CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708

CORRESPONDENCE

Dunson

NDA 20-708

JAN 10 1997

Tap Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your pending March 8, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot 3-Month, (leuprolide acetate for depot suspension), 11.25mg .

We also refer to your amendment dated May 2, 1996.

To complete our review of the Environmental Assessment (EA) section of your submission, we have the following comments:

1. You are claiming but it appears that you base this only on the market projections for this particular Lupron product. Calculation must be done using the entire product line.

2. The certification from Abbott included in attachment 15-2 is for rather than for the drug substance or packaging operations identified in the EA as being performed at Abbott. Please provide certification for Lupron Depot 3-Month.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Jr., Consumer Safety Officer, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-708
HFD-580/Div. Files
HFD-580/CSO/A.Dunson
HFD-580/MRhee
HFD-357/NSager
HFD-820/ DNDCII Division Director

Drafted by: ADunson/1.10.97/n20708ir

Concurrences:
MRhee1.10.97/TRumble1.10.97

INFORMATION REQUEST (IR)

MEMO OF TELECON

NDA: 20-708 **Drug:** Lupron Depot-3 month 11.25mg
Date: December 26, 1996 **Time:** 11:45 a.m.

External Participant: TAP Holdings, Inc. **Tele:** 847-317-4893

External Participant Lead: Aruna Dabholkar, M.D.

Telecon Recorder: Alvis Dunson, B.S. A.D.

Conversation:

I called Dr. Dabholkar and conveyed the Medical Officer review comments of Dr. Philip Corfman listed below.

1. Please add appropriate confidence intervals to Figure 1 (volume 4 page 38).

2. Please provide a comparable figure, also with confidence intervals, for Lupron Depot 3.75 mg, for both 1 month and 3 month continuous dosing.

3. Please convert the data in tables 2 through 6 (volume 4, pages 40-55) into figures, and provide appropriate confidence intervals, when available.

4. Please provide figures comparable to those requested in #3 above for Lupron Depot 3.75 for both 1 month and 3 month continuous dosing.

5. Please provide any data you may have for repeated use of Lupron Depot-3 month 11.25 mg.

6. Please provide a copy of the informed consent document. (The submission states in volume 4, page 84, that the document is filed in Appendix E, but it was not included).

I indicated that an amendment containing the above information must be submitted.

cc:
NDA Arch.
HFD-580
HFD-580/PCorfman
HFD-580/ADunson/1.2.97

Concurrences:
Lpauls 1.2.97

NDA 20-708

MAR 12 1996

TAP Pharmaceuticals, Inc.
Attention: Aruna Dabholkar, M.D.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lupron Depot® (leuprolide acetate for depot suspension), 22.5 mg
Therapeutic Classification:	S
Date of Application:	March 6, 1996
Date of Receipt:	March 7, 1996
Our Reference Number:	NDA 20-708

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 6, 1996, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Lana L. Pauls, M.P.H.
Project Manager
(301) 443-3510

Sincerely yours,

EMGalliers 3/12/96

Enid Galliers
Chief, Project Management Staff
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc
Orig. NDA
DISTRICT OFFICE
HFD-80/RBrown
HFD-510
HFD-510/ABey/PCorfman/LRarick/MRhee/HDavies/AJordan/KRaheja
HFD-510/LPauls/~~01.05.94~~/N~~20517~~.ACK
3.11.96 20705
ACKNOWLEDGEMENT - AC

LLP
3/11/96

STATUS MEETING MINUTES

Date: February 5, 1997 **Time:** 9:00 - 10: 00 A.M. **Location:** Parklawn; Room 17B-43

NDA: 20-708 **Drug Name:** Lupron Depot, 3-month 11.25 mg

Type of Meeting: Internal status meeting

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Alvis Dunson, B.S.

FDA Attendees:

Lisa Rarick, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Heidi Jolson, M.D., M.P.H. - Deputy Director, (DRUDP; HFD-580)
Philip Corfman, M.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC) at Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokineticist, Division of Pharmaceutical Evaluation II (DPEII; HFD-870)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
Alvis Dunson, B.S. - Consumer Safety Officer, DRUDP (HFD-580)

Meeting Objectives:

To discuss the status of reviews to meet the division goal date.

Discussion Points:

- Medical: approval for endometriosis but not for because 3 months may be longer therapy than required in the treatment of fibroids for the majority of women
- Chemistry: awaiting completion of EA review
- Biopharmaceutics: review completed (1/24/97) - approved with label changes
- Pharmacology: review completed (9/17/96) - approved

Decisions reached:

- Sponsor should monitor estradiol levels and resumption of normal menstruation after the conclusion of the on-going 6 month, multiple dose, pharmacokinetic and pharmacodynamic study (Study No. M96-506), designed to compare the currently approved Lupron Depot-1 month 3.75 mg and the Lupron Depot-3 month 11.25 mg.

