

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 20-263/S-012**

***Name:*** Lupron Depot-PED  
7.5 mg, 11.25 mg, 15 mg  
(leuprolide acetate for depot suspension)  
&  
Lupron Injection  
(leuprolide acetate)

***Sponsor:*** TAP Pharmaceuticals, Inc.

***Approval Date:*** August 13, 1999

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA 20-263/S-012**

## CONTENTS

### Reviews / Information Included in this Review

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<b>Approvable Letter(s)</b>	<b>X</b>
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<b>Medical Review(s)</b>	
<b>Chemistry Review(s)</b>	<b>X</b>
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<b>Pharmacology Review(s)</b>	
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<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Administrative Document(s)</b>	
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-263/S-012**

**APPROVAL LETTER**

NDA 19-732/S-016  
NDA 19-943/S-010  
NDA 20-011/S-016  
NDA 20-263/S-012  
NDA 20-517/S-006  
NDA 20-708/S-006

AUG 13 1999

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

Dear Dr Dabholkar:

Please refer to your supplemental new drug applications dated December 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot® (leuprolide acetate depot suspension).

We acknowledge receipt of your submissions dated June 21, 1999 and July 9, 1999.

These supplemental new drug applications provide for a new manufacturing site for the prefilled dual chamber syringe.

We have completed the review of these supplemental applications and they are approved.

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

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,



Moo-Jhong Rhee, Ph.D.  
Chemistry Team Leader, for the  
Division of Reproductive and Urologic Drug Products,  
(HFD-580)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

cc:

Archival NDAs 19-732, 19-943, 20-011, 20-263, 20-517, 20-708

HFD-580/Div. Files

HFD-580/J.Mercier

HFD-580/Raraick/Mann/Rhee/De

HFD-160/Cooney/Vincent

HFD-094/DDMS (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: JM/August 13, 1999

Initialed by: Rhee8.13.99/De8.13.99

final: August 13, 1999

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-263/S-012**

**APPROVABLE LETTER**

NDA 20-011/S-016  
NDA 19-732/S-016  
NDA 19-943/S-010  
NDA 20-263/S-012  
NDA 20-517/S-006  
NDA 20-708/S-006

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

JUN 25 1999

Dear Dr. Dabholkar:

Please refer to your supplemental new drug applications dated December 23, 1998, received December 28, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot® (leuprolide acetate for depot suspension).

We acknowledge receipt of your faxed submission dated June 21, 1999.

These supplements propose a new manufacturing site for manufacturing the prefilled dual chamber syringe.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

1.



2.

3.



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confidential commercial

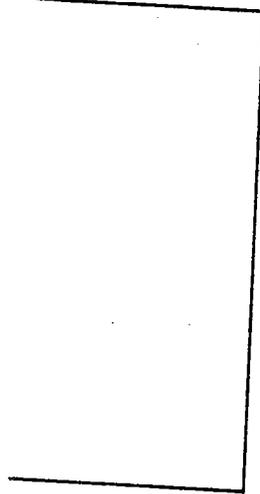
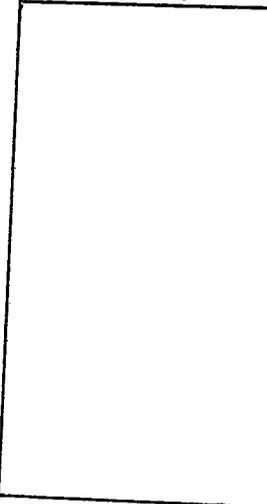
information from

Approvable Letter

S-012

NDA 20-011/S-016  
NDA 19-732/S-016  
NDA 19-943/S-010  
NDA 20-263/S-012  
NDA 20-517/S-006  
NDA 20-708/S-006

8.



Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

*William Mann, M.D.*

Lisa Rarick, M.D.  
Director

Division of Reproductive and Urologic Drug Products,  
(HFD-580)  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

*(for L RARICK)*

*Deputy Dir 6/25/99*

**Best Possible Copy**

NDA 20-011/S-016

NDA 19-732/S-016

NDA 19-943/S-010

NDA 20-263/S-012

NDA 20-517/S-006

NDA 20-708/S-006

Page 4

cc:

Archival NDAs 20-011, 19-732, 19-943, 20-263, 20-517, 20-708

HFD-580/Div. Files

HFD-580/J.Mercier/Rumble

HFD-580/Rarick/Mann/Rhee/De

HFD-95/DDMS

DISTRICT OFFICE

Drafted by: JM/June 25, 1999

Initialed by: Rumble 6.24.99/Rhee6.24.99/De6.25.99/Rarick6.25.99/Mann6.25.99

final: June 25, 1999

filename:

APPROVABLE (AE)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-263/S-012**

**CHEMISTRY REVIEW(S)**

JUN 16 1999

~~JUN 15 1999~~

CHEMIST REVIEW  
OF Supplement

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012  
Letterdate: 12-23-98  
Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES: None  
Letterdate:  
Stampdate:
5. RECEIVED BY CHEMIST: 1-3-99

6. APPLICANT NAME AND ADDRESS:

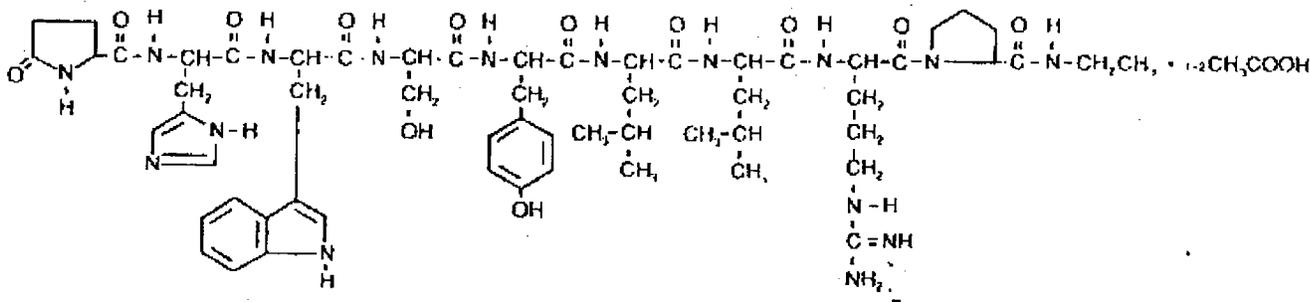
TAP Pharmaceuticals Inc.  
2355 Waukegan Road  
Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED<sup>R</sup>, Lupron<sup>R</sup>

8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate



10. DOSAGE FORM(S): Sterile Depot Suspension for Injection

11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml

12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty

13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection

14. RECORDS & REPORTS CURRENT: Yes

15. RELATED IND/NDA/DMF: This is part of a bundled supplements. Related applications include the following:

NDA 19732-scm016  
NDA 20011-scm016  
NDA 19943-scm010  
NDA 20517-scm006  
NDA 20708-scm006

**16. PRIOR APPROVAL SUPPLEMENT PROVIDES FOR: New manufacturing site for manufacturing the prefilled dual chamber syringe**

**17. COMMENTS:**

The prefilled dual chamber syringe was approved as a new container closure system in October 1995 (NDA 19-732/S009). The manufacturing was approved at Osaka plant in Japan. The manufacturer, Takeda Chemical Industries submitted this supplement to add an additional site for filling the syringes at Hikari plant. The diluent used to fill in these syringes will be manufactured at the Hikari plant. The active drug, [ ] will be manufactured at the previously approved sites (Shanan plant and Osaka plant). The syringe components, manufacturing method and the final product specifications and testing methods are the same as approved before. The new plant and the manufacturing process are validated. Three months of accelerated and RT stability has been included in the application for one production lot of each of Lupron Depot 3.75 mg, 7.5 mg, 11.25 mg and 15 mg and the results are satisfactory. Quality of the product manufactured at Hikari plant was compared with the corresponding one manufactured at the approved site, Osaka plant and no significant changes have been observed.

The new facility (Hikari plant) should be inspected according to CFR 314.70 and a request had been forwarded through EES on 28-December-1998. Overall recommendation is found 'acceptable' on 6/15/99 based on an inspection performed on 5-19-99.

