- You may experience hot flashes when using LUPRON (leuprolide acetate) Injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- If you need to use an alternate to the syringe supplied with LUPRON, insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need LUPRON so it will be at the pharmacy when you need it.
- This drug may be stored at room temperature (not above 86°F). Do not store near a radiator or other very warm place.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

Manufactured for TAP Pharmaceuticals Inc.
Deerfield, IL 60015, U.S.A.
by Abbott Laboratories
North Chicago, IL 60064

LUPRON DEPOT® 3.75 mg ℞
[lu 'pron dē 'pō]
(leuprolide acetate for depot suspension)

DESCRIPTION

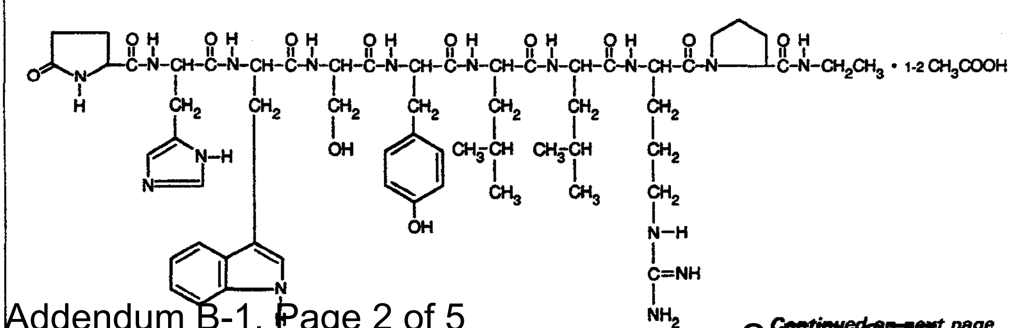
Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosol-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:
[See structure below.]
LUPRON DEPOT is supplied in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as a monthly intramuscular injection.
The single-dose vial of LUPRON DEPOT 3.75 mg 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 accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH.
During the manufacture of LUPRON DEPOT, acetic acid is lost leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long acting GnRH analog. A single monthly injection of LUPRON DEPOT 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 acetate over a period of one month.
In males receiving a single dose of LUPRON DEPOT 7.5 mg IM, there was an initial burst of leuprolide in plasma. Mean plasma leuprolide levels of about 0.80 ng/mL were maintained which slowly declined over a period of several weeks. In most of the patient volunteers, plasma leuprolide concentrations were undetected eight weeks after injection. However, three of these men had low, but detectable levels up to 12 weeks.
Absolute bioavailability from a 7.5 mg dose was estimated to be about 90%.
The metabolism, distribution and excretion of leuprolide in humans have not been fully determined.
The pharmacokinetics of the drug in hepatic- and renal-impaired patients have not been determined.
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for 6 months was shown to be comparable to danazol, 800 mg/day in relieving the clinical 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% respectively, of those patients who did not become 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 the study. This included all patients at end of treatment and those who elected to participate at the follow-up periods. 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 respectively.
[See Figure 1 on next page.]
There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT.

INDICATIONS AND USAGE

LUPRON DEPOT (leuprolide acetate for depot suspension) is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with LUPRON DEPOT for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.



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TAP—Cont.

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, she should be apprised of the potential hazard to the fetus.
4. Use in women who are breast feeding (see Nursing Mothers Section).
5. A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

WARNINGS

Safe use of leuprolide 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 nonhormonal 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.

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 should stop 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 nonhormonal 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. Those adverse events occurring in clinical studies with LUPRON DEPOT are associated with hypoestrogenism; like 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. The induced hypoestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. During one six-month treatment period, this bone loss should not be important. 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 is instituted. Repeated courses of treatment with gonadotropin-releasing hormone analogs are not advisable in patients with major risk factors for loss of bone mineral content.
6. Retreatment cannot be recommended since safety data beyond 6 months are not available.

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.

Drug/Laboratory Test Interactions: Administration of LUPRON DEPOT (leuprolide acetate for depot suspension) in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to 4 to 8 weeks after discontinuation of LUPRON DEPOT therapy 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 testes 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 with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. No clinical studies have been completed with leuprolide acetate in children to assess the reversibility of fertility suppression.

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 ($\frac{1}{300}$ to $\frac{1}{3}$ 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 (leuprolide acetate for depot suspension) 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 breastfed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Estradiol levels may increase during the first weeks following the initial injection, but then decline to postmenopausal 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.

In controlled studies comparing LUPRON DEPOT, 3.75 mg monthly and danazol (800 mg/day), or placebo, adverse reactions most frequently reported and thought to be possibly or probably drug-related are shown in Figure 2.

[See Figure 2 on next page.]

Cardiovascular System—Palpitations, Syncope, Tachycardia; *Gastrointestinal System*—Dry mouth, Thirst, Appetite changes; *Central/Peripheral Nervous System*—Anxiety,* Personality disorder, Memory disorder, Delusions: *Integumentary System*—Ecchymosis, Alopecia, Hair disorder; *Urogenital System*—Dysuria,* Lactation; *Miscellaneous*—Ophthalmologic disorders,* Lymphadenopathy.

In other clinical trials involving patients with prostate cancer and during postmarketing surveillance, the following adverse reactions were reported to have a possible, probable, or unknown relationship to LUPRON as ascribed by the treating physician. Often, it is difficult to assess causality in patients with prostate cancer. Reactions considered not drug related have been excluded.

Cardiovascular System—Congestive heart failure, ECG changes/ischemia, High blood pressure, Murmur, Phlebitis/thrombosis, Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli, Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*—Dysphagia, Gastrointestinal bleeding, Peptic ulcer, Rectal polyps, Hepatic dysfunction; *Endocrine System*—Decreased testicular size, Gynecomastia, Impotence, Libido increase, Thyroid enlargement; *Hemic and Lymphatic System*—Anemia, Decreased WBC, Hemoptysis; *Musculoskeletal System*—Bone pain; *Central/Peripheral Nervous System*—Peripheral neuropathy, Syncope/blackouts, Hearing disorder, Spinal fracture/paralysis; *Respiratory System*—Dyspnea, Sinus congestion, Cough, Pleural rub, Pneumonia, Pulmonary fibrosis, Respiratory disorders; *Urogenital System*—Frequency/urgency, Hematuria, Urinary tract infection, Bladder spasms, Incontinence, Testicular pain, Urinary obstruction, Penile swelling, Prostate Pain; *Miscellaneous*—Diabetes, Fever, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Inflammation.

Changes in Bone Density:

After six months of LUPRON DEPOT (leuprolide acetate for depot suspension) treatment, vertebral trabecular bone density measured by quantitative computed tomography (QCT) decreased by an average of 13.5% compared to pretreatment levels. A small number of original patients were retested at 6 and 12 months after completion of treatment. At 6 months, 9 patients had an average bone density change from baseline by QCT of −3.2%. At 12 months after completion of treatment, 6 patients had an average bone density change from baseline of −2.4%. These results show that there was partial to complete recovery of bone density in the post-treatment period in a small number of original patients who were retested. Use of LUPRON DEPOT for longer than the recommended six months or in the presence of other known risk

FIGURE 1

PERCENT OF PATIENTS WITH SYMPTOMS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP.

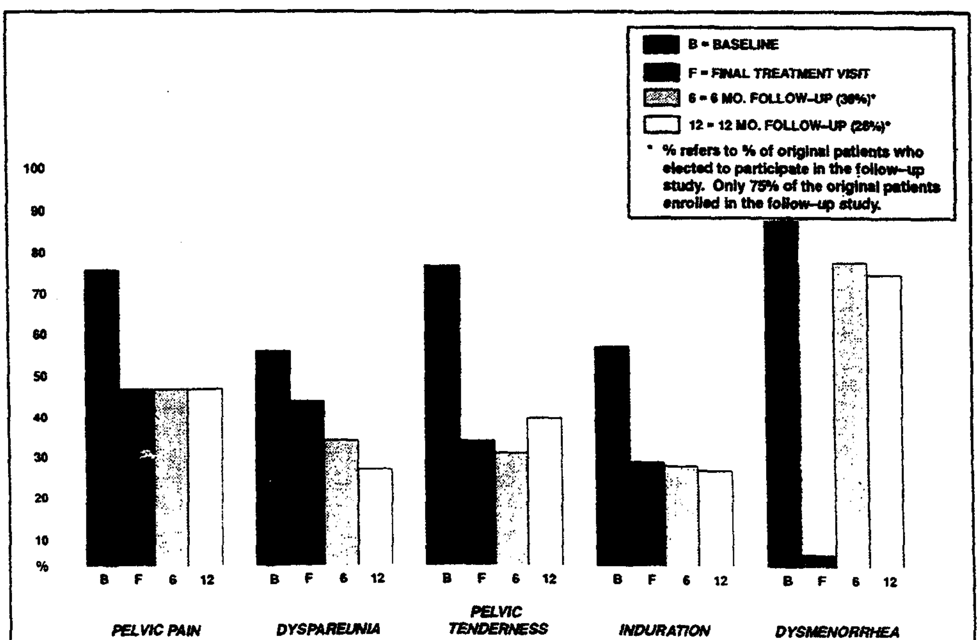
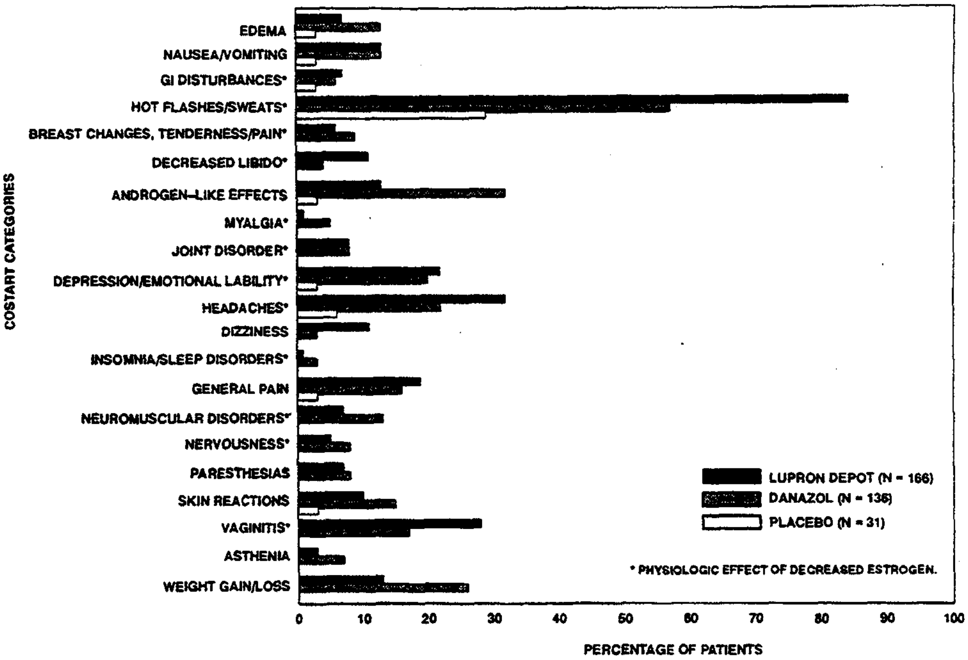


FIGURE 2
ADVERSE EVENTS REPORTED DURING 6 MONTHS OF TREATMENT
WITH LUPRON DEPOT 3.75 MG



factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values During Treatment:

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

Lipids: At enrollment, 4% of the LUPRON DEPOT patients and 1% of the danazol patients had total cholesterol values above the normal range. 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 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 group 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 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 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 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 compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT, but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

Other changes: In comparative studies, the following changes were seen in approximately 5% to 8% of patients. LUPRON DEPOT 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.

