CORRESPONDENCE

19-943

Takeda-Abbott Research & Development
Attn: Mr. Dean Sundberg
Director, Regulatory Affairs
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Mr. Sundberg:

Reference is made to your new drug application (NDA) for Lupron Depot 3.75 mg (leuprolide acetate for depot suspension) and to our letter of December 28, 1989, acknowledging withdrawal of this NDA.

For your information, we have the following comments:

A. Regarding the chemistry and manufacturing and controls information:

1. On page 17 (volume 1.2), the composition of the drug dosage form is for Lupron Depot 7.5 mg and thus is incorrect.

2. It appears that unlike Lupron Depot 7.5 mg, vials and ampules for the 3.75 mg product and diluent, respectively, are packaged in separate cartons. We recommend that the Lupron Depot 3.75 mg and vehicle be packaged together in a single carton.

3. The diluent ampule label was not included in the application. Moreover, carton labels for both vials and ampules must contain information on excipients.

4. The package insert should declare the strength of 3.75 mg leuprolide acetate in order to distinguish from the package insert of 7.5 mg strength approved for the treatment of prostatic cancer.

5. No expiration was proposed for the Lupron Depot 3.75 mg. We recommend that it carry a shelf-life of 24 months at 25° C as supported by the submitted stability data.

B. Regarding the clinical and statistical information:

1. An open-ended phrase such as "when surgery is not desirable" should not be used in the INDICATIONS AND USAGE section.

2. We beiieve that the use of GnRH analogs in the medical management of fibroids is for a limited subgroup of patients who need to undergo surgery for their fibroids. Among this subgroup of women, those women who would most benefit from a period of medically induced amenorrhea are women who have severe anemia which places them at risk for surgery, and/or will not allow for pre-surgical banking of their own blood. Since these women would most benefit from the use of a GnRH analog, we suggest that the

primary efficacy parameter not be volume reduction of the uterus, but rather a study should be designed to show that analogs would improve the hematologic status in these women when compared to more conventional medical treatment for anemia and/or severe menometrorrhagia. At this time, we believe that both placebo and Lupron treated women should be given iron, since oral iron therapy is considered standards of care for anemia.

3. Along with measurements of hematocrit, quantitation of degree of hypermenorrhea and improvement in this outcome would be important. Quantitation of improvement needs to be documented as changes in days and amount of bleeding with treatment.

4. Data on bone safety during treatment and especially in the recovery period should be accumulated in enough patients to obtain adequate statistical power. Also, the present NDA lacks adequate follow-up data at the end of the treatment period. Consideration should be given to providing normal standards of care for both Lupron-treated and placebo-treated patients, such as adequate calcium supplementation, etc.

5. If you would like to determine if analog therapy may reduce blood loss during surgery, the group of patients enrolled because of their anemia should be followed through to surgery. Such a study should be double-blind and randomized and have enough patients to show statistical significance for the outcome. In addition, the surgeon performing the surgery should be blinded. The number of surgeons unblinded should be greatly reduced, in order to obtain as homogenous a data source as possible. Efficacy parameters such as route of myomectomy or hysterectomy, difference in planes of dissection, intra-operative blood loss, etc., should be incorporated into the study.

6. The treatment period should be carefully thought out. Do the data suggest that three months of therapy is adequate? Why continue for six months, when three months of treatment may be adequate to provide maximal reduction?

7. A placebo-controlled study to determine the usefulness of analog therapy in the hysteroscopic removal of submucous myomas would be helpful. The single case presented to the Advisory Committee is provocative.

8. Women should not be included in the final data analysis if they are switched to a treatment or placebo arm during the study. Drop-outs should be taken into consideration in the trial and treated as such.

9. A placebo group should be included, but both treated and placebo groups should receive "standard care", determined at the time of institution of the clinical trials.

If you have any questions, please contact Mr. Peter Vaccari at (301) 443-3490.

Sincerely yours,

1/23/91

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-510
HFD-510/CHNiu/YChiu/VRagavan/PCorfman
HFD-511/PVaccari
Concurrences: REastep/1/9/CHNiu/1/10/VRagavan/
PCorfman/1/10/90/ft/PLV/1/25/90
Revised: PVaccari 1/19/90
Concurrences: VRagavan/1/22/PCorfman/1/23/90/ft/PLV/1/25/90

1-23-90

ADVICE LETTER

DEC 28 1989

Abbott Research & Development
Attn: Mr. Dean Sundberg
Director, Regulatory Affairs
One Abbott Park Road
Abbott Park, IL 60064-3500

Dear Mr. Sundberg:

We acknowledge the receipt of your communication dated December 18, 1989, requesting withdrawal of your pending new drug application for Lupron Depot 3.75 mg (leuprolide acetate for depot suspension).

In compliance with your request and as provided for in 21 CFR 314.65, the application is withdrawn. This withdrawal does not prejudice any future resubmission. You may request that the information contained in the withdrawn application be considered in conjunction with any resubmission.

Sincerely yours,

12/27/89

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-80
HFD-510
HFD-510/PCorfman/VRagavan/AJordan/KRahaja/YChiu/CHNiu
HFD-511/PVaccari 12/22/89/ft/dj/12.26.89/nl9943.wtd
Concurrences:REastep/12/26/89/ft/PLV/12/26/89

12-22-89

WITHDRAWAL

JUL 28 1989

NDA 19-943

Takeda-Abbott Research & Development
Attn: Mr. Dean Sundberg
Associate Director
Regulatory Affairs
Abbott Park, IL 60064

Dear Mr. Sundberg:

Reference is made to your pending new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot 3.75 mg.

We also refer to the July 25, 1989, telephone conversation between you and Mr. Peter Vaccari during which you agreed to an extension of the review period until after the October 17, 1989, Fertility and Maternal Health Advisory Committee meeting.

The new due date of your application will be October 31, 1989.

Sincerely yours,

/S/ 7/28/89

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch ✓
HFD-510
HFD-510/VRagavan/PCorfman
HFD-511/PVaccari 7/25/89/ft/ras/7.28.89/wang 0823v /S/ 7/28/89
Concurrences:REastep/7/26/89/ft/PLV/7/28/89

EXTENSION

Memorandum of Telephone Conversation

From: Peter Vaccari, CSO, HFD-510

To: Dean Sundberg, Takeda-Abbott Research & Development

Date: July 25, 1989

Subject: Extension of NDA 19-943, Lupron Depot 3.75 mg

I called Mr. Sundberg to ask if he would agree to an extension of the review period of this NDA until after the advisory committee meeting on October 17, 1989. He agreed and I informed him that the due date would be October 31, 1989.

cc: NDA 19-943
HFD-510
HFD-511/PVaccari/7/21/89 n19943.tel

Bannockburn Lake Office Plaz
2355 Waukegan Road
Deerfield, Illinois 60015

March 29, 1995

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drug Evaluation & Research
Food and Drug Administration
5800 Fishers Lane
Rockville, MD 20857

RE: **NDA 19-943; Lupron Depot® 3.75 mg for Management of Uterine Fibroids**
Amendment No. 008

Dear Dr. Sobel,

We have received the fax of March 28, 1995, providing for some minor modifications to the draft labeling provided in our submission of March 24, 1995.

