CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-728 DRUG PRODUCT: Leuprolide Acetate

FIRM: Bedford Labs DOSAGE FORM: Injection Solution

STRENGTH: 5 mg/mL, 2.8 mL per vial

CGMP STATEMENT/EIR UPDATE STATUS: ~~INCOMPLETE~~ Acceptable 1/23/98

Joe Buccine submitted a new EER on 1/14/98. On 5/21/98 EES said an inspection of was scheduled to be started on 5/4 and to be completed on 5/8.

BIO STUDY:

A waiver was requested. On 9/25/96 The Division of Bioequivalence informed Bedford that there were no further questions.

ANALYTICAL METHODS VALIDATION: **Incomplete**

Neither the DS nor the DP is compendial. An MV request and package have been prepared and are being sent to the PHI-DO FDA lab.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Yes. Stability data support a 24 month expiration period.

LABELING:
FPL was found to be satisfactory by Lillie Golson on 1/13/97.

STERILIZATION VALIDATION (IF APPLICABLE):
Ken Muhvich recommended approval on the basis of sterility assurance on 7/15/97.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Yes: remains adequate, as of 5/21/98.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Yes.

CHEMIST: Eugene L. Schaefer, Ph.D. DATE: May 27, 1998

5/27/98

TEAM LEADER: Mike Smela DATE:

5/28/98

X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\74728AP.SUM

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-728 Date of Submission: August 21, 1996

Applicant's Name: Bedford Laboratories™, Division of Ben Venue Laboratories, Inc.

Established Name: Leuprolide Acetate Injection 1 mg/0.2 mL, in 2.8 mL multiple dose vial

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 2.8 mL
Satisfactory as of August 21, 1996 submission

Carton Labeling: 2.8 mL
Satisfactory as of August 21, 1996 submission

Professional Package Insert Labeling:
Satisfactory as of August 21, 1996 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lupron® Injection

NDA Number: 19-010

NDA Drug Name: Leuprolide Acetate Injection

NDA Firm: TAP Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement #014: April 24, 1996
Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: 19-010
Basis of Approval for the Carton Labeling: 19-010

Post Approval Changes:

SOME SPECIAL ADVICE

Revise to make the following the second and fourth sentences, respectively, of bullet 8:

"Do not store near a radiator or other very warm place."
"Protect from light - store vial in carton until use."

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
PACKAGING -See applicant's packaging configuration in FTR			

Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	x		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	x		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. NONE			

FOR THE RECORD:

1. **Model Tap Holding's Lupron®; NDA 19-010/S-014 approved April 24, 1996. There is an insert for the palliative tx of prostatic cancer.**

2. **Firm originally submitted labeling for both prostate cancer and pediatric use**

(central precocious puberty). the latter indication is under NDA 20-263, which also has a Depot formulation. See attached matrix.

2. This is the first generic.

3. No patents or exclusivities exist. Patent #4005063 expired on January 25, 1996.

4. Inactive Ingredients appear to be consistent between the DESCRIPTION section and the statement of Components and Composition.

5. Storage recommendations for the RLD have been recently revised. See General Comment. Chemist has been notified, however, a chem. only letter issued on 5/15/96. He has requested that when our letter issues, we put him on the list so he can ad a comment concerning the submission of accelerated stability studies.

6. The strength on the carton and container are expressed "1 mg/0.2 mL" rather than "5 mg/mL" for 3 reasons: (1) it's the same as the innovator's labeling; (2) the dose is always 0.2 mL; and (3) the product is for outpatient use.

7. There is an "INFORMATION FOR PATIENTS" section at the end of the package insert. I telephoned Alvis Dunson, the CSO in HFD 510 to see if there was a separate PPI for Lupron®. He indicated that there did not appear to be one.