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 at present 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.

The recommended dose of LUPRON DEPOT (leuprolide acetate for depot suspension) is 3.75 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the suspension has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with LUPRON DEPOT is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

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

The vial of LUPRON DEPOT and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT (NDC 0300-3639-01) is available in a vial containing sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids. The singe-dose vial of LUPRON DEPOT 3.75 mg contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic & glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH. When mixed with 1 mL of diluent, LUPRON DEPOT (leuprolide acetate for depot suspension) is administered as a single monthly IM injection.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

No refrigeration necessary. Protect from freezing.

Revised: March, 1994

REFERENCE

1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500–502.

U.S. Patent Nos. 3,997,516; 4,005,063; 4,005,194; 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893 and 4,954,298.

TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.

LUPRON DEPOT manufactured by Takeda Chemical Industries, Ltd. Osaka, JAPAN 541

®—Registered Trademark

Shown in Product Identification Guide, page 334

LUPRON DEPOT® 7.5 mg

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[lu 'pron dē 'pō]

(leuprolide acetate for depot suspension)

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:

[See structure on bottom of next page.]

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

The single-dose vial of LUPRON DEPOT contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic and glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH.

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

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally. Following a single LUPRON DEPOT injection to patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT administration, but testosterone levels appear to be maintained at castrate levels. The metabolism, distribution, and excretion of leuprolide in humans have not been determined.

INDICATIONS AND USAGE

LUPRON DEPOT is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT does not differ from that of the original daily subcutaneous injection.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 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 (leuprolide acetate for depot suspension) in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this

Continued on next page

TAP—Cont.

drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "WARNINGS" section).

Laboratory Tests: Response to LUPRON DEPOT should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their monthly injection on time. Transient increases in acid phosphatase levels may occur sometime early in treatment. However, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline.

Drug Interactions: None have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were 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). In mice no 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 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.

Pregnancy Category X. See "CONTRAINDICATIONS" section.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see "WARNINGS" section).

In a clinical trial of LUPRON DEPOT, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

[See table at top of next column.]

	LUPRON DEPOT N = 56	(Percent)
Cardiovascular System		
Edema	7	(12.5%)
Gastrointestinal System		
Nausea/vomiting	3	(5.4%)
Endocrine System		
*Decreased testicular size	3	(5.4%)
*Hot flashes/sweats	33	(58.9%)
*Impotence	3	(5.4%)
Central/Peripheral Nervous System		
General pain	4	(7.1%)
Respiratory System		
Dyspnea	3	(5.4%)
Miscellaneous		
Asthenia	3	(5.4%)

*Physiologic effect of decreased testosterone.

Laboratory: Elevations of certain parameters were observed, but it is difficult to assess these abnormalities in this population.

SGOT (>2N)	4	(5.4%)
LDH (>2N)	11	(19.6%)
Alkaline phos (>1.5N)	4	(5.4%)

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT. *Cardiovascular System*—Angina, Cardiac arrhythmia; *Gastrointestinal System*—Anorexia, Diarrhea; *Endocrine System*—Gynecomastia, Libido decrease; *Musculoskeletal System*—Bone pain, Myalgia; *Central/Peripheral Nervous System*—Paresthesia, Insomnia; *Respiratory System*—Hemoptysis; *Integumentary System*—Dermatitis, Local skin reactions, hair growth; *Urogenital System*—Dysuria, Frequency/urgency, Hematuria, Testicular pain; *Miscellaneous*—Diabetes, Fever/chills, hard nodule in throat, Increased calcium, Weight gain, Increased uric acid.

The following additional adverse reactions have been reported with LUPRON (leuprolide acetate) Injection. Reactions considered by the treating physician as nondrug related are not included.

Cardiovascular System—Congestive heart failure, ECG changes/ischemia, High blood pressure, Hypotension, Myocardial infarction, Murmur, Phlebitis/thrombosis, Pulmonary emboli, Transient ischemic attack/stroke; *Gastrointestinal System*—Constipation, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Hepatic dysfunction, Peptic ulcer, Rectal polyps; *Endocrine System*—Breast tenderness or pain, Libido increase, Thyroid enlargement; *Hemic and Lymphatic System*—Anemia, Decreased WBC; *Musculoskeletal System*—Ankylosing spondylosis, Joint pain, Pelvic fibrosis; *Central/Peripheral Nervous System*—Anxiety, Blurred vision, Dizziness/lightheadedness, Headache, Hearing disorder, Sleep disorders, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Peripheral neuropathy, Spinal fracture/paralysis, Syncope/blackouts, Taste disorders; *Respiratory System*—Cough, Pleural rub, Pneumonia, Pulmonary fibrosis, Pulmonary infiltrate, Respiratory disorders, Sinus congestion; *Integumentary System*—Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Pigmentation, Skin lesions; *Urogenital System*—Bladder spasms, Incontinence, Penile swelling, Prostate pain, Urinary obstruction, Urinary tract infection; *Miscellaneous*—Depression, Hypoglycemia, Hypoproteinemia, Increased BUN, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

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 at present that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprolide acetate, 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.

The recommended dose of LUPRON DEPOT is 7.5 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the solution has been shown to be stable for 24 hours following reconstitution, 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.

The vial of LUPRON DEPOT and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT (NDC 0300-3629-01) is available in a vial containing sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids. The single-dose vial of LUPRON DEPOT contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic & glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH. When mixed with 1 mL of diluent, LUPRON DEPOT is administered as a single monthly IM injection.

No refrigeration necessary. Protect from freezing.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REFERENCE

1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept; 48(3):500-502.

Revised: March, 1994

U.S. Patent Nos. 3,997,516; 4,005,063; 4,005,194; 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; and 4,954,298.

®—Registered trademark

TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015–1595, U.S.A.
LUPRON DEPOT manufactured by Takeda Chemical Industries, Ltd. Osaka, JAPAN 541

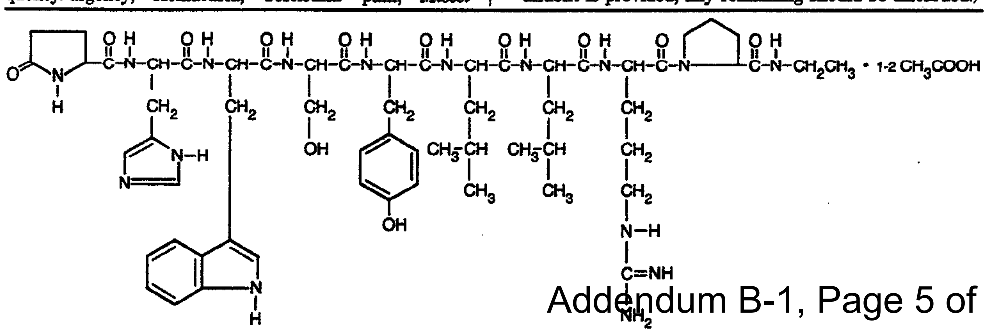
Shown in Product Identification Guide, page 334

LUPRON DEPOT-PED® ℞
(leuprolide acetate for depot suspension)
7.5 mg, 11.25 mg and 15 mg

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:

[See structure at top of next page.]



LUPRON DEPOT-PED is supplied in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, intended as a single intramuscular injection.

- The single-dose vial of LUPRON DEPOT-PED contains, respectively for each dosage strength, leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), DL-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH.

CLINICAL PHARMACOLOGY

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation of gonadotropins, chronic stimulation with leuprolide acetate results in suppression or "downregulation" of these hormones and consequent suppression of ovarian and testicular steroidogenesis. These effects are reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally. In adults, intramuscular injection of the depot formulation provides plasma concentrations of leuprolide acetate over a period of one month. The metabolism, distribution and excretion of leuprolide acetate in humans have not been determined.

In children with central precocious puberty (CPP) stimulated and basal gonadotropins are reduced to prepubertal levels. Testosterone and estradiol are reduced to prepubertal levels in males and females respectively. Reduction of gonadotropins will allow for normal physical and psychological growth and development. Natural maturation occurs when gonadotropins return to pubertal levels following discontinuation of leuprolide acetate.

ADDENDUM

B-2

PHYSICIANS' DESK REFERENCE®

Medical Consultant
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ated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (See "WARNINGS" section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of LUPRON (leuprolide acetate) Injection versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LUPRON (N = 98)	DES (N = 101)
	Number of Reports	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10

*Physiologic effect of decreased testosterone.

In this same study, the following adverse reactions were reported in less than 5% of the patients on Lupron.

Cardiovascular System —Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System* —Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System* —Libido decrease, Thyroid enlargement; *Musculoskeletal System* —Joint pain; *Central/Peripheral Nervous System* —Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System* —Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System* —Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System* —Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous* —Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

The following additional adverse reactions have been reported with LUPRON or LUPRON DEPOT (leuprolide acetate for depot suspension) during other clinical trials and/or during postmarketing surveillance. Reactions considered as nondrug related by the treating physician are excluded.

Cardiovascular System —Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System* —Hepatic dysfunction; *Endocrine System* —Libido increase; *Hemic and Lymphatic System* —Decreased WBC, Hemoptysis; *Musculoskeletal System* —Ankylosing spondylosis, Pelvic fibrosis; *Central/Peripheral Nervous System* —Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System* —Pulmonary infiltrate, Respiratory disorders; Integumentary System—Hair growth; *Urogenital System* —Penile swelling, Prostate pain; *Miscellaneous*—Hypoproteinemia, Hard nodule in throat, Weight gain, Increased uric acid.

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 at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate 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

The recommended dose is 1 mg (0.2 ml) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically.

NOTE: As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON (leuprolide acetate) Injection is a sterile solution supplied in a 2.8 ml multiple-dose vial, **NDC** 0300-3626-28. Refrigerate until dispensed. Patient may store unrefrigerated below 86°F. Avoid freezing. Protect from light—store vial in carton until use.