Since the diluent will be manufactured at the Hikari plant and it needs to be sterile, the application was also reviewed by a microbiologist (Dr. Carol K. Vincent, HFD-805) and it was found deficient.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

This application is 'approvable' pending satisfactory resolution of the microbiologist's concerned issues as delineated in the draft letter.

**Issue "Approvable" letter**

**19. REVIEWER NAME**  
Swapn K. De, Ph.D.

**SIGNATURE**

*Swapn K. De*  
6/15/99

**DATE COMPLETED**

6/15/99

cc:

Orig. NDA #20-263  
HFD-580/Division File  
HFD-580/Mercierj  
HFD-580/MRhee/SDe

*MJRhee* 6/16/99

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012

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Chemistry Review #1

S-012

Application: NDA 20263/012  
 Stamp: 28-DEC-1998  
 Regulatory Due: 28-APR-1999  
 Applicant: TAP HOLDINGS  
 2255 WAUKEEGAN RD  
 DEERFIELD, IL 60015

Action Goal:  
 District Goal: 24-MAR-1999  
 Brand Name: LUPRON DEPOT PEDIATRIC KIT  
 Estab. Name:  
 Generic Name: LEUPROLIDE ACETATE

Priority: 5S  
 Org Code: 580

Dosage Form: (FOR INJECTION)  
 Strength: (7.5,15,11.25)MG,5MG/ML

Application Comment: SUPPLEMENT PROVIDES FOR NEW MANUFACTURING SITE FOR  
 MANUFACTURING THE PREFILLED DUAL CHAMBER SYRINGE. SAME CHANGES  
 WILL BE APPLICABLE TO NDA 19943-SCM010, 20011-SCM016 AND 19732-  
 SCM016. (on 29-JAN-1999 by S. DE (HFD-580) 301-827-7516)

FDA Contacts: S. DE (HFD-580) 301-827-7516, Review Chemist

Overall Recommendation: ACCEPTABLE on 15-JUN-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610307

TAKEDA CHEMICAL INDUSTRIES LTD  
 4720 TAKEDA MITSUI  
 HIKARI, YAMAGUCHI, JA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVS OAI Status: NONE

Estab. Comment: TAKEDA CHEMICAL INDUSTRIES PROPOSED THIS NEW SITE TO BE  
 RESPONSIBLE FOR MANUFACTURING THE SYRINGE ASSEMBLY AS WELL AS  
 FILLING THE SYRINGE WITH DRUG PRODUCT FOLLOWING THE PREVIOUSLY  
 APPROVED PROCEDURE. THE DILUENT USED TO FILL THE SYRINGES WILL  
 ALSO BE MANUFACTURED AT THIS NEW SITE (HIKARI PLANT). THE ACTIVE  
 DRUG, [ ] WILL BE MANUFACTURED AT THE PREVIOUSLY  
 APPROVED SITES. THE NEW PLANT AND THE MANUFACTURING PROCESS ARE  
 VALIDATED. BATCH INSTRUCTIONS AND BATCH RECORD FOR ONE LOT ARE  
 SUBMITTED. THREE MONTHS OF ACCELERATED AND RT STABILITY DATA ARE  
 SUBMITTED FOR ONE PRODUCTION LOT EACH OF LUPRON DEPOT 3.75 MG, 7.5  
 MG, 11.25 MG AND 15 MG. (on 29-JAN-1999 by S. DE (HFD-580) 301-  
 827-7516)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-JAN-1999				DES
SUBMITTED TO DO	29-JAN-1999	PS			FERGUSONS
ASSIGNED INSPECTION	'02-FEB-1999	PS			EGASM
INSPECTION SCHEDULED	15-APR-1999		19-MAY-1999		IRIVERA
INSPECTION PERFORMED	24-MAY-1999		19-MAY-1999		EGASM
DO RECOMMENDATION	15-JUN-1999			ACCEPTABLE	EGASM
OC RECOMMENDATION	15-JUN-1999			INSPECTION ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

JUN 24 1999

CHEMIST REVIEW  
OF Supplement  
CHEMISTRY REVIEW #2

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012  
Letterdate: 12-23-98  
Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES:  
Letterdate: 6/21/99  
Stampdate:
5. RECEIVED BY CHEMIST: 1-3-99/6-21-99