Appended are two copies of the draft labeling; one plain copy and one copy showing the recommended changes from your fax of March 28, 1995.

As mentioned in our submission of March 24, 1995, TAP Pharmaceuticals Inc. commits to providing a draft patient package insert within four weeks of receipt of the approval letter. In addition, TAP commits to performing a Phase 4 Pharmacokinetic Study.

Sincerely,

S. Albert Edwards for
Dean P. Sundberg
Director, Regulatory Affairs

DPS:bjs

March 24, 1995

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 148-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

RE: Lupron Depot 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 007

Dear Dr. Sobel:

Attached is a draft copy of the revised labeling for NDA 19-943. This revision incorporates all the changes requested in your letter dated March 22, 1995, and agreed to by the sponsor and the Division on March 24, 1995. The revised labeling also incorporates changes (under subsection of Metabolism) recommended by Biopharmaceutics reviewer on March 24, 1995. All revisions are underlined for ease of review.

The Sponsor, TAP Pharmaceuticals Inc., commits to develop and submit a draft copy of Patient Package Insert within four weeks from the date of approval.

The Sponsor also commits to conduct the Phase 4 pharmacokinetic study as recommended in the letter dated March 22, 1995.

All the adverse events from Study M90-411 were submitted in the 4 Month Safety Update (Submission dated July 29, 1994).

The required information for this amendment is attached.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317 4893

AD/pjp

March 9, 1995

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 006

Dear Dr. Sobel:

Pursuant to 21 CFR § 314.60, the Sponsor, TAP Pharmaceuticals Inc., submits this amendment to NDA 19-943 submitted on March 30, 1994

This amendment contains the figures requested on March 6, 1995, and a brief summary. A desk copy of these figures is being faxed today.

Also submitted are results of additional analysis performed and submitted to the medical reviewers on February 21, 1995 (Attachment #1).

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

February 15, 1995

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

ORIGINAL

RE: Lupron Depot® 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 005

Dear Dr. Sobel:

Pursuant to 21 CFR § 314.60, the Sponsor, TAP Pharmaceuticals Inc., submits this amendment to NDA 19-943 submitted on March 30, 1994.

This amendment contains the revised labeling (package insert) for Lupron Depot 3.75 mg. The labeling is revised as recommended by the Biopharmaceutics reviewer (Dr. Ahn).

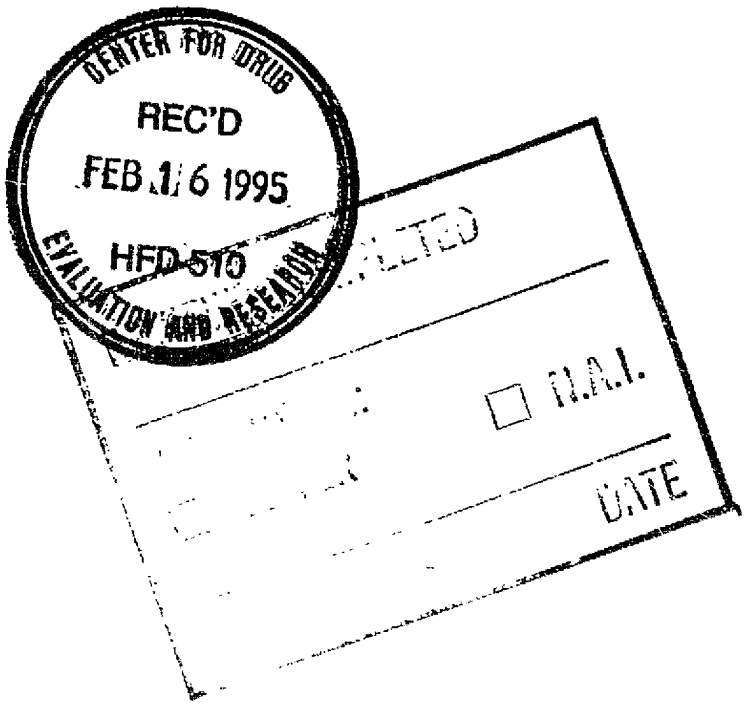
Attached are four copies of the draft labeling, and a description of the revisions.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment



TAP PHARMACEUTICALS INC.

ORIG AMENDMENT BS BM

ORIGINAL

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

February 13, 1995

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 004

Dear Dr. Sobel:

Pursuant to 21 CFR § 314.60, the Sponsor, TAP Pharmaceuticals Inc., submits this amendment to NDA 19-943 submitted on March 30, 1994.

This amendment contains the results of additional analyses requested by the medical reviewers. The desk copies of these analyses were submitted on December 6, 1994, December 8, 1994 and February 9, 1995, respectively.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

REVIEWS COMPLETED
CSO ACTION:
DARECD
FEB 14 1995
HFD-510
EVALUATION AND RESEARCH
CENTER FOR DRUG

TAP PHARMACEUTICALS INC.

BD

January 9, 1995

ORIGINAL

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 003

Dear Dr. Sobel:

Pursuant to 21 CFR § 314.60, the Sponsor, TAP Pharmaceuticals Inc., submits this amendment to NDA 19-943 submitted on March 30, 1994.

This amendment contains the Pharmacokinetic/Pharmacodynamic modeling for the Pharmacokinetic Study M91-374. The information was requested by Dr. Ahn (Division of Biopharmaceutics) on December 20, 1994 and should be considered as a minor amendment.

REVIEWS COMPLETED
CSO ACTION: ☐ N.A.I.
☐ LETTER
DATE
INITIALS

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

CENTER FOR DRUG
REC'D
JAN 10 1995
HFD-510
EVALUATION AND RESEARCH

Faxed 1-13-95

TAP PHARMACEUTICALS INC.

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

November 1, 1994

Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DESK COPY

RE: **NDA 19-943**
(Lupron Depot®3.75 mg for Management of Uterine Fibroids)

Attention : Annette Bay, M.D.
Lisa Rarick, M.D.

ORIGINAL

Recently, while attempting to respond to some issues raised by Abbott Canada regarding NDA 19-943, a patient in the pivotal study M90-411 (#1089, Lupron Depot 7.5 mg, Stratum A) was discovered to have some conflicting source documentation regarding her original diagnosis of fibroids. Retrospectively, it appears that this patient may have actually had adenomyosis rather than fibroids, although at the time of study entry she was diagnosed and documented as having fibroids. The study site was contacted for further clarification but, unfortunately, due to the death of the principal investigator, we were unable to resolve this issue definitively.