Each 0.2 ml contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Revised: August, 1993.

U.S. Patent Nos. 4,005,063 and 4,005,194.

Reference: 1. MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48 (3):500–502.

INFORMATION FOR PATIENTS

NOTE: Be sure to consult your physician with any questions you may have or for information about LUPRON (leuprolide acetate) Injection and its use.

WHAT IS LUPRON?

LUPRON (leuprolide acetate) Injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH), a hormone which occurs naturally in your body.

Normally, your body releases small amounts of LH-RH, and this leads to events which stimulate the production of sex hormones.

However, when you inject LUPRON Injection, the normal events that lead to sex hormone production are interrupted and testosterone is no longer produced by the testes.

LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.

If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LUPRON

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the .2 or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the .2 or 20 unit mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the .2 or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90° angle.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

SOME SPECIAL ADVICE

- You may experience hot flashes when using LUPRON (leuprolide acetate) Injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- If you need to use an alternate to the syringe supplied with LUPRON, insulin syringes should be utilized.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need LUPRON so it will be at the pharmacy when you need it.
- This drug may be stored at room temperature (not above 86°F). Do not store near a radiator or other very warm place.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

Manufactured for TAP Pharmaceuticals Inc.
Deerfield, IL 60015, U.S.A.
by Abbott Laboratories
North Chicago, IL 60064

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

- General information
- Information on endometrosis
- Information on uterine fibroids

LUPRON DEPOT® 3.75 mg ℞

[*lu 'pron dē pō*]

(leuprolide acetate for depot suspension)

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- tyrosol-D- leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:

[See table at top of next page.]

LUPRON DEPOT is supplied in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as a monthly intramuscular injection.

The single-dose vial of LUPRON DEPOT 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 accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

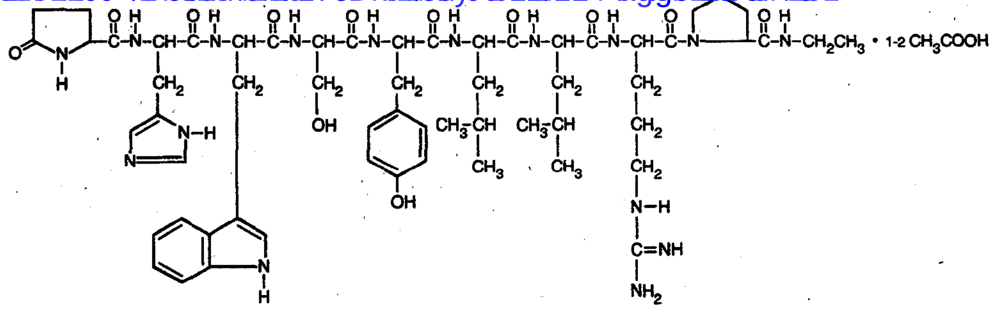
During the manufacturing process of LUPRON DEPOT, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long acting GnRH analog. A single monthly injection of LUPRON DEPOT 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 acetate 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, a 1 mg bolus 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 two compartment model.

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

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached mean 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 leuprolide concentrations.

Excretion: Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% 0f 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.

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 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.

[See Figure 1 below.]

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% respectively, of those patients who did not become pregnant.

Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at six and 12 months following discontinuation of treatment for the various symptoms evaluated during the study. This included all patients at end of treatment and those who elected to participate in the follow-up periods. 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 six months and 26% at 12 months respectively.

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 ≥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.

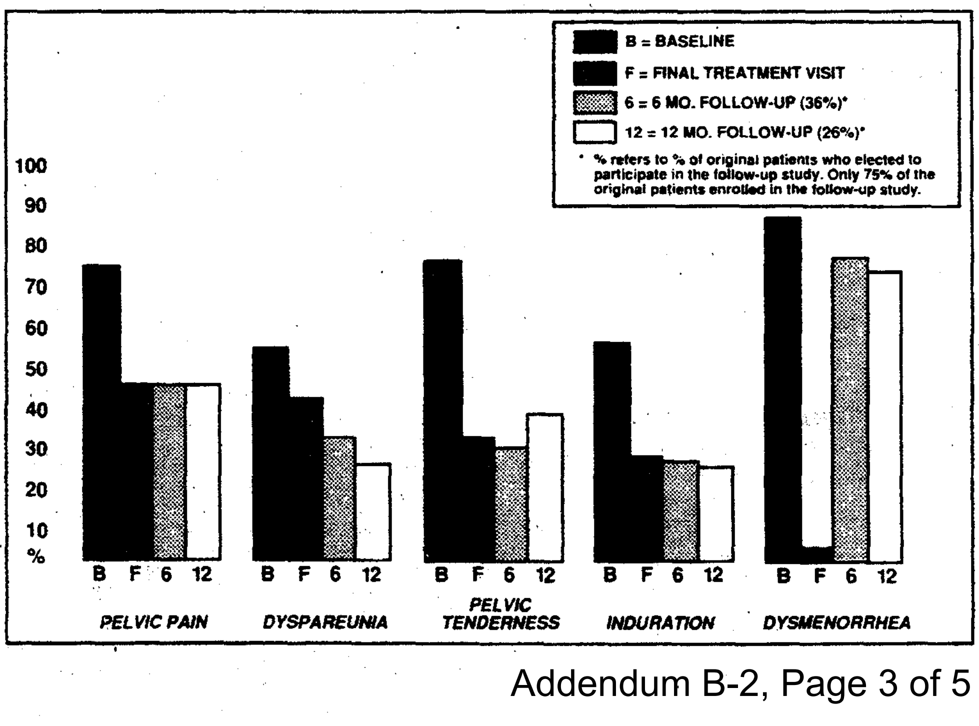
In another controlled clinical study, enrollment was based on hematocrit ≤30% and/or hemoglobin ≤10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥6% hematocrit and ≥2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥36% and hemoglobin of ≥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.

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



INDICATIONS AND USAGE

Endometriosis:

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older treated for 6 months. LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions.

Uterine Leiomyomata (Fibroids):

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

LUPRON DEPOT 3.75 mg and iron therapy are 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 clinical trial results below). LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT is up to 3 months.

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, she should be apprised of the potential hazard to the fetus.
4. Use in women who are breast feeding (see Nursing Mothers section).
5. A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

Continued on next page

TAP—Cont.

WARNINGS

Safe use of leuprolide 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 nonhormonal 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.

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 should stop 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 nonhormonal 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. The induced hypoestrogenic state also results in a small 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 important. 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 is instituted. Repeated courses of therapy with gonadotropin-releasing hormone analogs beyond six months are not advisable in patients with major risk factors for loss of bone mineral content.
6. Retreatment cannot be recommended since safety data beyond six months are not available.

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.

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 one to three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to one to two months after discontinuation of LUPRON DEPOT therapy 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 with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to six months. 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 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 breastfed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

Pediatric Use: See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

ADVERSE REACTIONS

Estradiol levels may increase during the first weeks following the initial injection, 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.

[See figure 2 below.]

Endometriosis: In controlled studies comparing LUPRON DEPOT, 3.75 mg monthly and danazol (800 mg/day), or placebo, adverse reactions most frequently reported and thought to be possibly or probably drug-related are shown in Figure 2.

Cardiovascular System—Palpitations, Syncope, Tachycardia; *Gastrointestinal System*—Dry mouth, Thirst, Appetite changes; *Central/Peripheral Nervous System*—Anxiety,* Personality disorder, Memory disorder, Delusions; *Integumentary System*—Ecchymosis, Alopecia, Hair disorder; *Urogenital System*—Dysuria,* Lactation; *Miscellaneous*—Ophthalmologic disorders,* Lymphadenopathy.

Uterine Leiomyomata (Fibroids): In controlled clinical trials comparing LUPRON DEPOT 3.75 mg and placebo, adverse events reported in >5% of patients and thought to be potentially related to drug are noted in the following table.

	Lupron Depot N=166(%)	Placebo N=163(%)
Body as a Whole		
Asthenia	14 (8.4)	8 (4.9)
General pain	14 (8.4)	10 (6.1)
Headache*	43 (25.9)	29 (17.8)
Cardiovascular System		
Hot flashes/sweats*	121 (72.9)	29 (17.8)
Metabolic and Nutritional Disorders		
Edema	9 (5.4)	2 (1.2)
Musculoskeletal System		
Joint disorder*	13 (7.8)	5 (3.1)
Nervous System		
Depression/emotional lability*	18 (10.8)	7 (4.3)
Urogenital System		
Vaginitis*	19 (11.4)	3 (1.8)

Symptoms reported in <5% of patients included: *Body as Whole*—Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System*—Tachycardia; *Digestive System*—Appetite changes, Dry mouth, GI disturbances, Nausea/vomiting; *Metabolic and Nutritional Disorders*—Weight changes; *Musculoskeletal System*—Myalgia; *Nervous System*—Anxiety, Decreased libido,* Dizziness, Insomnia, Nervousness,* Neuromuscular disorders,* Paresthesias; *Respiratory System*—Rhinitis; *Integumentary System*—Androgen-like effects, Nail disorder, Skin reactions; *Special Senses*—Conjunctivitis, Taste perversion; *Urogenital System*—Breast changes,* Menstrual disorders.

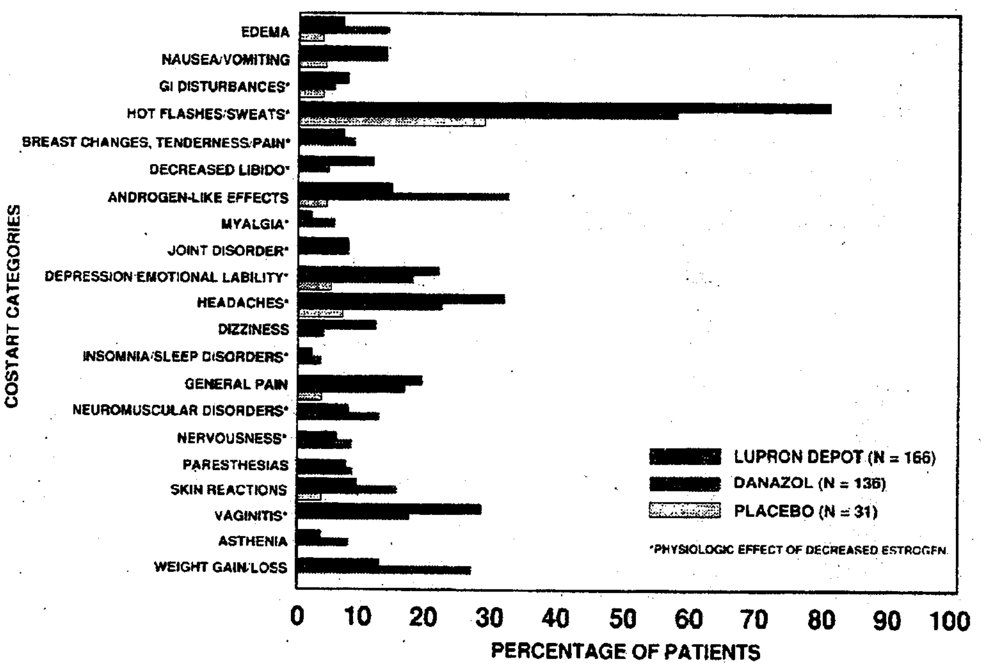
*=Physiologic effect of the drug.