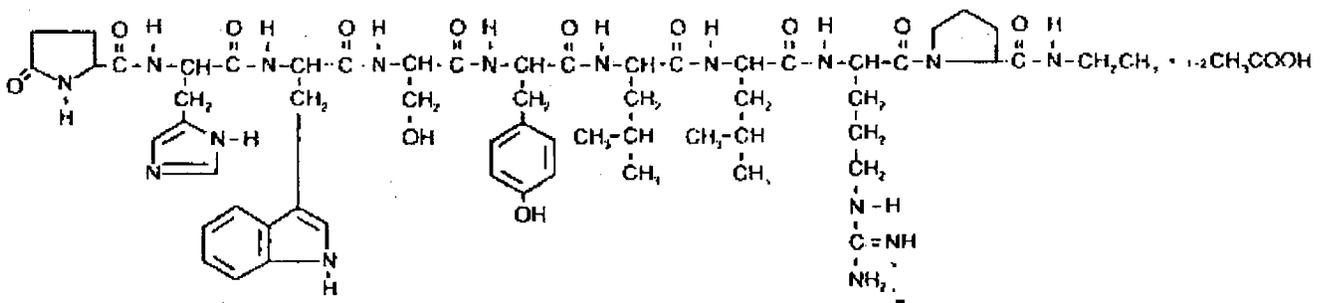
6. APPLICANT NAME AND ADDRESS:

TAP Pharmaceuticals Inc.  
2355 Waukegan Road  
Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED<sup>R</sup>, Lupron<sup>R</sup>
8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate



10. DOSAGE FORM(S): Sterile Depot Suspension for Injection
11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml
12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty
13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection
14. RECORDS & REPORTS CURRENT: Yes
15. RELATED IND/NDA/DMF: This is part of a bundled supplements. Related applications include the following:

NDA 19732-scm016  
NDA 20011-scm016  
NDA 19943-scm010  
NDA 20517-scm006  
NDA 20708-scm006

**16. PRIOR APPROVAL SUPPLEMENT PROVIDES FOR: New manufacturing site for manufacturing the prefilled dual chamber syringe**

**17. COMMENTS:**

The amendment sent by the sponsor on 21-June-1999 was the response of the microbiologist's comments (send to the sponsor on 18 June-1999). The response, as reviewed by the microbiologist (Dr. Carol K. Vincent, HFD-805) is still found to be deficient.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

This application is 'approvable' pending satisfactory resolution of the microbiologist's concerned issues as delineated in the draft letter of the microbiologist's review.

**Issue "Approvable" letter**

**19. REVIEWER NAME**  
Swapan K. De, Ph.D.

**SIGNATURE**  
*Swapan K. De*  
6/24/99

**DATE COMPLETED**  
6/24/99

**cc:**

Orig. NDA #20-263  
HFD-580/Division File  
HFD-580/Mercierj  
HFD-580/MRhee/SDe

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012

*MJ Rhee 6/24/99*

AUG 13 1999

CHEMIST REVIEW  
OF **Supplement**  
CHEMISTRY REVIEW #2

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012  
Letterdate: 12-23-98  
Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES:  
Letterdate: 6/21/99 [fax]; 7/9/99  
Stampdate: 7-12-99
5. RECEIVED BY CHEMIST: 1-3-99/6-21-99/7-14-99

6. APPLICANT NAME AND ADDRESS:

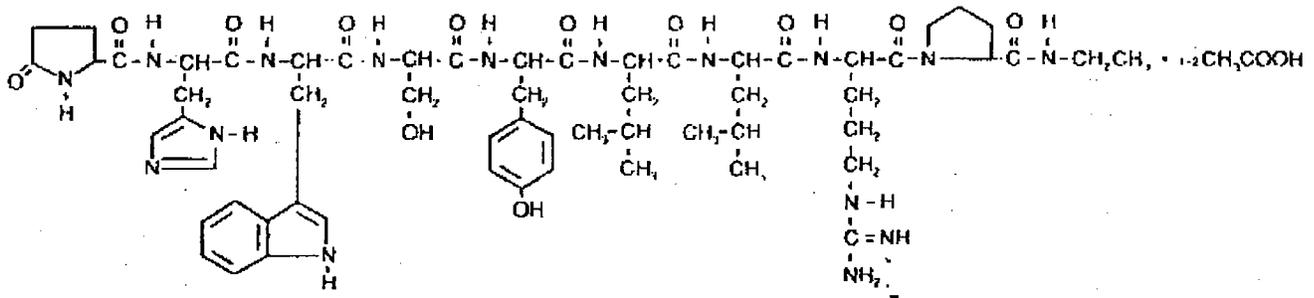
TAP Pharmaceuticals Inc.  
2355 Waukegan Road  
Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED<sup>R</sup>, Lupron<sup>R</sup>