Because of this confusing clinical picture, the data was re-analyzed with this patient removed from all efficacy-evaluable analyses. While deletion of this single patient has very slightly altered previously reported N's, means, medians, percentages and numeric p-values (usually affecting only the Stratum A analyses), statistical significance and the conclusions for the combined strata analysis, as originally presented in the NDA, remain unaltered.

There were only two instances where a numeric change in a p-value resulted in a change in statistical significance. Both affected the Stratum A analyses only.

1. Table 16 (the protocol-defined hematologic responders) under "AND" definition, at week 12, the Lupron Depot 7.5 mg dosage group is now marginally significant vs placebo (p value changed from 0.050 to 0.054).

2. Table 22 (the clinically-defined hematologic responders), under "OR" definition, at the final visit, the Lupron Depot 7.5 mg dosage group is now marginally significant vs placebo (p value changed from 0.049 to 0.051).

These two revised tables from M90-411 summary are attached for your review. A desk copy of SAS Data Files for all NDA studies was submitted to Division's Statistician along with the NDA and the results can be reproduced using that data.

Again, these slight changes have not affected the overall results and conclusions presented in NDA 19-943. Also the intent-to-treat analysis submitted in the study summary of M90-411 remains unchanged.

Please note that these changes do not affect the adverse events and safety analysis reported in the NDA or the 4 - Month Safety Update submitted on July 29, 1994, because all of the safety analyses incorporate the data for all patients entered into the study.

If any further information or a meeting is necessary with regards to this NDA review please do not hesitate to call me.

Sincerely,

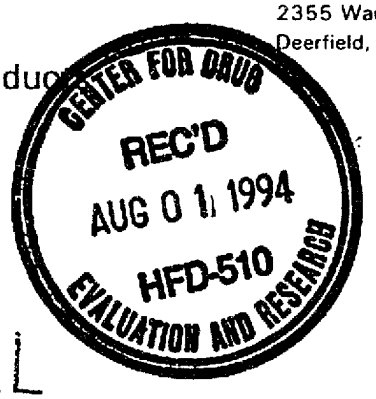
Aruna Dabholkar, M.D.
Regulatory Product Manager

TAP PHARMACEUTICALS INC. SU

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

July 29, 1994

Division of Metabolism and Endocrine Drug Produc
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Attn: Doctor Sobel ORIGINAL

RE: Lupron Depot® 3.75 mg for Management of Leiomyoma Uteri
NDA 19-943
Amendment No. 002 **4-Months Safety Update**

Dear Doctor Sobel:

The sponsor, TAP Pharmaceuticals Inc., submits this amendment (Four Months Safety Update) to the New Drug Application under the provisions of Section 505(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50(d)(5)(vi)(b).

This amendment consists of 10 volumes numbered 3.1 to 3.10 containing updated safety data from the clinical study M90-411.

The updated safety data are incorporated in the clinical overview section of the NDA 19-943. The revised pages (Adverse Events section) of the text and the End-of-Text Tables from the NDA 19-943 are also submitted in this amendment.

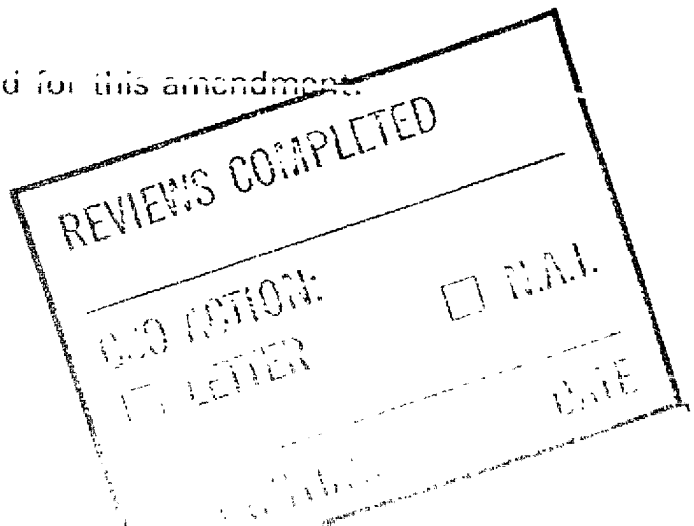
Please direct any questions you may have on this amendment to my attention.

Attached is the information required for this amendment.

Sincerely,

S. Albert Edwards for

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317 4893



July 3, 1990

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Roger Eastep, Supervisory CSO

RE: **Lupron Depot 3.75, Uterine Fibroid Protocol Meeting**

Dear Mr. Eastep,

This letter is to acknowledge the meeting scheduled for Monday July 9, 1990, at 9:30 A.M. in conference room L, third floor.

Attending from TAP Pharmaceuticals will be:

James Miller, M.D.
Robert Browneller
John Seely, Ph.D.
Dean Sundberg

From Abbott will be:

James Lancaster, Ph.D.

We will bring an overhead projector.

A copy of the proposed protocol will be sent Federal Express to your attention.

Thanks for setting up the meeting.

Sincerely,

Dean P. Sundberg
Director, Regulatory Affairs
(708) 317-5750

DPS/lms

June 8, 1990

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Mr. Roger Eastep, Supervisory CSO

RE: **Lupron Depot 3.75 mg, Uterine Fibroids, NDA 19-943**

Dear Mr. Eastep,

Following the advisory committee meeting we have planned to do additional clinical work to ultimately obtain approval for this indication. We have developed a protocol outline and are now finalizing it. We would like to meet with appropriate divisional representatives to jointly decide what the appropriate outcome parameters are so, if necessary, we can adjust the protocol and proceed with our clinical work.

The timing for the meeting is dictated by the availability of our hematologist consultant. He is available the week of July 9-12. Anytime that week would be acceptable, although an early afternoon meeting would allow us to fly in and out in the same day.

We checked the calender for Drs. Ragavan and Sobel and found they are both available that week.

We would have about 6-8 people attending this meeting. I will let you have the list when a date has been set.

I appreciate your efforts in this case especially with the short-handed staff situation.

Sincerely,

Dean P. Sundberg
Director, Regulatory Affairs
(708) 317-5780

DPS/lms

Meeting Scheduled for 7/9/90 NAT

ABBOTT RESEARCH & DEVELOPMENT
One Abbott Park Road
Abbott Park, IL 60064-3500

December 18, 1989

AJ 1/4/90
IND
NDA ORIG AMENDMENT

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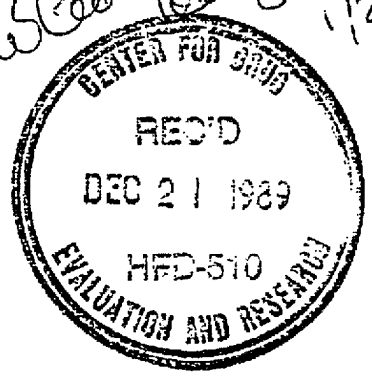

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Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, M.D., Director

Re: Lupron Depot (leuprolide acetate for depot suspension)
NDA 19,943

Notice of Withdrawal

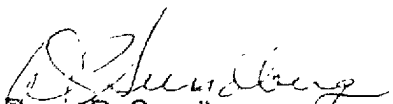
Dear Doctor Sobel:

Following the advisory committee vote not to recommend approval of Lupron Depot for the treatment of uterine fibroids, we have decided to withdraw NDA 19,943 under the provisions of CFR 314.65.