In one controlled clinical trial, patients 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 palpitations, syncope, glossitis, ecchymosis, hypesthesia, confusion, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In other clinical trials involving patients with prostate cancer and during postmarketing surveillance, the following adverse reactions were reported to have a possible, probable, or unknown relationship to LUPRON as ascribed by the treating physician. Often, it is difficult to assess causality in patients with prostate cancer. Reactions considered not drug related have been excluded.

Cardiovascular System—Congestive heart failure, ECG changes/ischemia, High blood pressure, Murmur, Phlebitis/thrombosis, Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli, Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*—Dysphagia, Gastrointestinal bleeding, Peptic ulcer, Rectal polyps, Hepatic dysfunction; *Endocrine System*—Decreased testicular size, gynecomastia, Impotence, Libido increase, Thyroid enlargement; *Hemic and Lymphatic System*—Anemia, Decreased WBC, Hemoptysis; *Musculoskeletal System*—Bone pain; *Central/Peripheral Nervous System*—Peripheral neuropathy, Syncope/blackouts, Hearing disorder, Spinal fracture/paralysis; *Respiratory System*—Dyspnea, Sinus conges-

FIGURE 2–ADVERSE EVENTS REPORTED DURING 6 MONTHS OF TREATMENT WITH LUPRON DEPOT 3.75 MG



tion, Cough, Pleural rub, Pneumonia, Pulmonary fibrosis, Respiratory disorders; *Urogenital System*—Frequency/urgency, Hematuria, Urinary tract infection, Bladder spasm, Incontinence, Testicular pain, Urinary obstruction, Penile swelling, Prostate pain; *Miscellaneous*—Diabetes, Fever, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Inflammation.

Changes in Bone Density:

Endometriosis: A controlled study in endometriosis patients showed that vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.9% at six months compared with the pretreatment value. Earlier studies in endometriosis patients, utilizing quantitative computed tomography (QCT), demonstrated that in the few patients who were retested at six and 12 months, partial to complete recovery of bone density was recorded in the post-treatment period. Use of LUPRON DEPOT for longer than six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Uterine Leiomyomata (Fibroids): In one study, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QRD) revealed a mean decrease of 2.7% at three months compared with the pretreatment value. It would be anticipated that this loss of bone mineral density would be complete to partially reversible following discontinuation of therapy. Use of LUPRON DEPOT 3.75 mg for uterine leiomyomata for longer than three months 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 clinical trials with LUPRON DEPOT, regular laboratory monitoring revealed that SGOT levels were more than twice the upper limit of normal in only one patient. There was no other clinical or laboratory evidence of abnormal liver function.

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: At enrollment, 4% of the LUPRON DEPOT patients and 1% of the danazol patients had total cholesterol values above the normal range. 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 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 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 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 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 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 compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

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 g/dL), and the LDL/HDL ratio (−0.1 to +0.5) were observed across studies. In the one study in which triglyceride levels were determined, the mean increase from baseline was 32 mg/dL.

Other Changes

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

Uterine Leiomyomata (Fibroids):

Hematology: (See Clinical Pharmacology, Clinical Studies section.) In LUPRON DEPOT 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.

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 at present 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.

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, in accord with the following directions:

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the suspension has been shown to be stable for 24 hours following reconstitution, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

Endometriosis: The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with LUPRON DEPOT is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

Uterine Leiomyomata (Fibroids): Recommended duration of therapy with LUPRON DEPOT 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.

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

The vial of LUPRON DEPOT and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT is available in a vial containing sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The singe-dose vial of LUPRON DEPOT 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 accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH. When mixed with 1 mL of diluent, LUPRON DEPOT (leuprolide acetate for depot suspension) is administered as a single monthly IM injection.

LUPRON DEPOT 3.75 mg is available in a single use kit (NDC 0300-3639-01) and in a six pack of drug only (NDC 0300-3639-06).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

No refrigeration necessary. Protect from freezing.

Revised: April, 1995

REFERENCE

1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500–502.

U.S. Patent Nos. 4,005,063; 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; and 4,954,298.

TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.
LUPRON DEPOT manufactured by Takeda
Chemical Industries, Ltd. Osaka, JAPAN 541
®—Registered Trademark

Shown in Product Identification Guide, page 337

LUPRON DEPOT® 7.5 mg ℞

[lu'pron dĕ'pō]

(leuprolide acetate for depot suspension)

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:

[See structure on bottom of next page.]

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

The single-dose vial of LUPRON DEPOT contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic and glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and acetic acid, NF to control pH.

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

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally. Following a single LUPRON DEPOT injection to patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT administration, but testosterone levels appear to be maintained at castrate levels. The metabolism, distribution, and excretion of leuprolide in humans have not been determined.

INDICATIONS AND USAGE

LUPRON DEPOT (leuprolide acetate for depot suspension) is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT does not differ from that of the original daily subcutaneous injection.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg ($\frac{1}{600}$ to $\frac{1}{6}$ 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 in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "WARNINGS" section).

Laboratory Tests: Response to LUPRON DEPOT should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the

Continued on next page

ADDENDUM

B-3

DANISH MEDICINES
AGENCY

11 February 2010

PRODUCT RESUMÉ
for

Procren Depot

Powder and solvent for injection fluid, suspension

0. D.SP.NR. (Danish specialty number for medicines)

1. NAME OF MEDICATION
Procren Depot

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Leuprorelin acetate 3.75 mg and 11.24 mg

Excipients are listed under item 6.1.

3. PHARMACEUTICAL FORM
Powder and solvent for injection fluid, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Prostate cancer
(i) metastatic prostate cancer

(ii) locally-advanced prostate cancer, as an alternative to surgical castration.

(iii) As an adjuvant therapy to radiation therapy on patients with a high risk of local or locally-advanced prostate cancer.

(iv) As an adjuvant therapy for radical prostatectomy in patients with locally-advanced prostate cancer with a high risk of disease progression.

Endometriosis

4.2 Posology and method of administration
Prostate cancer:
Adult: 3.75 mg s.c. every 4 weeks or 11.25 mg s.c. every 12 weeks.

Endometriosis:

Adults: 3.75 mg s.c. every 4 weeks or 11.25 mg s.c. every 12 weeks.
Start treatment on day 1-5 of menstruation period.

The treatment time normally should not exceed 6 months due to the risk of demineralizing bones.

Adults:
Dose adjustment not necessary.

Reduced liver and kidney function:
No clinical examinations have been performed of patients with reduced liver and kidney function.

Children:
There are no approved indications for using leuprorelin on children.

4.3 Contraindications

- Sensitivity to the active ingredients or to any of the excipients.
- Sensitivity to gonadotropin-releasing hormone (GnRH) or other GnRH analogs.
- Pregnancy
- Procren Depot must not be given to women with undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

There have been reports of isolated cases of anaphylaxis in connection with the monthly dosing of leuprolide acetate.

Procren Depot 3.75 mg contains purified gelatin, which in rare cases can produce anaphylactic symptoms. Patients should be monitored after the medicine is administered.

Prostate cancer
Procren Depot should only be used when treatment for prostate cancer is arranged by a physician with specialized expertise in malignant illnesses and their treatment.

The symptoms may temporarily get worse or further signs and symptoms of prostate cancer may appear during the first few weeks of treatment with leuprorelin acetate.
Simultaneous treatment with an anti-androgen medication (e.g. cyproteron) may be advantageous. See the relevant product resume.

A small number of patients may experience a temporary increase in bone pain, which can be treated symptomatically.

As with LH-RH (luteinizing hormone - releasing hormone) agonists, isolated cases of urinary tract obstructions and spinal cord compression have been observed, which may be contributing factors for paralysis with or without fatal complications.

Patients with metastasis in the spinal cord and/or with urinary obstruction should be monitored carefully during the first few weeks of treatment.

If there are complications, the usual treatment should be implemented.

Laboratory analyses

The effect of leuprorelin should be carefully monitored by measuring the plasma concentration of testosterone and prostate-specific antigen. With most patients, the testosterone level is above the baseline during the first week of treatment, then it falls to the baseline level or lower during the second week of treatment. The neutralization level is reached within two to four weeks. When the first neutralization level is achieved, it should be maintained as long as the patients are receiving their injections on time.

Endometriosis

Procren Depot should only be used when endometriosis is being treated by a physician with specialized expertise in gynecological diseases.

In the early phase of the treatment, sex steroids temporarily rise above the baseline due to the physiological effect of the medication. Therefore, it is possible to observe an increase in clinical signs and symptoms over the course of the first few days of treatment, however they will dissipate with continued treatment using the proper doses.

Bone mineral density

With any hypoestrogenic condition, there can be changes to the bone mineral density. The reduction in bone density may be reversible after discontinuing leuprorelin.

4.5 Interaction with other medications and other forms of interaction

None known.
No pharmacokinetic interaction studies have been completed with other medications and leuprorelin.

4.6 Pregnancy and breastfeeding

Pregnancy:
Leuprorelin has pharmacological effects that are harmful for pregnancy. Procren Depot is contraindicated during pregnancy.

There is a theoretical risk of miscarriage or fetal abnormalities when using LHRH agonists during pregnancy. Reproduction toxicity has been seen in animal experiments. The potential risk to humans is not known.

Before starting treatment with leuprorelin, pregnancy should be ruled out, and a non-hormonal contraceptive should be used for the first month of treatment. If pregnancy does occur, the treatment should be discontinued.

Breastfeeding:
Should not be used.
It is not known if leuprorelin is excreted in human breast milk. No animal experiments have been conducted. An assessment whether to discontinue treatment or stop breastfeeding should carefully consider the benefits to the mother versus the benefits of breastfeeding for the child.

4.7 Effects on the ability to drive motor vehicles or operate machinery

No comment.
Procren Depot does not affect, or affects only to an insignificant level, the ability to drive motor vehicles or operate machinery.

4.8 Side-effects

Most side-effects are caused by the specific pharmacological reactions to leuprorelin, i.e. changes to the sex hormone levels.

The most common side effect is blushing, which initially appears in more than half of all patients. This tends to subside over time.