8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate



10. DOSAGE FORM(S): Sterile Depot Suspension for Injection

11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml

12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty

13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection

14. RECORDS & REPORTS CURRENT: Yes

15. **RELATED IND/NDA/DMF:** This is part of a bundled supplements. Related applications include the following:

NDA 19732-scm016  
NDA 20011-scm016  
NDA 19943-scm010  
NDA 20517-scm006  
NDA 20708-scm006

16. **PRIOR APPROVAL SUPPLEMENT PROVIDES FOR:** New manufacturing site for manufacturing the prefilled dual chamber syringe

17. **COMMENTS:**

The amendment sent by the sponsor on 07-July-1999 was the response of the "approvable" letter from the Agency (send to the sponsor on 25 June-1999). The response is found satisfactory (see attached review) as reviewed by the microbiologist (Dr. Carol K. Vincent, HFD-805).

18. **CONCLUSIONS AND RECOMMENDATIONS:**

Based on the information provided by the firm and the microbiologist's recommendation, this supplement may be approved.

**Issue "Approval" letter**

19. **REVIEWER NAME**  
Swapan K. De, Ph.D.

**SIGNATURE**

*Swapan K. De*  
8/13/99

**DATE COMPLETED**  
8/12/99

cc:

Orig. NDA #20-263  
HFD-580/Division File  
HFD-580/Mercierj  
HFD-580/MRhee/SDe

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012a2

*MJRhee 8/13/99*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-263/S-012**

**MICROBIOLOGY REVIEW(S)**

FEB 23 1999

MICROBIOLOGIST'S REVIEW OF SUPPLEMENT FOR  
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580  
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805  
FEBRUARY 11, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

NDA / Supplement Number: NDA 19-732 / SCM-016  
NDA 20-517 / SCM-006

NB: These supplements are reviewed in tandem.

Drug Product: NDA 19-732 / SCM-016 Lupron Depot® 7.5mg [leuprolide acetate depot suspension]  
NDA 20-517 / SCM-006 Lupron Depot® -3 month 22.5mg and -4 month 30mg [leuprolide acetate depot suspension]

Received for Review: January 4, 1999

COMIS User Fee Goal Date: April 28, 1999

COMIS User Fee Due Date: June 26, 1999

Applicant:  
TAP Pharmaceuticals Inc.  
Bannockburn Lake Office Plaza  
2355 Waukegan Road  
Deerfield, IL 60015

Manufacturer and Site:  
Takeda Chemical Industries  
4720 Mitsui Aza Takeda  
Hikari, Yamaguchi 743-8502  
Japan

Supplement Provides For: New manufacturing site in Hikari, Japan for the manufacture of the prefilled dual chamber syringe.

Dosage Form / Route of Administration: Pre-filled syringe; for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

Conclusions and Recommendations: We do not recommend approval of the supplements because inadequate sterilization process validation information for a new manufacturing location has been provided.