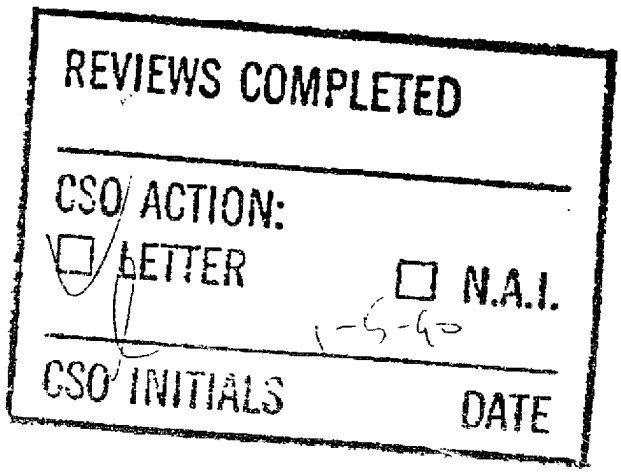
We have decided to pursue additional clinical data to provide the necessary information in support of Lupron Depot approval for this indication.

We will be working with you and your staff to design study protocol(s) necessary to accomplish this task.

Sincerely,



Dean P. Sundberg
Director, Regulatory Affairs
(708) 937-3979



DPS/lms

cc: Mr. Peter Vaccari, CSO

TAKEDA ABBOTT PHARMACEUTICALS
Abbott Park, IL 60064

mber 7, 1989

NDA ORIG AMENDMENT
8m

tion of Metabolism and Endocrine Drug Products, HFD-510
ument Control Room 14B-03
er for Drugs and Biologics
and Drug Administration
Fishers Lane
ville, MD 20857

9/13/89

tion: Solomon Sobel, M.D., Director

Lupron Depot® (leuprolide acetate for depot suspension) 3.75 mg
NDA 19-943
Amendment No. 002

ar Doctor Sobel:

are amending the original new drug application dated December 30, 1988 to provide:

- Response to clinical questions received by telefax August 7, 1989.
- Written summary entitled "Treatment of Leiomyomata Uteri with GnRH Agonists: Focus on Role as Surgical Adjunct" and the scientific literature upon which this is based.

erely,

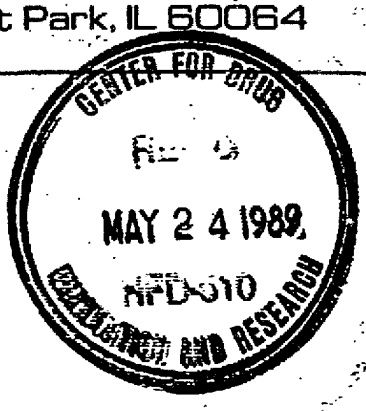
P. Sundberg
ctor, Regulatory Affairs
937-3979

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
CSO INITIALS DATE

items

uments

TAKEDA-ABBOTT RESEARCH & DEVELOPMENT
Abbott Park, IL 60064



withdrawn 7/6/89

NDA ORIG AMENDMENT
54

May 19, 1989

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, M.D., Director

Re: Lupron Depot® (leuprolide acetate for depot suspension), 3.75 mg
NDA 19-943
Amendment No. 001 **Safety Update**

Dear Doctor Sobel:

Appended is the first safety update to the uterine fibroid new drug application, NDA 19-943. This update provides information on 44 of 63 patients treated with Lupron Depot® in the three clinical studies comprising the NDA. We believe the data continues to show Lupron Depot is a safe well-tolerated product and the primary concern of bone mineral density changes are showing the expected recovery trend.

Sincerely,

Dean P. Sundberg
Director, Regulatory Affairs
(312) 937-3979

DPS/sms

Attachments

DAL/DPD5/19

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
1-10-89
CSO INITIALS DATE

withdrawn

TAKEDA-ABBOTT RESEARCH & DEVELOPMENT
Abbott Park, IL 60064

December 30, 1988

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, M.D., Director

Re: Lupron Depot® (leuprolide acetate for depot suspension), 3.75 mg

Original
New Drug Application

Dear Doctor Sobel:

In accordance with section 505(h) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314, Takeda-Abbott Research and Development herewith submits an Original New Drug Application for Lupron Depot® (leuprolide acetate for depot suspension), 3.75 mg in the treatment of leiomyoma uteri (uterine fibroids).

Included in the submission are three double-blind clinical studies which show convincingly that treatment with Lupron Depot® decreases the uterine volume and provides a beneficial hematological response. As expected, there is a trend toward decreases in bone mineral density. However, early post-dosing information shows bone mineral density recovery. We will continue to collect post treatment bone mineral density data and provide this information in safety updates to this NDA.

Sincerely,

Dean P. Sundberg
Associate Director, Regulatory Affairs
(312) 937-3979

DPS/419/sms

Attachment

NDA 19-943
Lupron (leuprolide acetate)
TAP Pharmaceuticals

May 4, 1994

Memorandum of 45-day Meeting

Attendees:

Dr. Corfman
Dr. Rarick
Dr. Niu
Ms. Pauls
Dr. Ahn (HFD-427)

Not Present:

Dr. Sobel
Dr. Troendle
Dr. Chiu
Dr. Jordan
Dr. Raheja
Dr. Turner (HFD-344)
Mr. Marticello (HFD-713)

Purpose:

To determine whether the Lupron (leuprolide acetate) NDA (resubmission) is acceptable for filing. Lupron is indicated for the treatment of leiomyomata uteri (fibroids).

Discussion:

The various disciplines discussed their portions of the application as follows:

Clinical:	Acceptable for filing; expected review completion date 08/94.
Chemistry:	Acceptable for filing; review completed 04/89; must review labelling only.
Pharmacology:	Acceptable for filing; review completed 04/12/94.
Statistics:	Acceptable for filing.
Biopharmaceutics:	Acceptable for filing; however, firm has yet to provide data on metabolism as previously requested. This information must be received prior to an approval letter.

Conclusions:

Acceptable for filing. In addition, Ms. Pauls indicated that the user fee goal date for the application is March 30, 1995. She asked if all disciplines could have final reviews completed by the end of January 1995. All present responded affirmatively. The January time frame was chosen to allow for 2 weeks at the division level, and sufficient time for draft reviews to be finalized at the supervisory level.