- Sponsor should submit separate labels for each indication
- Schedule labeling meeting for next week to discuss revised label
- Dr. Rarick to consider approvability of Lupron-Depot

Unresolved Issues: None

Action Items:

	Item:	**Responsible Person:**	**Due Date:**
♦	Submission of separate labels for each indication	TAP	February 7, 1997
♦	Schedule labeling meeting	Alvis Dunson	February 5, 1997
♦	Inform sponsor of the additional information required from Study No. M96-506	Gary Barnette	February 14, 1997

Signature, minutes preparer

Concurrence, Chair

Post Meeting Notes:

- Chemistry; review completed (2/5/97) - approved
- Sponsor submitted latest proposed labeling on 2/7/97
- Labeling meeting scheduled for 2/10/97

drafted: ADunson/1.17.97/n20715stm

cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/2.10.97

Concurrences:
PCorfman, GBarnette, MRhee2.10.97/LRarick, HJolson2.11.97/LPauls2.13.97,

ORIGINAL

MEETING MINUTES

Date: April 16, 1996 **Time:** 11:15 - 11:45 AM **Location:** Parklawn; Room 14-56

NDA: 20-708 **Drug Name:** Lupron (leuprolide acetate), 11.25 mg

External Participant: none

Type of Meeting: Internal Filing Meeting

Meeting Chair: Lana L. Pauls, M.P.H. **External Participant Lead:** none

Meeting Recorder: Lana L. Pauls, M.P.H.

FDA Attendees:

Solomon Sobel, M.D. - Director, Division of Metabolism and Endocrine Drug Products (DMEDP; HFD-510)
Lisa Rarick, M.D. - Acting Deputy Director II, DMEDP (HFD-510)
Phillip Corfman, M.D. - Medical Team Leader, DMEDP (HFD-510)
Annette Bey, M.D. - Medical Officer, DMEDP (HFD-510)
Jean Fourcroy, M.D., Ph.D. - Medical Officer, DMEDP (HFD-510)
Helen Davies, Ph.D. - Chemistry Team Leader I, Division of New Drug Chemistry II (DNDC II) @ DMEDP (HFD-510)
Moo-Jhong Rhee, Ph.D. - Chemist, DNDC II @ DMEDP (HFD-510)
Lana L. Pauls, M.P.H. - Project Manager, DMEDP (HFD-510)
Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, DPE II (HFD-870)

External Constituents: none

Meeting Objectives:

To determine whether the application is acceptable for filing. Lupron, 11.25 mg is proposed for two indications:

1. The management of endometriosis; and
2. The management of uterine fibroids.

Discussion Points: see below

Decisions reached:

- Medical - Acceptable for filing (AF); if approved, a Phase 4 study in diagnosed patients may be requested
- Chemistry - AF; Environmental Assessment expected May 3
- Pharmacology - AF; labeling review only

- Biopharmaceutics - AF; if approved a Phase 4 study examining drug accumulation may be requested
- Statistics - no review necessary
- Microbiology - will be consulted upon receipt (expected May 3)
- DSI - no audits necessary
- Virtual (e-mail) status meeting will be used as a means of determining progress of review team
- UF Goal Date = March 7, 1997

Unresolved Issues: none

Action Items:

	Item:	Responsible Person:	Due Date:
♦	Determine if protocol M94-139 was submitted for prior review	Lana Pauls	April 17, 1996

Signature, minutes preparer

Concurrence, Chair

cc:
NDA Arch:
HFD-510
HFD-510/DJenkins/Attendees
HFD-870/KGBarnette/ADorantes
HFD-510/LPauls/04.19.96

Concurrences:
ABey, PCorfman 04.23.96/JFourcroy, LRarick, MJRhee, HDavies, SSobel, GBarnette, ADorantes 04.24.96

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

[illegible] Lake Cook Road
675 Waukegan Rd.
Deerfield, IL 60015

ORIGINAL

ORIG AMENDMENT

February 7, 1997

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA: 20-708
Lupron Depot®-3 Month 11.25 mg
(leuprolide acetate for depot suspension)
Amendment

Dear Dr. Rarick:

This is to inform the Division that all the safety data from Study M93-139 was submitted in the initial submission of NDA 20-708, and was noted in the NDA cover letter. Therefore, there are no safety updates to report at this time for the NDA.