See Review Notes, below.

cc:

NDA 19-732 / SCM-016

NDA 20-517 / SCM-006

HFD-580/CKish / SDe

HFD-160/Consult file/CKVincent [HFD-805]

Drafted by: CKVincent/01-29-99 C:\CKV97\NDA20517.006

Carol K. Vincent, HFD-805

2-11-99

Patc 2/23/99

JUN 28 1999

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information from

Microbiology Review #1

S-012

JUN 28 1999

MICROBIOLOGIST'S REVIEW NO. 2 OF SUPPLEMENT FOR  
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580  
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805

JUNE 23, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

**NDA / Supplement Number:**

NDA 19-732 / SCM-016  
NDA 19-943 / SCM-010  
NDA 20-011 / SCM-016  
NDA 20-263 / SCM-012  
NDA 20-517 / SCM-006  
NDA 20-708 / SCM-006

**Drug Product:** Lupron Depot® [leuprolide acetate depot suspension]

**Document Date:** December 23, 1998

**Amendment:** June 21, 1999 [fax]

**Amendment received for review:** June 21, 1999

**COMIS User Fee Due Date:** June 26, 1999 **COMIS User Fee Goal Date:** April 28, 1999

**Name and Address of Applicant:**

TAP Pharmaceuticals, Inc.  
Bannockburn Lake Office Plaza  
2355 Waukegan Road  
Deerfield, IL 60015

**Name and Address of Manufacturer:**

Takeda Chemical Industries  
4720 Mitsui Aza Takeda  
Hikari, Yamaguchi 743-8502  
Japan

**Supplement Provides For:** New manufacturing site in Hakari, Japan for the manufacture of the prefilled dual chamber syringe.

**Dosage Form:** Pre-filled syringe for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

**Conclusions and Recommendations:** The subject supplements are **approvable** pending satisfactory review of sterilization process validation information requested herein. See **E: Review Notes:** below.

cc:

NDA 19-732 / SCM-016  
NDA 19-943 / SCM-010  
NDA 20-011 / SCM-016  
NDA 20-263 / SCM-012  
NDA 20-517 / SCM-006  
NDA 20-708 / SCM-006  
HFD-580/Rarick/MRhee/SDe/LPauls/JMercier  
HFD-160/Consult file/CKVincent [HFD-805]  
Drafted by: CKVincent/06-22-99

C:\CKV99\NDA19732.016



Carol K. Vincent, HFD-805

06-23-99  
PAC 6/24/99

JUN 28 1999

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information from

Microbiology Review #2

S-012

AUG 12 1999

MICROBIOLOGIST'S REVIEW NO. 3 OF SUPPLEMENT FOR  
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580  
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805

AUGUST 11, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

**NDA / Supplement Number:**

NDA 19-732 / SCM-016  
NDA 19-943 / SCM-010  
NDA 20-011 / SCM-016  
NDA 20-263 / SCM-012  
NDA 20-517 / SCM-006  
NDA 20-708 / SCM-006

**Drug Product:** Lupron Depot® [leuprolide acetate depot suspension]

**Document Date:** July 9, 1999

**Received for review:** June July 16, 1999

**COMIS User Fee Due Date:** August 25, 26, 1999

**Name and Address of Applicant:**

TAP Pharmaceuticals, Inc.  
Bannockburn Lake Office Plaza  
2355 Waukegan Road  
Deerfield, IL 60015

**Name and Address of Manufacturer:**

Takeda Chemical Industries  
4720 Mitsui Aza Takeda  
Hikari, Yamaguchi 743-8502  
Japan

**Supplement Provides For:** New manufacturing site in Hakari, Japan for the manufacture of the prefilled dual chamber syringe.

**Dosage Form:** Pre-filled syringe for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

**Conclusions and Recommendations:** We recommend approval for the subject supplements.

See E: Review Notes: below.

cc:

NDA 19-732 / SCM-016  
NDA 19-943 / SCM-010  
NDA 20-011 / SCM-016  
NDA 20-263 / SCM-012  
NDA 20-517 / SCM-006  
NDA 20-708 / SCM-006  
HFD-580/Rarick/MRhee/SDe/LPauls/JMercier  
HFD-160/Consult file/CK Vincent [HFD-805]  
Drafted by: CK Vincent/08-03-99

C:\CKV99\19732106.3RD



Carol K. Vincent, HFD-805

8-11-99



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of trade secret and/or

confidential commercial

information from

Microbiology Review # 3

S-012

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-263/S-012**

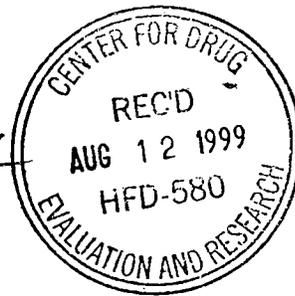
**CORRESPONDENCE**



TAP HOLDINGS INC.  
parent of TAP Pharmaceuticals Inc.