Lana L. Pauls, M.P.H.

cc:
NDA Arch
HFD-510
HFD-344/GTurner
HFD-427/Ahn/JHunt
HFD-510/LRipper
HFD-510/EGalliers/Attendees (present or absent listed above)
HFD-713/DMarticello/ENevius
HFD-510/LPauls/05.04.94/N19943.45D

Concurrences:
LRarick, PCorfman, CNiu 05.04.94

NDA 19-943
Lupron Depot

July 9, 1990

Memorandum of Meeting

Representing TAP Pharmaceuticals:

James Lancaster, Ph.D. (Abbott)
John Seely, Ph.D.
James MIller, M.D.
Robert Browneller
Dean Sundberg

FDA Staff:

Solomon Sobel, M.D.
Ridgely Bennett, M.D.
Phill Price, M.D.
Vanaja Ragavan, M.D.
Lisa Rarick, M.D.
Yong Chen (Chinese Visitor)
Roger Eastep

Purpose: The company requested this meeting to discuss its proposed protocol for treatment of uterine fibroids (copy attached). The NDA previously submitted had been found not approvable and had been withdrawn by the company.

Discussion and Conclusions:

1. The protocol proposed to "stratify" patients into two inclusion criteria categories: a) Oqualification based on symptomatology (pain) and, b) qualification based on vaginal bleeding/ hematologic factors. The first group would likely not be candidates for surgery, while the second group likely would be, although there was no surgical endpoint with regard to the protocol, i.e., surgery after treatment with drug would be at the option of the physician and patient.

   Dr. Sobel questioned the validity of the proposed stratification, stating that it was essentially the same as trying to do two different studies under the same protocol. He suggested that, since pain was the less important of the two endpoints (and less likely to cause a patient to seek medical help), the study could be legitimately stratified by first including patients with vaginal bleeding/hematological factors, then subdividing those patients with regard to pain symptoms.

It was recommended by FDA that patients for such a study might best be found in inner city areas because of the higher prevalence of uterine fibroids in the non-white population, and that follow up should not be a problem if the patient understands that when surgery is necessary after drug treatment, the chances of a blood transfusion being necessary would be reduced.

2. The firm asked whether it would be possible to obtain approval of an indication for effectively treating symptoms of uterine fibroids, especially in patients who were incapacitated by condition. FDA staff questioned whether enough such patients could be recruited to do the studies even if such a patient population existed.

3. The visitors stated that the firm would revise the protocol in accord with the recommendations of the FDA.

Roger Eastep, SCSO

cc: NDA Arch
HFD-510
HFD-510/All Attendees
HFD-510/REastep/7.9.90/ft/dj/7.23.90/n19943.001

concurrences: VRagavan7/16/90; LRarick7/17/90; PPrice7/18/90; RBennett7/20/90; SSobel7/20/90

JAN 10 1989

February 21, 1989

NDA 19-943
Lupron Depot 3.75 mg
Takeda-Abbott Pharmaceuticals

Minutes of 45-Day meeting

Representing FDA:

Dr. Solomon Sobel
Dr. Philip Corfman
Dr. Vanaja Ragavan
Dr. Yuan-Yuan Chiu
Dr. Chien-Hua Niu
Dr. Alex Jordan
Dr. Krishan Raheja
Mr. Dan Jarticello HFD-713
Mr. John Hunt HFD-425
Dr. Bob Young HFD-344
Mr. Peter Vaccari

Chemistry: Data sufficient for review.

Pharmacology: Data sufficient for review.

Medical: Data sufficient for review. Application will probably be presented to the advisory committee later this year.

Biostatistics: Data sufficient for filing.

Biopharm: No pharmacokinetic studies using the 3.75 mg dose were submitted. However, since the 7.5 mg dose is now approved, a commitment for a phase 4 pharmacokinetic study would satisfy this requirement.

Conclusion: Application can be filed.

pl 3/1/89

Peter Vaccari, CSO

cc: NDA Arch
HFD-510
HFD-510/Attendees/REastep
HFD-511/PVaccari 2/24/89/ft/jaf/2/28/89 wang 0128v
Concurrences: KRaheja/AJordan/2/21/CHNiu/YChiu/VRagavan
PCorfman/SSobel/2/27/89/ft/PLV/2/28/89

19-943

5-003

NDA 19-732/S-009 ←
NDA 19-943/S-003
NDA 20-011/S-006
NDA 20-263/S-006

OCT 26 1995

TAP Holdings Inc.
Attention: Aruna Dabholkar, M.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your December 30, 1994, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

> Lupron Depot (leuprolide acetate for depot suspension), 7.5 mg (NDA 19-732);
> Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg (NDA 19-943);
> Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg (NDA 20-011); and
> Lupron Depot (leuprolide acetate for depot suspension), 7.5, 11.25, and 15.0 mg (NDA 20-263).

We acknowledge receipt of your amendments dated May 24, September 1 (NDA 19-732) and September 7 (NDAs 19-943, 20-011, and 20-263), 1995.

These supplemental applications provide for an additional container/closure system (pre-filled, dual-chamber syringe) filled with Lupron Depot and diluent.

We have completed the review of these supplemental applications and they are approved, effective on the date of this letter.

We remind you that you must comply with the requirements for approved NDAs set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDAs 19-943, 19-732, 20-011, and 20-263
HFD-510
HFD-510/CNiu/YYChiu
HFD-80
DISTRICT OFFICE
HFD-232

drafted: LPauls/October 23, 1995/N19732AP.S09

Concurrences:
CNiu, SMoore 10.23.95

APPROVAL

nDA 19943

.310 Rv.

MAR - 1 1995 Paul's

NDA 19-943
Lupron Depot® 3.75 mg
Leuprolide Acetate Depot

SUBMISSION DATE: March 30, 1994
May 20, 1994
January 09, 1995
February 15, 1995

TAP Pharmaceuticals Inc.
Deerfield, IL

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: Resubmission

Code: 3S

SYNOPSIS: The sponsor submitted a new NDA seeking approval for marketing Lupron Depot® 3.75 mg for a new indication for leiomyomata uteri. **(Note: Leiomyomata uteri is a gynecologic disorder characterized by the presence of benign uterine neoplasms of myometrial origin. It occurs in 20-25% of all women in their third and fourth decades, and is the most common solid pelvic tumor in women.)** Lupron Depot® 3.75 mg will be given once monthly for treating this disease.