Examinations Very common (≥ 1/10)	Weight gain, weight loss
Common (≥ 1/100 to < 1/10)	Increase in prostate-specific antigen.
Uncommon (≥ 1/1000 to < 1/100)	EKG changes, abnormal liver function test, increased prothrombin time (PT), increased partial thromboplastin time (PTT), low thrombocyte numbers, low number of white blood cells, increased number of white blood cells.
Unknown (cannot be estimated based on existing data)	[Heart] murmur
Heart Uncommon (≥ 1/1000 to < 1/100)	Tachycardia
Unknown (cannot be estimated based on	Palpations, angina, bradycardia, heart

existing data)	arrhythmia, congestive heart failure, myocardial infarction.
Blood and lymphatic system Uncommon (≥ 1/1000 to < 1/100) Unknown (cannot be estimated based on existing data)	Anemia, thrombocytopenia, erythrocytosis and leukopenia Lymphadenopathy.
Nervous system Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to < 1/100) Rare - very rare (<1/1000) Unknown (cannot be estimated based on existing data)	Headache, dizziness. Paresthesia, peripheral neuropathy, taste disturbances, memory problems, syncope. Hypertonia, apoplexy, carpal tunnel syndrome (women). Hypotonia. Hypesthesia, lethargy, neurological disturbances, cramps.
Eyes Uncommon (≥ 1/1000 to < 1/100)	Vision disturbances, dry eyes.
Ears and inner ear Uncommon (≥ 1/1000 to < 1/100)	Impaired hearing, tinnitus
Airway, thorax and mediastinum Common (≥ 1/100 to < 1/10) Rare - very rare (<1/1000) Unknown (cannot be estimated based on existing data)	Dyspnea Interstitial pneumonia Cough, nose bleeding, bloody cough, lung embolism, lung fibrosis, sinus block
Gastrointestinal canal Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to < 1/100) Unknown (cannot be estimated based on existing data)	Nausea, vomiting Gastrointestinal discomfort, dry mouth Constipation, diarrhea, inflammation of the mouth, epigastralgia. Distended abdomen, trouble swallowing, duodenal ulcer, gastrointestinal bleeding,

	stomach ulcers, rectal polyps.
Kidneys and urinary tract Very common (≥ 1/10)	Nocturia, dysuria.
Uncommon (≥ 1/1000 to <1/100)	Urinary incontinence, urinary tract obstruction, hematuria, bladder spasms
Skin and subcutaneous tissue Very common (≥ 1/10)	Increased tendency to perspire, eczema, acne.
Common (≥ 1/100 to < 1/10)	Pruritus, hirsutism seborrhea.
Uncommon (≥ 1/1000 to < 1/100)	Alopecia, ecchymosis, fingernail disorders.
Unknown (cannot be estimated based on existing data)	Abnormal smells from the skin, sensitivity to light, dry skin, pigmentation, urticaria.
Bones, joints, muscles and connective tissue Very common (≥1/10)	Bone pain, especially at the start of treatment.
Uncommon (≥ 1/1000 to < 1/100)	Myalgia (women), arthralgia, shoulder pain, low back pain, stiffness, trouble walking
Unknown (cannot be estimated based on existing data)	Swelling (temporal bone), Bechterew's disease, pelvic fibrosis, spinal cord fracture, paralysis, tendovaginitis-like symptoms.
Endocrine system Very common (≥ 1/10)	Virilisation.
Very rare (<1/10,000)	Pituitary apoplexy in patients with pituitary-adenomas.
Unknown (cannot be estimated based on existing data)	Diabetes, swollen thyroid.
Metabolism and nutrition Common (≥ 1/100 to <1/10)	Increased appetite
Uncommon (≥1/1000 to < 1/100)	Hyperlipidemia: (increased triglycerides,

	increased total cholesterol or LDL cholesterol, increased uric acid); hypercalcemia (women), hyperkalemia, hyperglycemia.
Unknown (cannot be estimated based on existing data)	Increased serum carbamide, increased creatinine, dehydration, hypoglycemia, hypoproteinemia, reduced potassium.
Infections and parasitic diseases Very common (≥ 1/10)	Urinary tract infection.
Common (≥ 1/100 to <1/10)	Influenza syndrome, rhinitis.
Uncommon (≥ 1/1000 to < 1/100)	Fever.
Unknown (cannot be estimated based on existing data)	Pharyngitis.
Benign, malignant and non-specific tumors (incl. cysts and polyps) Rare - very rare (<1/1000)	Necrosis of myoma
Unknown (cannot be estimated based on existing data)	Skin/ear carcinoma
Vascular disease Very common (≥ 1/10)	Blushing.
Not known (cannot be estimated based on existing data)	Ischemia, thrombosis, lymphatic edema, varicose veins, hypertension, hypotension, phlebitis.
General symptoms and reactions at administration site Very common (≥ 1/10)	Fatigue, local reactions at the injection site, edema, pain.
Uncommon (≥ 1/1000 to < 1/100)	Fever
Rare - very rare (< 1/1000)	Abscess, induration and hematoma at injection site.
Unknown (cannot be estimated based on existing data)	Inflammation, chills, thirst, ecchymosis

Immune system Very rare (<1/10,000)	Anaphylactic reaction
Liver and gallbladder Uncommon (≥ 1/1000 to < 1/100) Unknown (cannot be estimated based on existing data)	Usually temporary: Increased transaminase and alkaline phosphates; altered liver count. Jaundice, liver dysfunction, increase bilirubin.
Reproductive system and mammary glands Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to < 1/100) Unknown (cannot be estimated based on existing data)	 Erectile dysfunction. Testicular pain, testicular atrophy. Breast discomfort, chest pain, vaginal dryness Gynecomastia, milk secretion, menstruation disturbances including break-through bleeding, blotching and persistent vaginal bleeding, perineal pain, ovary hyperstimulation syndrome (OHSS), pain during intercourse (women) Prostate pain
Mental disorders Very common (≥ 1/10) Common (≥ 1/100 to 1/10) Uncommon (≥ 1/1000 to < 1/100) Very rare (<1/10,000) Unknown, (cannot be estimated from existing data)	 Reduced libido Depression, mood swings, nervousness, insomnia, sleep disturbances, anxiety, sadness, personality disorders. Irritability Suicidal thoughts and attempts Delusions, increased libido

4.9 Overdose

There have been no reports of overdosing during treatment with Procren Depot.

Leuprorelin acetate is delivered over a long period of time. Injections with a shorter interval than prescribed may affect the clinical reaction.

4.10 Delivery
A.

5 PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification
L 02 AE 02 - Gondotropin-releasing hormone analogs.

5.1 Pharmacodynamic properties
A synthetic nonapeptide, analogous to the naturally occurring LHRH. Leuprorelin is approximately 70 times more active than natural LHRH. When administering LHRH analogs, there is an initial increase release of FSH and LH, and thereby also of sex hormones in both men and women. After approximately 2 weeks, this release is blocked followed by reduced testosterone production among men and a reduced estradiol production in women. Since many prostate tumors are dependent on androgen, this can result in an inhibition of tumor growth and atrophy of the reproductive organs.

5.2 Pharmacokinetic properties
Leuprorelin acetate is released at a constant rate over a period of 4 weeks (3.75 mg) or 12 weeks (11.25 mg) and causes testosterone suppression, which is equivalent with what is seen with a daily injection of 1 mg leuprorelin acetate. **3.75 mg:** One dose provides a maximum serum concentration of 20 ng/ml after 4 hours. After 4 weeks, the concentration is 0.36 ng/ml. **11.25 mg:** One dose provides an immediate increase of leuprorelin acetate. Maximum plasma concentration after 3 weeks is 21.82 ng/ml on average. After 4 weeks, the concentration is 0.26 ng/ml, and after 12 weeks the concentration is 0.17 ng/ml on average. The half-life is approximately 3 hours.

5.3 Preclinical safety data
None.

6 PHARMACEUTICAL INFORMATION

6.1 Excipients
Powder for injection fluid 3.75 mg leuprorelin acetate: gelatin; lactic acid/glycol acid copolymer (75/25 mol %); mannitol.

Powder for injection fluid 11.25 mg leuprorelin acetate: lactic acid (+/-): mannitol.

Solvents: Carmellose sodium, mannitol; polysorbate 80; water for injection fluid.

6.2 Incompatibilities
None.

6.3 Shelf life

Powder and solvent for injection fluid 3.75 mg:	2 years
powder and solvent injection substance 11.25 mg:	3 years
Ready-to-use injection fluid:	Use immediately after reconstituting

6.4 Special precautions for storage
None

6.5 Package types and package sizes
Powder for injection fluid: Vials.
Solvent: Ampules.

6.6 Rules for destruction and other handling
Dissolve powder for injection fluid (3.75 mg) in **1 ml** solvent immediately before use.

Dissolve powder for injection fluid (11.25 mg) in **2 ml** solvent immediately before use.

Unused medication and waste should be immediately destroyed in accordance with local guidelines.

7 MARKETING AUTHORIZATION HOLDER
Abbott Scandinavia AB
Box 509
S-169 29 Solna
Sweden

Representative
Abbott Laboratories A/S
Emdrupvej 28C
2100 Copenhagen E

8 MARKETING AUTHORIZATION NUMBER(S)

3.75 mg:	13612
11.25 mg:	18660

9 DATE OF FIRST MARKETING AUTHORIZATION

21 June 1985

10 DATE OF TEXT REVISION

11 February 2010

ADDENDUM

B-4

8-
8-6

PDR® 44 EDITION 1990

PHYSICIANS' DESK REFERENCE®

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is the case with other nasally inhaled corticosteroids, nasal septal perforations have been observed in rare instances. Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing's syndrome, could occur.

OVERDOSAGE

I.V. flunisolide in animals at doses up to 4 mg/kg showed no effect. One spray bottle contains 6.25 mg of NASALIDE; therefore acute overdosage is unlikely.

DOSAGE AND ADMINISTRATION

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen. Full therapeutic benefit requires regular use, and is usually evident within a few days. However, a longer period of therapy may be required for some patients to achieve maximum benefit (up to 3 weeks). If no improvement is evident by that time, NASALIDE® (flunisolide) should not be continued.

Patients with blocked nasal passages should be encouraged to use a decongestant just before NASALIDE administration to ensure adequate penetration of the spray. Patients should also be advised to clear their nasal passages of secretions prior to use.

Adults: The recommended starting dose of NASALIDE is 2 sprays (50 mcg) in each nostril 2 times a day (total dose 200 mcg/day). If needed, this dose may be increased to 2 sprays in each nostril 3 times a day (total dose 300 mcg/day).

Children 6 to 14 years: The recommended starting dose of NASALIDE is one spray (25 mcg) in each nostril 3 times a day or two sprays (50 mcg) in each nostril 2 times a day (total dose 150-200 mcg/day). NASALIDE is not recommended for use in children less than 6 years of age as safety and efficacy studies, including possible adverse effects on growth, have not been conducted.