ORIGINAL

~~NDA SUPPLEMENT~~  
SLM-012-AC  
file



Jannocktown Lake Office Plaza  
355 Waukegan Rd  
Deerfield IL 60015

July 9, 1999

Lisa M. Rarick, MD  
Director, Division of Reproductive and Urologic  
Drug Products (HFD-580)  
Attn: Central Document Room 17 B-20  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

NDA 20-011/S-016  
NDA 19-732/S-016  
NDA 19-943/S-010  
NDA 20-263/S-012  
NDA 20-517/S-006  
NDA 20-708/S-006

Mary Kay Rybeck  
August 17, 1999

**RE: NDA 19-732/S-016  
Lupron Depot \*7.5 mg  
(leuprolide acetate for depot suspension)  
Amendment to Supplemental Application for New  
Manufacturing Site (Hikari Plant) for Pre-Filled Dual  
Chamber Syringe**

Dear Dr. Rarick:

TAP Holdings Inc, in accordance with 21CFR314.110(1), amends the supplemental application for a new manufacturing site for the pre-filled dual chamber syringe in response to the approvable letter dated June 25, 1999 for NDA 20-011/S-016, NDA 19-732/S-016, NDA 19-943/S-010, NDA 20263/S-012, NDA 20-517/S-006, and NDA 20-708/S-006.

The field copy of this amendment is being submitted to the Division. In accordance with 21 CFR 314.5(K)(3), TAP Holdings Inc. certifies that the field copy is a true copy of the information submitted in this amendment to the supplemental application.

Following are the comments from the approvable letter and the responses of TAP Holdings Inc. to those comments:

1

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Redacted 3 page(s)

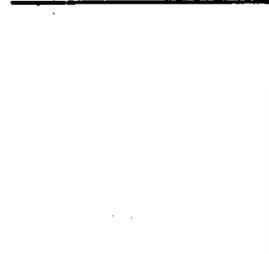
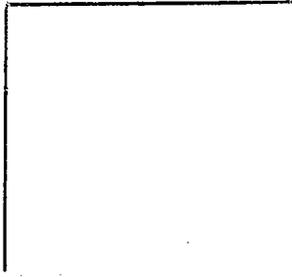
of trade secret and/or

confidential commercial

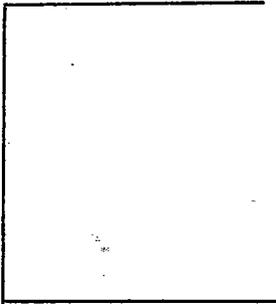
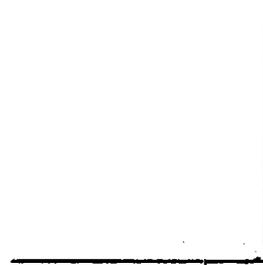
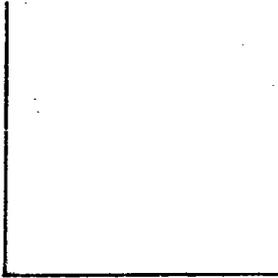
information from

Correspondence (Amendment to Suppl. Application)

S-012

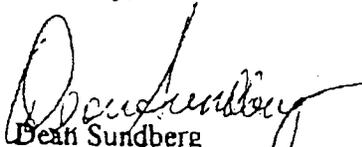


8.



Please do not hesitate to contact me at 847-317-5780 if you have any questions.

Sincerely,

  
Dean Sundberg  
Director, Regulatory Affairs





**TAP HOLDINGS INC.**  
parent of TAP Pharmaceuticals Inc.

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

ORIGINAL

SUPPL NEW CORRESP

SNC-012

July 1, 1999

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

NDA 20-011/S-016  
19-732/S-016  
19-943/S-010  
20-263/S-012  
20-517/S-006  
20-708/S-006



**RE: Lupron Depot/Hikari Plant SNDAs**

Dear Dr. Rarick,

This is to notify that the sponsor TAP Holdings Inc. intends to file amendments to these supplemental applications as requested in the approvable letter dated June 25, 1999.