One pharmacokinetic study (protocol M89-374) was conducted using the U.S. approved Lupron Depot® 3.75 mg formulation in 10 female healthy volunteers with normal ovarian function. After the administration of the 3.75 mg intramuscular injection, there was the characteristic immediate rise in plasma drug concentrations. This immediate rise was generally similar among subjects and concentrations ranged from 4.60 to 10.02 ng/mL (mean 6.83 ng/mL) at four hours post-dosing when the first blood sample was drawn. Following this initial rise, plasma leuprolide levels of approximately 0.23 ng/mL to 0.34 ng/mL were maintained up to four and one-half weeks post-dosing. **(Note:** In a teleconference with Ann Hsu of Abbott and Aruna Dabholkar of TAP on 01/19/95, it was learned that the sponsor had measured the plasma levels of leuprolide using a RIA method which could not differentiate between intact leuprolide and one of the metabolites (i.e., M-I). Therefore, the plasma levels of leuprolide in this study should be considered as those of intact leuprolide and a metabolite). The sponsor conducted Pharmacokinetic/Pharmacodynamic modeling upon request. A marked clockwise hysteresis could be observed in the plot of mean estradiol plasma levels vs leuprolide/M-I plasma levels. The sponsor also submitted information on the metabolism and excretion of leuprolide. A biologically inactive pentapeptide metabolite (M-I) was identified and quantitated in serum and urine by a technique. Other metabolites could be separated but could not be quantified at physiological levels due to no cross-reactivity with the antibody used in the leuprolide In the teleconference on 01/19/95 it was learned that metabolism occurs in all tissues. It was indicated by the sponsor on 02/07/95 that the sponsor did not conduct any multiple dose pharmacokinetic studies. The sponsor submitted raw data (plasma drug levels and hormonal levels) in a diskette upon request.

It was also indicated by the sponsor that the formulation which was used in clinical trials is the same formulation that is on the market.

This reviewer was informed of the following through conversations with the reviewing medical officer of HFD-510:

1. In a clinical trial as recommended by the Agency's Advisory Committee, Lupron Depot® 3.75 mg was administered with 525 mg of iron as ferrous sulfate. Patients with Uterine Fibroids would be anemic patients due to bleeding.

2. The primary efficacy endpoint was the change in hematological status in anemic patients whose bleeding is secondary to fibroids (i.e., hemoglobin levels and hematocrit value).

3. The recommended therapy will be for 3 months before the surgery.

4. In a clinical trial patients were divided into three groups and each group received Lupron Depot® 7.5 mg plus iron, Lupron Depot® 3.75 mg plus iron, or only iron. No differences in clinical responses were found between a group with Lupron Depot® 7.5 mg plus iron and a group with Lupron Depot® 3.75 mg plus iron.

5. It is documented that the administration of leuprolide decreases the systemic levels of estradiol through an indirect mechanism. Leuprolide suppresses pituitary gonadotropins which are important in stimulating secretion of hormones by the gonads. Systemic estradiol levels were used as a pharmacodynamic marker.

This was only a pharmacokinetic/ pharmacodynamic study of leuprolide acetate where female subjects participated. The Division of Biopharmaceutics is of the opinion that there is a lack of significant female data available.

RECOMMENDATION:

The Division of Biopharmaceutics (HFD-420) has reviewed NDA 19-943 with its submissions dated March 30, 1994, May 20, 1994, January 09, 1995 and February 15, 1995. HFD-420 feels that a new pharmacokinetic study in patients is needed but this could be conducted post-approval if the NDA is approved based upon clinical safety and efficacy data. The new study should be a multiple dose design where 3 monthly doses of Lupron Depot® 3.75 mg plus iron are given to at least 10 patients with uterine fibroids. A reasonable number of blood samples should be collected over 4 weeks following the first dose to characterize the plasma profiles of leuprolide and estradiol. Additionally, trough levels of leuprolide and estradiol (i.e., 4, 8 and 12 weeks) should be determined. Leuprolide plasma samples should be analyzed with the technique which can identify intact leuprolide and a metabolite.

Please convey the Recommendation, the Comments and the Labeling Comments to the sponsor.

(Note: Attachments are being retained in the Division of Biopharmaceutics and can be obtained upon request.)

TABLE OF CONTENTS

BACKGROUND: Lupron® (leuprolide acetate) 5 mg/mL Injection was approved under NDA 19-010 in April, 1985 for the palliative treatment of advanced prostate cancer. Lupron® Injection was designed to be administered daily by subcutaneous injection.

Lupron Depot® (leuprolide acetate for depot suspension) was designed to provide continuous release of leuprolide over a four week period when administered as a monthly intramuscular injection. Lupron Depot® 7.5 mg was approved under NDA 19-732 for the palliative treatment of advanced prostate cancer on January 26, 1989. The Division of Biopharmaceutics requested a Phase IV study to determine the metabolism and excretion of leuprolide acetate. Subsequently, Lupron Depot® 3.75 mg was approved by the Agency for the management of endometriosis (NDA 20-011) on October 22, 1990. NDA 19-943 was originally submitted without any pharmacokinetic studies using the 3.75 mg dose in December 1988 and following an Advisory Committee vote (October, 1989) it was withdrawn in December 1989. A protocol for pharmacokinetic study (M89-374) was submitted under IND 27,350 on July 20, 1990. The protocol was not reviewed by the Division of Biopharmaceutics because the study had been initiated.

STUDY M89-374

Title: A Study of Leuprolide Blood Levels and Hormonal Response After a Lupron Depot Injection in Female Subjects.

Investigator:

Objective: The objectives were to determine the pharmacokinetic profile of a single 3.75 mg dose of Lupron Depot® in female subjects and to detail the hormonal response to this dose with emphasis on length of time for normal endocrine activity to be re-established.

Test Drug: Lupron Depot® was supplied as a two part package: a single-dose vial containing sterile lyophilized microspheres of 3.75 mg leuprolide acetate (lot no. 23-853-AR) incorporated in a biodegradable copolymer, and a 1.5 mL ampoule of diluent (lot no. 23-854-AR).

Study Design: This was an open, single-center, single-dose, pharmacokinetic and hormonal response study in ten normal female volunteers (mean age of 33 years) with normal ovarian function. Each subject was administered a single 3.75 mg dose of Lupron Depot® intramuscularly during the first three days of a menstrual cycle.

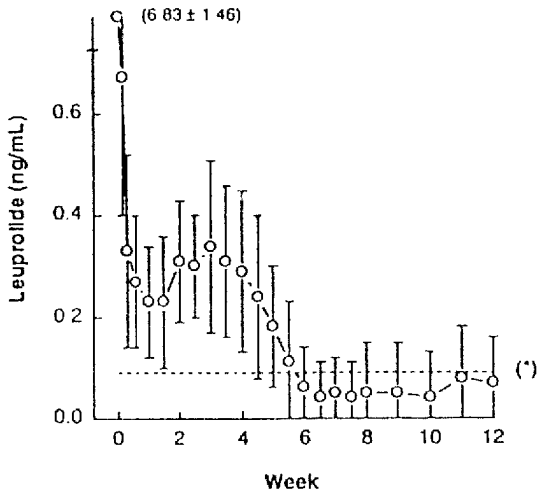
Blood Sampling: Five mL blood samples for leuprolide plasma levels determination were obtained prior to dosing, four hours post-dosing, on Days 1, 2, 4, 7, twice a week thereafter until Week 8, then followed by weekly blood draws until Week 12. Fifteen mL blood samples were also obtained during the mid-luteal phase of the pre-dosing menstrual cycle for endocrine determinations (FSH, LH, estradiol, and progesterone) and then weekly post-dosing until ovarian function resumed.