Maximum total daily doses should not exceed 8 sprays in each nostril for adults (total dose 400 mcg/day) and 4 sprays in each nostril for children under 14 years of age (total dose 200 mcg/day). Since there is no evidence that exceeding the maximum recommended dosage is more effective and increased systemic absorption would occur, higher doses should be avoided.

After the desired clinical effect is obtained, the maintenance dose should be reduced to the smallest amount necessary to control the symptoms. Approximately 15% of patients with perennial rhinitis may be maintained on as little as 1 spray in each nostril per day.

HOW SUPPLIED

Each 25 ml NASALIDE® (flunisolide) nasal solution spray bottle (NDC 0033-2906-40) (NSN 6505-01-132-9979) contains 6.25 mg (0.25 mg/mL) of flunisolide and is supplied in a nasal pump dispenser with dust cover and a patient leaflet of instructions.

Store at controlled room temperature, 15°–30°C (59°–86°F)

Revised 12/88

NORINYL® 1+35 Tablets ℞
(norethindrone and ethinyl estradiol)
NORINYL® 1+50 Tablets ℞
(norethindrone and mestranol)

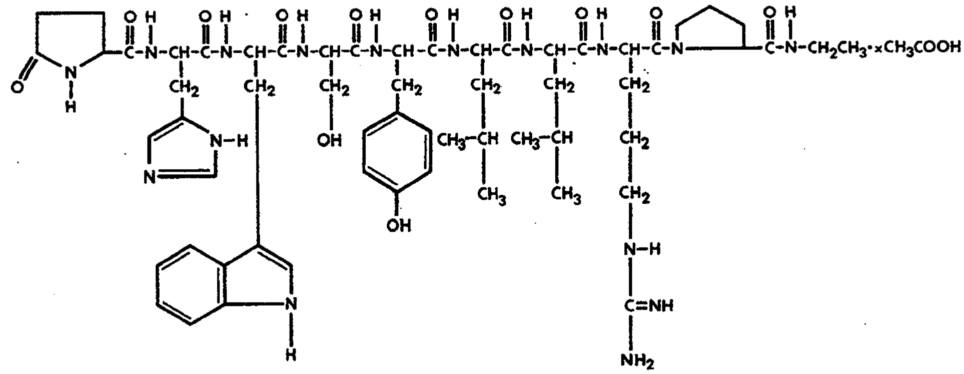
Refer to entry under BREVICON® Tablets (norethindrone and ethinyl estradiol).

Shown in Product Identification Section, page 433

NOR-Q.D® ℞
(norethindrone)
Tablets 0.35 mg.

Refer to entry under BREVICON® Tablets (norethindrone and ethinyl estradiol).

Shown in Product Identification Section, page 433



SYNACORT® ℞
(hydrocortisone)
Cream 1%
Cream 2.5%
SYNALAR® ℞
(fluocinolone acetonide)
Cream 0.025%
Cream 0.01%
Ointment 0.025%
Topical Solution 0.01%
SYNALAR-HP® ℞
(fluocinolone acetonide)
Cream 0.2%
SYNEMOL® ℞
(fluocinolone acetonide)
Cream 0.025%

Refer to entry under LIDEX® (fluocinonide) Cream 0.05%.

TAP Pharmaceuticals
NORTH CHICAGO, IL 60064

LUPRON® ℞
[lu 'pron]
leuprolide acetate injection

DESCRIPTION

LUPRON (leuprolide acetate) Injection 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:
[See structural formula above].

LUPRON is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 ml multiple-dose vial containing 5 mg/ml of leuprolide acetate, sodium chloride for tonicity adjustment, 9 mg/ml of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to three years.

Leuprolide acetate is not active when given orally. Bioavailability by subcutaneous administration is comparable to that by intravenous administration. Leuprolide acetate has a plasma half-life of approximately three hours. The metabolism, distribution and excretion of leuprolide acetate in man have not been determined.

INDICATIONS AND USAGE

LUPRON (leuprolide acetate) Injection is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In a controlled study comparing LUPRON 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years treatment. The objective response to treatment was also similar for the two groups.

CONTRAINDICATIONS

There are no known contraindications to the use of LUPRON.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported. Worsening of symptoms may contribute to paralysis with or without fatal complications.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "ADVERSE REACTIONS" section).

Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information for Patients: See Information for Patients which appears after the "HOW SUPPLIED" section.

Laboratory Tests: Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued. Transient increases in acid phosphatase levels occurred sometimes early in treatment. However, by the fourth week, the elevated levels usually decreased to values at or near baseline.

Drug Interactions: None have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were 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). In mice no 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 with analogs similar to leuprolide acetate have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 20 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (See "WARN-

Continued on next page

TAP Pharmaceuticals—Cont.

INGS" section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.
Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.
In a comparative trial of LUPRON (leuprolide acetate) Injection versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Reactions considered not drug related are excluded.

	LUPRON (N = 98)	DES (N = 101)
	Number of Reports	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
Decreased testicular size	7	11
Gynecomastia/breast tenderness or pain	7	63
Hot flashes	55	12
Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4
Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10

In this same study, the following adverse reactions were reported in less than 5% of the patients on Lupron.
Cardiovascular System—Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*—Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ucler, Rectal polyps; *Endocrine System*—Libido decrease, Thyroid enlargement; *Musculoskeletal System*—Joint pain; *Central/Peripheral Nervous System*—Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*—Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*—Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*—Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*—Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).
The following additional adverse reactions have been reported with Lupron in another clinical trial and/or during postmarketing surveillance. Reactions considered by the treating physician as nondrug related are not included.
Cardiovascular System—Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System*—Hepatic dysfunction; *Endocrine System*—Libido increase; *Hemic and Lymphatic System*—Decreased WBC, Hemoptysis; *Musculoskeletal System*—Ankylosing spondylosis, Pelvic fibrosis; *Central/Peripheral Nervous System*—Hearing disorder, Peripheral neuropathy, Spinal fracture/paralysis; *Respiratory System*—Pulmonary infiltrate, Respiratory disorders; *Urogenital System*—Penile swelling, Prostate pain; *Miscellaneous*—Hypoproteinemia.

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 at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate 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

The recommended dose is 1 mg (0.2 ml) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be be varied periodically.
NOTE: As with all parenteral products, inspect container's solution for discoloration and particulate matter before each use.

HOW SUPPLIED

LUPRON (leuprolide acetate) Injection is a sterile solution supplied in a 2.8 ml multiple-dose vial, **NDC** 0300-3626-28. Refrigerate until dispensed. Patient may store unrefrigerated below 86°F. Avoid freezing. Protect from light—store vial in carton until use.
Each 0.2 ml contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.
Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.
Revised: November, 1986.
U.S. Patent Nos. 4,005,063 and 4,005,194.

INFORMATION FOR PATIENTS

NOTE: Be sure to consult your physician with any questions you may have or for information about LUPRON (leuprolide acetate) Injection and its use.

WHAT IS CANCER?

Cancer is a disease characterized by uncontrolled growth and spread of abnormal body cells. Normally, the cells that make up all parts of the body reproduce themselves in an orderly manner so that growth occurs, worn out tissues are replaced and injuries repaired. Occasionally, certain cells grow into a mass of tissue called a tumor. Some tumors are benign; others are malignant, or cancerous.
Benign tumors may interfere with body function and may require surgical treatment but they do not invade neighboring tissue and seldom threaten life. However, malignant tumors invade and destroy normal tissue. By a process called metastasis, cells break away from a malignant tumor and spread through the blood and lymphatic systems to other parts of the body where they form new tumors. Sometimes cancer grows and spreads rapidly; sometimes the process takes years.
One very common place for cancer to develop in men is the prostate gland.

WHAT IS THE PROSTATE?

The prostate is a male sex gland about the size of a chestnut. It lies just below the urinary bladder and surrounds the first inch of the urethra, the canal that carries urine from the bladder during urination. The secretion of the prostate provides part of the fluid for ejaculation.

TREATMENT OF PROSTATIC CANCER

Your doctor has a choice of treatments for prostatic cancer including surgery, radiation and drugs. The best choice for a particular patient usually depends on whether the cancer was found early or in an advanced stage.
The growth and function of the normal prostate gland is dependent upon the male hormone testosterone. If you have a prostatic tumor, its growth is usually stimulated by testosterone as well. For this reason, decreasing the body's supply of testosterone often controls tumor growth and relieves pain and difficulty in urinating.
The primary source of testosterone is the testes; therefore, one way to reduce production of testosterone is to remove the testes by surgery.
Another way is for men to take a female hormone, estrogen. This also causes the body to stop making testosterone. Estrogens have potential side effects such as swelling of the breasts, fluid retention, blood clotting problems, and decrease in libido and impotence.
Another choice is LUPRON which will also decrease testosterone production. LUPRON has potential side effects, such as hot flashes and decrease in libido and impotence. It may also initially aggravate signs and symptoms of your disease by temporary stimulation of the tumor during the first one to two weeks of treatment.

WHAT IS LUPRON?

LUPRON (leuprolide acetate) Injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH), a hormone which occurs naturally in your body.
Normally, your body releases small amounts of LH-RH, and this leads to events which stimulate the production of testosterone.
However, when you inject LUPRON Injection, the normal events that lead to testosterone production are interrupted and testosterone is no longer produced by the testes.
LUPRON must be injected because, like insulin which is injected by diabetics, LUPRON is inactive when taken by mouth.
If you were to discontinue the drug for any reason, your body would begin making testosterone again.

DIRECTIONS FOR USING LUPRON

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use LUPRON. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the .2 mark.
4. Take cover off needle and push the cover into the appropriate hole in the Daily Dose Reminder area. Push the needle through the center of the rubber stopper on the LUPRON bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the .2 mark.
7. Toward the end of a two-week period, the amount of LUPRON left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the .2 mark.
9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down on the syringe rest. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Hold the syringe alongside the skin and slide the needle quickly just under the skin as far as it will go. Inject the drug by pushing in the plunger as far as it will go.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. A waste area is provided in the LUPRON Patient Administration Kit. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

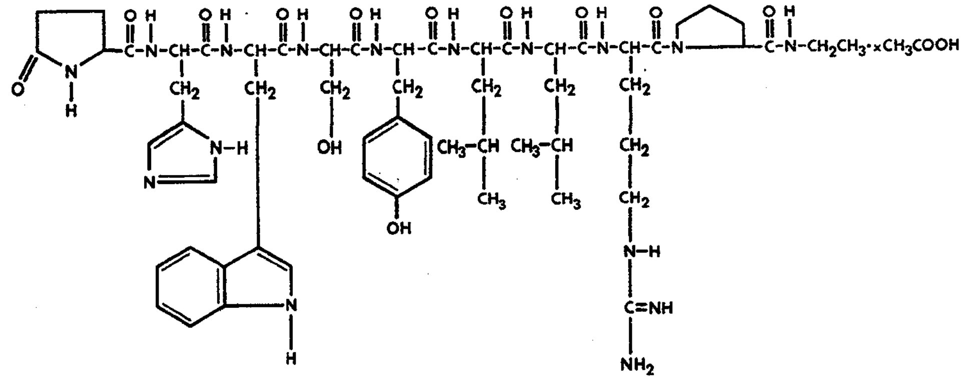
SOME SPECIAL ADVICE

- You may experience hot flashes when using LUPRON (leuprolide acetate) Injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure LUPRON keeps working for you.
- Use only the syringes provided in the kit, as other types may dispense an incorrect dose. If for any reason you cannot use one of the syringes, contact your doctor or pharmacist for advice.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need your next LUPRON kit so it will be at the pharmacy when you need it.