Sincerely,

*A. Dabholkar*  
Aruna Dabholkar, M.D.

Associate Director, Regulatory Affairs

AD/mea

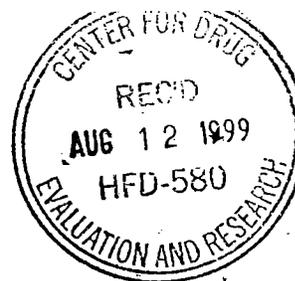
REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSO INITIALS	DATE

*[Handwritten initials and date]*



TAP HOLDINGS INC.  
parent of TAP Pharmaceuticals Inc.

ORIGINAL



*FILE*  
*NDA SUPP AMEND*  
*SCM-012BI*

Knockburn Lake Office Plaza  
55 Waukegan Rd.  
Deerfield, IL 60015

June 21, 1999

Division of Reproductive and Urologic Drug Products, HFD-580  
Document Control Room 17B-20  
Center for Drug Evaluation & Research  
Food and Drug Administration  
5800 Fishers Lane  
Rockville, MD 20857

*NDA 20-011/S-016*  
*NDA 19-732/S-016*  
*NDA 19-943/S-010*  
*NDA 20-263/S-012*  
*NDA 20-517/S-006*  
*NDA 20-708/S-006*

*Mary Kay Beckie*  
*SAP Regulatory Affairs*  
*August 17, 1999*

RE: Lupron Depot® 7.5mg (leuprolide acetate depot suspension)

NDA 19-732, S-016  
Amendment No. 001

Dear Dr. Rarick,

The sponsor, TAP Holdings Inc., submits this Amendment to the supplemental Application under the provisions of Section 505(I) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.60 (a).

This amendment includes the data requested by the microbiology reviewer, communicated to the sponsor via a draft letter on June 16, 1999.

Attached is the information required for this amendment.

Sincerely,

Aruna Dabholkar, M.D.  
Associate Director, Regulatory Affairs  
(847) 317-4893 phone  
(847) 317-5795 fax

AD/mea

Attachments



Food and Drug Administration  
Rockville MD 20857

NDA 20-263/S-012

Tap Holdings, Inc.  
2355 Waukegan Road  
Deerfield, IL 60015

DEC 30 1998

Attention: Aruna Dabholkar, M.D.  
Associate Director, Regulatory Affairs

Dear Dr. Dabholkar:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lupron Depot-PED<sup>®</sup> 7.5mg, 11.25mg & 15mg (leuprolide acetate/injection/depot suspension)

NDA Number: 20-263

Supplement Number: S-012

Date of Supplement: December 23, 1998

Date of Receipt: December 28, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 26, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Sincerely,

Lana Pauls  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 20-263/S-012

Page 2

cc:

Original NDA 20-263/S-012

HFD-580/Div. Files

HFD-580/CSO/C. Kish

SUPPLEMENT ACKNOWLEDGEMENT



TAP HOLDINGS INC.  
parent of TAP Pharmaceuticals Inc.

ORIGINAL

NDA NO. 20263 REF. NO. 012  
NDA SUPPL FOR SCM

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

December 23, 1998

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: Lupron Depot-PED® 7.5mg, 11.25mg & 15mg**  
**(leuprolide acetate/injection/depot suspension)**

**NDA 20-263**

**Supplemental Application for new manufacturing site for manufacturing the  
prefilled dual chamber syringe**

Dear Dr. Rarick,

The sponsor, TAP Pharmaceuticals Inc., Submits this supplemental Application under the provisions of Section 505(I) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.70 (b) (2) (vi) and (viii).

This supplement requests for approval of a new manufacturing site for the manufacturing of the prefilled dual chamber syringe.

All the required information is submitted under NDA 19-732, in a supplemental application of this date. Attached is the form 356h with this request to cross reference.

Sincerely,

Aruna Dabholkar, M.D.  
Associate Director, Regulatory Affairs  
(847) 317-4893 phone  
(847) 317-5795 fax

AD/mea  
Attachment

*Reviewed  
Smaforone  
5/6/99*