RESULTS:

Pharmacokinetics:

Following the administration of a 3.75 mg leuprolide intramuscular injection, there was an immediate rise in plasma drug/M-I concentrations ranging from 4.60 to 10.02 ng/mL (mean 6.83 ng/mL) at four hours post-dosing. The initial burst of leuprolide/M-I in the plasma declined to a mean of approximately 0.30 ng/mL within two days and remained relatively stable for 4.5 weeks after dosing. Leuprolide/M-I concentrations decreased thereafter to below the acceptable quantifiable limit by week 6 in most subjects (Figure 1).

Figure 1. Mean ± SD Leuprolide Concentration vs. Week after a 3.75 Mg Dose of Leuprolide Depot



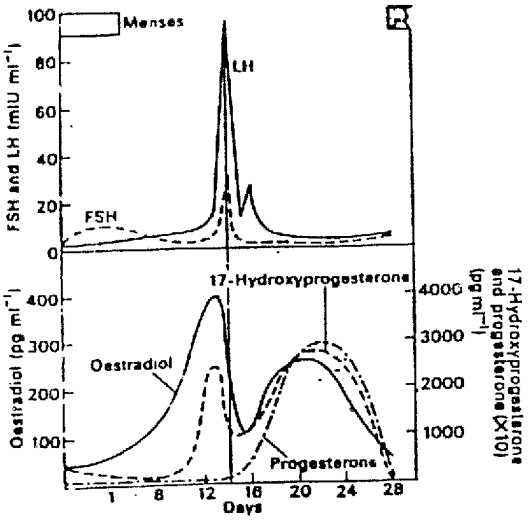
(*) Dotted line represents the detection limit of the assay

Between Week 6 to 12, leuprolide/M-I was detected only sporadically in some subjects with the exception of two subjects (101 and 105) who exhibited sustained leuprolide/M-I concentrations during that time period. Subject 105 had a detectable level in the pre-dosing sample, which was similar to the levels obtained during the later samples. Plasma leuprolide/M-I levels reappeared in three subjects at weeks 11 and 12 after being undetectable previously. The sponsor claims that the reason for this reappearance was most likely due to random nonspecific binding in the radioimmunoassay.

The mean cumulative AUC at Week 4 was approximately 75% (range 50% to 96%) and approximately 85% by week 5.

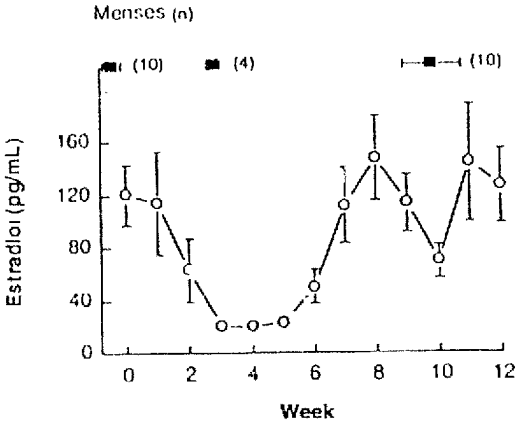
Pharmacodynamics:
The pharmacological response to leuprolide/M-1 was assessed by measuring systemic concentrations of estradiol, progesterone, LH and FSH and the time of menstrual bleeding. Assessment of pharmacological response is complicated by the large variation in hormonal concentrations depending on the phase of the menstrual cycle (Figure 2).

Figure 2. Fluctuation in LH, FSH, Progesterone and Estradiol During the Normal Menstrual Cycle (from Ref. 1)



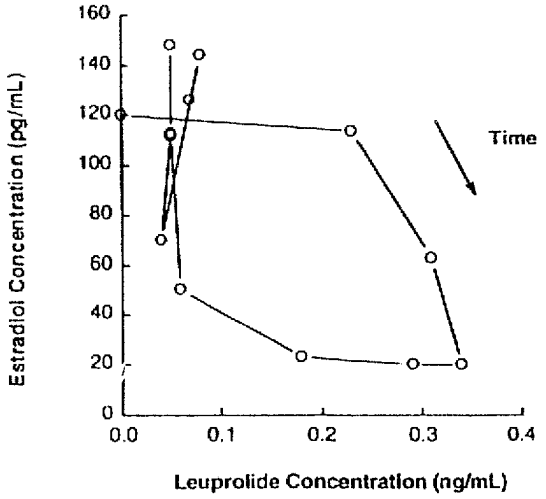
Estradiol was selected as the best measure of pharmacological response to leuprolide (Figure 3). Onset for complete suppression of estradiol (< 20 pg/mL) occurred within one to three weeks following dosing and persisted for five to eight weeks after Lupron Depot® injection.

Figure 3. Mean ± SD Time of Menses and Mean ± SEM Estradiol and Progesterone Concentrations vs. Week after a 3.75 Mg Dose of Leuprolide Depot



Four subjects did not appear to be down-regulated as quickly as the other subjects. A marked clockwise hysteresis was observed in the plot of mean plasma estradiol levels vs. leuprolide/M-I levels (Figure 4).

Figure 4 Mean Estradiol Concentration vs. Mean Leuprolide Concentration



The sponsor indicated that the use of an effect compartment model to account for the time delay was considered inappropriate to describe the response to leuprolide because of its indirect mechanism of action. However, it is possible that an indirect model can be used to describe the relationship between leuprolide levels and plasma estradiol levels.

Leuprolide was effective in suppressing hormonal production: Complete suppression of estradiol concentration was achieved in all subjects following administration of Lupron Depot®. Despite the range in leuprolide concentrations of individual subjects, no graded pharmacologic response could be measured.

Metabolism and Excretion:

A has been used to determine serum and urine levels of leuprolide in pharmacokinetic studies. In experimental animals it was shown that leuprolide is metabolized to shorter peptides, pentapeptide (M-I), tripeptides (M-II and M-III) and dipeptide (M-IV) (Attachment). M-II, M-III and M-IV cross-reacted very weakly with the antibody used in the for leuprolide, whereas the crossreactivity of M-I was high (70%) at the 50% displacement point, indicating that the presence of M-I interfered with the leuprolide assay.