- This drug may be stored at room temperature (not above 86°F). Do not store near a radiator or other very warm place.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

Manufactured for TAP Pharmaceuticals
North Chicago, IL 60064, U.S.A.
by Abbott Laboratories
North Chicago, IL 60064

LUPRON DEPOT® ℞
[*lu'pron dē'pō*]
(leuprolide acetate for depot suspension)



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:
[See structural formula above right].
LUPRON DEPOT is available in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as a monthly intramuscular injection.
The single-dose vial of LUPRON DEPOT contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic and glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), and water for injection, USP.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.
In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.
Leuprolide acetate is not active when given orally. Following a single LUPRON DEPOT injection to patients, mean peak leuprolide acetate plasma concentration was almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. Nondetectable leuprolide acetate plasma concentrations have been observed during chronic LUPRON DEPOT administration, but testosterone levels appear to be maintained at castrate levels. The metabolism, distribution, and excretion of leuprolide acetate in humans have not been determined.

INDICATIONS AND USAGE

LUPRON DEPOT is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT does not differ from that of the original daily subcutaneous injection.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]
LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 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 (leuprolide acetate for depot suspension) in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see "WARNINGS" section).
Laboratory Tests: Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their monthly injection on time. Transient increases in acid phosphatase levels may occur sometime early in treatment. However, by the fourth week, the elevated levels can be expected to decrease to values at or near baseline.
Drug Interactions: None have been reported.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were 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). In mice no 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 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.
Pregnancy Category X. See "CONTRAINDICATIONS" section.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.
Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see "WARNINGS" section).

In a clinical trial of LUPRON DEPOT, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LUPRON DEPOT N = 56	(Percent)
Cardiovascular System		
Edema	7	(12.5%)
Gastrointestinal System		
Nausea/vomiting	3	(5.4%)
Endocrine System		
*Decreased testicular size	3	(5.4%)
*Hot flashes/sweats	33	(58.9%)
*Impotence	3	(5.4%)
Central/Peripheral Nervous System		
General pain	4	(7.1%)
Respiratory System		
Dyspnea	3	(5.4%)
Miscellaneous		
Asthenia	3	(5.4%)

*Physiologic effect of decreased testosterone.

Laboratory: Elevations of certain parameters were observed, but it is difficult to assess these abnormalities in this population.

SGOT (>2N)	4	(5.4%)
LDH (>2N)	11	(19.6%)
Alkaline phos (>1.5N)	4	(5.4%)

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT. *Cardiovascular System* —Angina, Cardiac arrhythmia; *Gastrointestinal System* —Anorexia, Diarrhea; *Endocrine System* —Gynecomastia, Libido decrease; *Musculoskeletal System* —Bone pain, Myalgia; *Central/Peripheral Nervous System*—Paresthesia, Insomnia; *Respiratory System* —Hemoptysis; *Integumentary System* —Dermatitis, Local skin reactions, hair growth; *Urogenital System* —Dysuria, Frequency/urgency, Hematuria, Testicular pain; *Miscellaneous* —Diabetes, Fever/chills, hard nodule in throat, Increased calcium, Weight gain, Increased uric acid.
The following additional adverse reactions have been reported with LUPRON (leuprolide acetate) Injection. Reactions considered by the treating physician as nondrug related are not included.
Cardiovascular System —Congestive heart failure, ECG changes/ischemia, High blood pressure, Hypotension, Myocardial infarction, Murmur, Phlebitis/thrombosis, Pulmonary emboli, Transient ischemic attack/stroke; *Gastrointestinal System* —Constipation, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Hepatic dysfunction, Peptic ulcer, Rectal polyps; *Endocrine System* —Breast tenderness or pain, Libido increase, Thyroid enlargement; *Hemic and Lymphatic System* —Anemia, Decreased WBC; *Musculoskeletal System* —Ankylosing spondylosis, Joint pain, Pelvic fibrosis; *Central/Peripheral Nervous System* —Anxiety, Blurred vision, Dizziness/lightheadedness, Headache, Hearing disorder, Sleep disorders, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Peripheral neuropathy, Spinal fracture/paralysis, Syncope/blackouts, Taste disorders; *Respiratory System* —Cough, Pleural rub, Pneumonia, Pulmonary fibrosis, Pulmonary infiltrate, Respiratory disorders, Sinus congestion; *Integumentary System* —Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Pigmentation, Skin lesions; *Urogenital System* —Bladder spasms, Incontinence, Penile swelling, Prostate pain, Urinary obstruction, Urinary tract infection; *Miscellaneous* —Depression, Hypoglycemia, Hypoproteinemia, Increased BUN, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

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 at present that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprolide acetate, 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.
The recommended dose of LUPRON DEPOT is 7.5 mg, incorporated in a depot formulation. The lyophilized micros-

Continued on next page

TAP Pharmaceuticals—Cont.

pheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

Although the solution has been shown to be stable for 24 hours following reconstitution, 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.

The vial of LUPRON DEPOT and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT (NDC 0300-3629-01) is available in a vial containing sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids. The single-dose vial of LUPRON DEPOT contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic & glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), and water for injection, USP. When mixed with 1 mL of diluent, LUPRON DEPOT is administered as a single monthly IM injection.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

U.S. Patent Nos. 4,005,063; 4,005,194 and patent pending (LUPRON DEPOT).

Reference:

1. MacLeod TL, Eisen A, Sussman GL, et al: Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987 Sept;48(3):500-502.

TAP Pharmaceuticals
North Chicago, IL 60064 U.S.A.
LUPRON DEPOT manufactured
by Takeda Chemical Industries, Ltd.
Osaka, Japan
R-Registered

EDUCATIONAL MATERIAL

All Free to the medical profession

Lupron® Injection

"Introduction to Lupron® (leuprolide acetate) Injection"—product monograph.

"Information for Patient Instruction"—a brochure to help professionals answer patients' questions about Lupron and to aid in subcutaneous self-injection.

Lupron Depot®

"An Introduction: Lupron Depot the Next Generation of GnRH Agonist Analogs"—product monograph.

"Questions and Answers on Lupron Depot the First Once-a-Month GnRH Agonist"—a bruchure that answers many common questions posed by the health professional.

"Treatment with Lupron Depot"—a brochure for the patient that briefly describes prostate cancer and how Lupron Depot is used to treat it.

ToppMed, Inc.

5015 BIRCH STREET
NEWPORT BEACH, CA 92660

TOPPFAST™

Physician-Formulated Diet Supplement

DESCRIPTION

Each serving delivers 120 calories consisting of 10 grams of protein, 19 grams of carbohydrate, 1 gram of fat, 1 gram of fiber, 240 mg. of sodium, 545 mg. of potassium and at least ⅕ of the RDA for vitamins.

USE

ToppFast is used as a meal substitute or as a total dietary intake supplement (5 servings per day) which is to be physician monitored per published protocol.

NUTRITION INFORMATION

	1 Serving	5 Servings
Serving Size	1 scoop (33.5 g)	
Servings per container	21	
Calories	120	600
Protein	10 g	50 g
Carbohydrate	19 g	95 g
Fat	1.0 g	5.0 g
*Sodium (715 mg/100 g)	240 mg	1200 mg**
*Potassium	545 mg	2725 mg**
Fiber	1.0 g	5.0 g

Percentage of U.S. Recommended Daily Allowances For Adults and Children Over 12 Years of Age

	1 Serving	5 Servings
Protein	20%	100%
Vitamin A	40%	200%
Vitamin C	40%	200%
Thiamine	35%	175%
Riboflavin	35%	175%
Niacin	40%	200%
Calcium	20%	100%
Iron	40%	200%
Vitamin D	20%	100%
Vitamin E	40%	200%
Vitamin B6	40%	200%
Folic Acid	20%	100%
Vitamin B12	40%	200%
Phosphorus	20%	100%
Iodine	20%	100%
Magnesium	20%	100%
Zinc	20%	100%
Copper	30%	150%
Biotin	20%	100%
Pantothenic Acid	20%	100%
*Vitamin K	20 mcg	100 mcg**
*Manganese	0.8 mg	4 mg**
*Chromium	40 mcg	200 mcg**
*Selenium	40 mcg	200 mcg**
**Molybdate	100 mcg	500 mcg**

*U.S. RDA HAS NOT BEEN ESTABLISHED.

**THE FOOD AND NUTRITION BOARD OF THE NATIONAL RESEARCH COUNCIL RECOMMENDS THESE QUANTITIES OF THESE ESSENTIAL TRACE MINERALS AS BEING WITHIN THE RANGE REQUIRED IN THE DIET OF AN ADULT.

INGREDIENTS

Calcium sodium caseinate, fructose, nonfat milk, natural and artificial flavors, calcium sulfate, cellulose, partially hydrogenated soybean oil, guar gum, corn syrup solids, potassium chloride, salt, potassium and sodium citrate, magnesium oxide, ascorbic acid, ferrous fumarate, alpha tocopheryl acetate, niacinamide, dipotassium phosphate, vitamin A palmitate, zinc oxide, mono- and di-glycerides, d-calcium pantothenate, manganese sulfate, cupric sulfate, artificial color (including FD&C yellow #5), pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, sodium molybdate, folic acid, chromium chloride, vitamin D_3, sodium selenite, biotin, potassium iodide, vitamin K, cyanocobalamin.

Tyson and Associates, Inc.