Also attached is the separate package insert for Lupron Depot-3 Month 11.25 mg as requested yesterday.

Please note that the final printed package insert will be printed in three colors like the current package insert for Lupron Depot 3.75 mg.

The package insert is submitted electronically (Microsoft Word) on a diskette as requested. A copy is being sent by facsimile. A paper copy with all annotations is also enclosed.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp
Attachment

Noted
(This label is likely to be further revised)
CR/pjp
02.14.97.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
AD 2/28/97
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 10 1997
HFD-580

Since there is no new safety information, no letter is required.
CR/pjp
02.27.97.

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lake Office Plaza
Waukegan Rd
Deerfield, IL 60015

March 6, 1997

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA: 20-708
Lupron Depot®-3 Month 11.25 mg
(leuprolide acetate for depot suspension)
Amendment

Dear Dr. Rarick:

Submitted are the four copies of the final draft of the labeling (Package Insert) for Lupron Depot-3 Month 11.25 mg.

Also enclosed is the final draft of Patient Information pamphlet.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp
Attachment

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

nnockburn Lake Office Plaza
35 Waukegan Rd.
eerfield, IL 60015

ORIGINAL

February 27, 1997

NEW CORRESP

Noted.
Suggested Div. Division
area marked Center
Comm
03.06.97

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA: 20-708
Lupron Depot®-3 Month 11.25 mg
(leuprolide acetate for depot suspension)
Amendment

Dear Dr. Rarick:

Attached is the draft Patient Information Pamphlet (Attachment 1) for Lupron Depot-3 Month 11.25 mg.

Also enclosed is the diskette containing revised package insert for this product. The revisions on today's copy are:

1. Addition of the N's in the legend of FIGURE I under CLINICAL STUDIES section. A range is included for the N's because all patients did not provide data on each of the pain parameters at each visit.
2. Appropriate comment is added for the Plasma Enzymes section.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR ... RECD FEB 2 ... 1997 HFD-520 EVALUATION AND RES...

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Deerfield Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

ORIGINAL

PRIO AMENDMENT

January 22, 1997

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA: 20-708
Lupron Depot®-3 Month 11.25 mg
(leuprolide acetate for depot suspension)
Amendment

Dear Dr. Rarick:

Pursuant to 21 CFR 314.60, the sponsor, TAP Holdings Inc. is submitting this amendment to our NDA 20-708 for Lupron Depot-3 Month 11.25mg.

The amendment contains the response to the deficiency letter dated January 10, 1997.

All information required for this amendment is attached.

We request you to continue the evaluation of this New Drug Application.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp
Attachment

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Bannockburn Lake Office Plaza
1355 Waukegan Rd
Deerfield, IL 60015

Noted NAI KRarick 1/5/97

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
AD 2/28/97
CSO/INITIALS DATE

ORIG AMENDMENT

January 3, 1997

This information was used for my review of the NDA (21-xxx) 01.13.97

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 0 6 1997
HFD-580

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA: 20-708
Lupron Depot®-3 Month 11.25 mg
(leuprolide acetate for depot suspension)
Amendment

Dear Dr. Rarick:

Pursuant to 21 CFR 314.60, the sponsor, TAP Holdings Inc. is submitting this information amendment to our NDA 20-708 for Lupron Depot-3Month 11.25mg.

The information submitted here was requested by the Medical Reviewer on December 26, 1996.

A response to each requested item is provided with all available comparative data for the 1-month and the 3-month Lupron Depot formulations. The data are presented in the requested format of figures with confidence intervals.

Please note that Lupron Depot-3Month 11.25mg demonstrates a pharmacokinetic profile and estradiol suppression for three months, which is similar to that seen with Lupron Depot 3.75mg for one month. Therefore, a similar efficacy and safety profile is expected for the two formulations. This has been demonstrated for Lupron Depot-3Month 22.5mg administered every 3 months to advanced prostate cancer patients(Approved NDA 20-517).

All information required for this amendment is attached.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp
Attachment

ORIGINAL

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Bannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

May 1, 1996

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot®-3 Month 11.25 mg (leuprolide acetate for depot suspension)
NDA 20-708
Amendment

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60 (a), the sponsor is amending the NDA 20-708 with the enclosed information. Submitted in this amendment are two copies of the Environmental Assessment and four copies of the Aseptic Process Validation package.

Sincerely,

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

AD/pjp
Attachment

REVIEWS COMPLETED
ACTION
☐ A.P. ☐ N.A.I. ☐ MEMO
OSE INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 0 2 1996
HFD-510