To examine whether M-I was present in serum and urine in humans receiving leuprolide, and to determine accurate concentrations of intact leuprolide and M-I, a method by which the two compounds were separated by utilizing the cross-reactivity of the antibody was developed. The detection limit of the method was 0.05 ng/mL for leuprolide and M-I, and the recovery of the compounds added to serum and urine was over 88% with a coefficient of variation of less than 5%. The method was used to determine serum and urinary levels of leuprolide and M-I for 4 weeks after a single intramuscular injection of 3.75 mg of Lupron Depot® in **five male patients with prostate cancer.** Metabolites, other than M-I, could not be determined because antibodies against these metabolites have not yet been obtained. The peak concentrations

of M-I (0.86 ng/mL) were about 20 fold lower than the peak concentrations of the parent leuprolide (10.8 ng/mL).

Figure 1. Serum Concentrations of Leuprolide (TAP-144) and its M-I Pentapeptide Metabolite in Prostatic Cancer Patients Given a Single 3.75 Mg Subcutaneous Dose of a Depot Formulation.

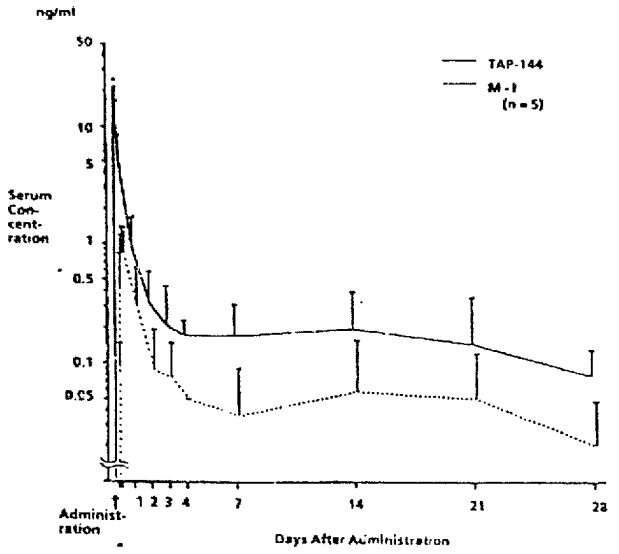
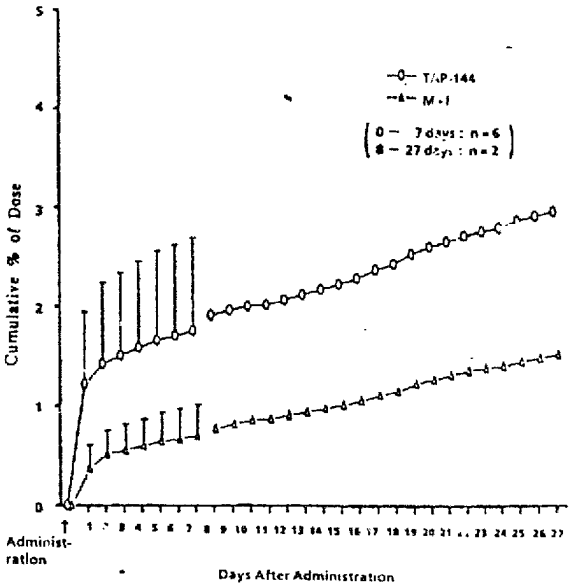


Figure 2. Cumulative Urinary Excretion of Leuprolide (TAP-144) and its M-I Pentapeptide Metabolite by Prostatic Cancer Patients Given a Depot Formulation (3.75 Mg) Subcutaneously.



It was noted by the reviewer that total serum concentrations of the parent compound and the metabolite (M-I) in male prostate cancer patients were about double those in female healthy volunteers up to 2 days and then approximately same as those in female healthy volunteers up to 2 weeks. One week after dosing, mean serum M-I concentrations were approximately 20 % of leuprolide concentrations.

COMMENTS:

1. It was stated that "the mean cumulative AUC at week 4 was approximately 75% and approximately 85% by week 5". It was learned through a teleconference call on January 19, 1995 that the method was used to measure plasma leuprolide concentrations but method could not differentiate intact leuprolide and one of the metabolites (i.e., M-I). Therefore, what the sponsor measured in plasma was intact leuprolide plus metabolite (i.e., M-I). It is also noted that after 6 weeks plasma leuprolide concentrations were below the acceptable quantifiable limit of the assay. Therefore, the creditability on % mean cumulative AUC which is calculated from AUC of total 12 weeks is questioned.

2. The sponsor conducted pharmacokinetic/pharmacodynamic (PK/PD) analyses upon request. Although it may be true that the use of "an effect compartmental model" to account for the time delay is inappropriate to describe the response to leuprolide, it is possible that indirect model analyses could be used to describe the relationship between leuprolide and estradiol plasma levels. Therefore, it is encouraged that the sponsor expend more effort to carry out PK/PD analyses on the newly requested data, possibly using indirect model analyses as appropriate

LABELING COMMENTS:

1. Under the Pharmacokinetic section of the CLINICAL PHARMACOLOGY section, the following statement;

> "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 burst in plasma concentration, with peak levels occurring at four hours postdosing. Following the ....."

should be changed to;

> " 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 burst in plasma concentration, with peak concentrations ranging from 4.6 to 10.02 ng/mL at four hours postdosing. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Following the initial burst....."

2. Under the Pharmacokinetic section of the CLINICAL PHARMACOLOGY section, the following statement should be deleted;

> "The absolute bioavailability for the depot formulations was estimated to be approximately 80%, relative to a 1 mg bolus dose administered intravenously to healthy male volunteers."

3. Under the Pharmacokinetic section of the CLINICAL PHARMACOLOGY section, the following statement;

> "In rats and dogs, administration of ^{14}C-labelled leuprolide was shown to be metabolized to smaller inactive peptides. These fragments....."

should be changed to·

> "In rats and dogs, administration of ^{14}C-labelled leuprolide was shown to be metabolized to smaller inactive peptides, pentapeptide (M-I), tripeptides (M-II and M-III), and dipeptide (M-IV). These fragments....."

4. Under the Pharmacokinetic section of the CLINICAL PHARMACOLOGY section, the following statement;

> "The major metabolite (M-I) plasma concentrations measured in 5 patients reached....."

should be changed to;

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

3/01/95

Hae-Young Ahn, Ph.D.
Reviewer, Division of Biopharmaceutics

PD initiated by J.Hunt 1/31/95
Biopharm Day (2/28/95, Ludden, Malinowski, M. Chen, N. Fleischer, Hepp, Hussain and Hunt)

FT initiated by J. Hunt 3/1/95

cc: NDA 19-943, HFD-510, HFD-340 (Vish), HFD-427 (Ahn and M. Chen), HFD-426 (Fleischer), Chron, Drug. Review, FOI (HFD-19), PK/PD