1661 LINCOLN BLVD.
SUITE 300
SANTA MONICA, CA 90404

PRODUCTS

L-Alanine	(600mg)	50c
L-Arginine	(700mg)	100c
L-Aspartic Acid	(600mg)	50c
L-Carnitine	(250mg)	30c
L-Cysteine Mono HCl	(750mg)	50c
L-Cystine	(700mg)	100c
L-Citrulline	(600mg)	50c
GABA	(500mg)	100c
L-Glutamic Acid	(500mg)	100c
L-Glutamine	(500mg)	100c
Glycine	(600mg)	100c
L-Histidine	(600mg)	50c
L-Isoleucine	(600mg)	50c
L-Leucine	(600mg)	50c
L-Lysine	(500mg)	100c
L-Methionine	(500mg)	30c
L-Ornithine	(600mg)	100c
Alphaketoglutaric Acid	(500mg)	100c
D-Phenylalanine	(500mg)	100c
L-Phenylalanine	(600mg)	100c
Proline	(600mg)	50c
L-Serine	(600mg)	50c
Taurine	(500mg)	100c
L-Threonine	(500mg)	60c
L-Tryptophan	(500mg)	100c
L-Tyrosine	(800mg)	100c
L-Valine	(600mg)	50c
Riboflavin 5 ' Phosphate	(5mg)	100t
[illegible]	(20mg)	100t

ALPHA PLUS™

(Urea Cycle Intermediates)

U.S.P. Crystalline Amino Acid Formulation. 700 mg Capsules

DOSAGE AND ADMINISTRATION

1–2 capsules daily.

HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1232-1

AMINOLETE™

U.S.P. Crystalline Amino Acid Formulation. 700 mg Capsules

DOSAGE AND ADMINISTRATION

1–3 capsules half an hour before meals.

HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1205-1

AMINOMINE™

(Excitatory neurotransmitters and L-Glutamine)

U.S.P. Crystalline Amino Acid Formulation. 700 mg Capsules

DOSAGE AND ADMINISTRATION

1–3 capsules half an hour before meals.

HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1129-1

AMINOPLEX®

DESCRIPTION

U.S.P. crystalline amino acid formulation. Formula contains 740 mg Anhydrous of 19 crystalline L-amino acids including neurotransmitter precursors and sulfur amino acids, and supplies 130 mg Nitrogen per capsule. Balanced formulation replacement based on quantitative Amino Acid Fractionation.

COMPOSITION

L-Lysine, L-Tryptophan, L-Arginine, L-Isoleucine, L-Leucine, L-Alanine, L-Threonine, L-Histidine, L-Cystine, L-Methionine, L-Glutamine, L-Tyrosine, L-Aspartic Acid, L-Valine, L-Glutamic Acid, L-Phenylalanine, Glycine, L-Serine, L-Cysteine HCl.

DOSAGE AND ADMINISTRATION

1–3 capsules half an hour before meals.

HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1116-1

AMINOSINE™

(Arginine-free Amino Acid Formulation)

U.S.P. Crystalline Amino Acid Formulation. 700 mg Capsules

DOSAGE AND ADMINISTRATION

1–3 capsules half an hour before meals.

HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1207-1

AMINOSTASIS™

(Branched Chain Amino Acid Formulation)

DESCRIPTION

U.S.P. crystalline amino acid formulation. Formula contains 700 mg of 12 crystalline L-amino acids supplying 107 mg Nitrogen per capsule. Formula is a rich source of the branched chain amino acids.

COMPOSITION

L-Lysine, Glycine, L-Leucine, L-Methionine, L-Arginine, L-Phenylalanine, L-Valine, L-Isoleucine, L-Histidine, L-Threonine, L-Tyrosine, L-Tryptophan.

DOSAGE AND ADMINISTRATION

2–6 capsules three times a day half an hour before meals.

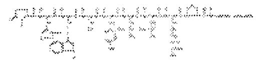
HOW SUPPLIED

Bottles of 100 capsules—NDC 53335-1200-1

LUPRON® INJECTION
(leuprolide acetate)
Rx 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 INJECTION is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption

Bioavailability by subcutaneous administration is comparable to that by intravenous administration.

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, a 1 mg bolus 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 has not been determined.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with leuprolide acetate. 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

In a controlled study comparing LUPRON 1 mg/day given subcutaneously to DES (diethylstilbestrol), 3 mg/day, the survival rate for the two groups was comparable after two years of treatment. The objective response to treatment was also similar for the two groups.

INDICATIONS AND USAGE

LUPRON INJECTION (leuprolide acetate) is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS

1. LUPRON INJECTION is contraindicated in patients known to be hypersensitive to GnRH, GnRH agonist analogs or any of the excipients in LUPRON INJECTION: Reports of anaphylactic reactions to GnRH agonist analogs have been reported in the medical literature.
2. LUPRON is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON may cause fetal harm when administered to a pregnant woman. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy. If this drug is administered during pregnancy or if the patient becomes pregnant while taking any formulation of LUPRON, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Initially, LUPRON, like other LH-RH agonists, causes increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate cancer, may occasionally develop during the first few weeks of LUPRON treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON, pregnancy must be excluded (see **CONTRAINDICATIONS** section).

Periodic monitoring of serum testosterone and prostate-specific antigen (PSA) levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** and **ADVERSE REACTIONS** sections). Patients with known allergies to benzyl alcohol, an ingredient of the drug's vehicle, may present symptoms of hypersensitivity, usually local, in the form of erythema and induration at the injection site.

Information for Patients

See **INFORMATION FOR PATIENTS** which appears after the **REFERENCE** section.

Laboratory Tests

Response to leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

Drug Interactions

See **CLINICAL PHARMACOLOGY, Pharmacokinetics** section.

Drug/Laboratory Test Interactions

Administration of leuprolide acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were 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 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 full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

Pregnancy

Teratogenic Effects

Pregnancy Category X

(see **CONTRAINDICATIONS** and **WARNINGS** sections)

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, LUPRON produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in major fetal malformations throughout gestation. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON in rabbits and with the highest dose in rats. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug.

Nursing Mothers

It is not known whether leuprolide acetate is excreted in human milk. LUPRON should not be used by nursing mothers.

Pediatric Use

See labeling for LUPRON INJECTION for Pediatric Use for the safety and effectiveness in children with central precocious puberty.

Geriatric Use

In the clinical trials for LUPRON INJECTION, the majority (69%) of subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON in this population.

ADVERSE REACTIONS

Clinical Trials

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase

in bone pain (see **WARNINGS** section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

Potential exacerbation of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction which, if aggravated, may lead to neurological problems or increase the obstruction.

In a comparative trial of LUPRON INJECTION (leuprolide acetate) versus DES, in 5% or more of the patients receiving either drug, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician. Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug related are excluded.

	LUPRON (N=98)	**DES (N=101)**
	Number of Reports	
Cardiovascular System		
Congestive heart failure	1	5
ECG changes/ischemia	19	22
High blood pressure	8	5
Murmur	3	8
Peripheral edema	12	30
Phlebitis/thrombosis	2	10
Gastrointestinal System		
Anorexia	6	5
Constipation	7	9
Nausea/vomiting	5	17
Endocrine System		
*Decreased testicular size	7	11
*Gynecomastia/breast tenderness or pain	7	63
*Hot flashes	55	12
*Impotence	4	12
Hemic and Lymphatic System		
Anemia	5	5
Musculoskeletal System		
Bone pain	5	2
Myalgia	3	9
Central/Peripheral Nervous System		
Dizziness/lightheadedness	5	7
General pain	13	13
Headache	7	4
Insomnia/sleep disorders	7	5
Respiratory System		
Dyspnea	2	8
Sinus congestion	5	6
Integumentary System		
Dermatitis	5	8
Urogenital System		
Frequency/urgency	6	8
Hematuria	6	4

Urinary tract infection	3	7
Miscellaneous		
Asthenia	10	10

* Physiologic effect of decreased testosterone.

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON.

Cardiovascular System—Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli; *Gastrointestinal System*—Diarrhea, Dysphagia, Gastrointestinal bleeding, Gastrointestinal disturbance, Peptic ulcer, Rectal polyps; *Endocrine System*—Libido decrease, Thyroid enlargement; *Musculoskeletal System*—Joint pain; *Central/Peripheral Nervous System*—Anxiety, Blurred vision, Lethargy, Memory disorder, Mood swings, Nervousness, Numbness, Paresthesia, Peripheral neuropathy, Syncope/blackouts, Taste disorders; *Respiratory System*—Cough, Pleural rub, Pneumonia, Pulmonary fibrosis; *Integumentary System*—Carcinoma of skin/ear, Dry skin, Ecchymosis, Hair loss, Itching, Local skin reactions, Pigmentation, Skin lesions; *Urogenital System*—Bladder spasms, Dysuria, Incontinence, Testicular pain, Urinary obstruction; *Miscellaneous*—Depression, Diabetes, Fatigue, Fever/chills, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Infection/inflammation, Ophthalmologic disorders, Swelling (temporal bone).

In an additional clinical trial and from long-term observation of both studies, the following additional adverse events (excluding those considered not drug related) were reported for patients receiving LUPRON. *Cardiovascular System*—Bradycardia, Carotid bruit, Extrasystole, Palpitations, Perivascular cuffing (eyes), Ruptured aortic aneurysm, Stroke, Tachycardia, Transient ischemic attack; *Gastrointestinal System*—Flatus, Dryness of mouth and throat, Hepatitis, Hepatomegaly, Occult blood (rectal exam), Rectal fistula/erythema; *Endocrine System*—Libido increase, Thyroid nodule; *Musculoskeletal System*—Ankylosing spondylosis, Arthritis, Blurred disc margins, Bone fracture, Muscle stiffness, Muscle tenderness, Pelvic fibrosis, Spasms/cramps; *Central/Peripheral Nervous System*—Auditory hallucinations/tinnitus, Decreased hearing, Decreased reflexes, Euphoria, Hyperreflexia, Loss of smell, Motor deficiency; *Respiratory System*—Chest tightness, Decreased breathing sounds, Hemoptysis, Pleuritic chest pain, Pulmonary infiltrate, Rales/rhonchi, Rhinitis, Strep throat, Wheezing/bronchitis; *Integumentary System*—Boil (pubic), Bruises, Hives, Keratosis, Mole, Shingles, Spiders; *Urogenital System*— Blisters on penis, Inguinal hernia, Penile swelling, Post void residual, Prostatic pain, Pyuria; *Miscellaneous*—Abdominal distention, Facial swelling/edema, Feet burning, Flu, Eyelid growth, Hypoproteinemia, Accidental injury, Knee effusion, Mass, Pallid, Sallow, Weakness.

Postmarketing

During postmarketing surveillance which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) 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 (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System – Hypotension, Myocardial infarction; *Endocrine System* - Diabetes; *Gastrointestinal System* – Hepatic dysfunction; *Hemic and Lymphatic System* – Decreased WBC; *Integumentary System* – Hair growth; *Central/Peripheral Nervous System* – Spinal fracture/paralysis, Hearing disorder; *Miscellaneous* – Hard nodule in throat, Weight gain, Increased uric acid; *Musculoskeletal System* – Tenosynovitis-like symptoms; *Respiratory System* – Respiratory disorders.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.