8. Request post-approval revisions to "SOME SPECIAL ADVICE" at earliest opportunity.

Date of Review:
January 13, 1997

Date of Submission:
August 21, 1996

Primary Reviewer:

Date:
1/23/97

Secondary Reviewer:

Date:

Team Leader:

Date:
1/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

CORRESPONDENCE

BEDFORD
LABORATORIES™

AMENDMENT

N/Am

May 7, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA -74-728/Facsimile Amendment
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial

Dear Sir/Madam:

We would like to amend our unapproved abbreviated new drug application 74-728, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial by responding to your letter dated April 7, 1998.

The number associated with the responses given below correspond to the number identifying the deficiencies in your communication. FDA 356h form is provided in Attachment I.

5/21/98

MAY 08 1998

GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

5-19-98

B. We acknowledged the following:

1. results will be validated before their report of analysis will be accepted for bulk release.

2. A satisfactory Method Validation is required to support this ANDA. The required samples will be submitted under separate cover when requested by the Agency.

3. Also, a satisfactory compliance evaluation is necessary for approval.

We trust this meets your approval. If you have any questions or comments, the phone numbers for contact are (440) 232-3320, ext, 333 direct and (440) 439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

FAX TRANSMISSION

BEN VENUE LABORATORIES
270 Northfield Road
Bedford, oh 44146
(440) 232-3320, Ext.333
Fax: (440) 439-6398

To: Sheila O'Keefe
Fax #: (301) 827-4337
From: Shahid Ahmed
Subject: Leuprolide Acetate Injection, ANDA 74-728

Date: May 7, 1998
Pages: 3, including this cover sheet.

COMMENTS:

Dear Ms. O'Keefe

Attached is our response to the FACSIMILE AMENDMENT to the deficiency letter that we had received on April 7, 1998. Attachments I to V will be forwarded in hard copy.

Any questions or comments, feel free to give me a call.

Sincerely,

P. Patel for
Shahid Ahmed

Sheila,
Fax Amend is incomplete. Pls recode this as NC and advise firm their amend will be minor when there is a complete response.
Thanks
5/11/98

Called him talked to Shahid Ahm told him it would be minor. He thanked me for the call.
5/11/98

APR 7 1998

ANDA: 74-728

APPLICANT: Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. 21 CFR 211.84(d)(2) requires that a supplier's test results be validated before a supplier's report of analysis may be accepted. Please commit to for the drug substance, or state that you have already done so, if that is the case.

2. A satisfactory Methods Validation is needed to support the ANDA. We will schedule the study when the testing issues are resolved.

3. A satisfactory compliance evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 7 1998

FACSIMILE AMENDMENT

ANDA 74728

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bedford Laboratories PHONE: (440) 232-3320x333

ATTN: Shahid Ahmed FAX: (440) 439-6398

FROM: Sheila O'Keefe PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial.

Reference is also made to your amendment(s) dated March 3, 1998.

Attached are 3 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

CMC comments attached

X:\new\ogdadmin\macros\faxfax.frm

BEDFORD
LABORATORIES™

March 3, 1998

NDA ORIG AMENDMENT

N/A M

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA -74-728/Minor Amendment
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial

Dear Sir/Madam:

We would like to amend our unapproved abbreviated new drug application 74-728, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial by responding to your letter dated January 27, 1998.

The number associated with the responses given below correspond to the number identifying the deficiencies in your communication. FDA 356h form is provided in Attachment I.

1.

MAR 1 1 1998

GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD LABORATORIES™

Office of Generic Drugs
ANDA 74-728

Leuprolide Acetate Inj.
March 3, 1998

Also, we would like to revise

Revised active drug substance specification is provided in this amendment in Attachment IV.

We trusts this meets your approval. If you have any questions or comments, the phone numbers for contact are (440) 232-3320, ext, 333 direct and (440) 439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

JAN 27 1998

ANDA: 74-728

APPLICANT: Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial.

The chemistry deficiencies presented below represent FACSIMILE deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

JAN 27 1998

ANDA 74-728

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bedford Laboratories PHONE: (216) 232-3320 ext. 218

ATTN: Margaret Van Dine ~~Robert V. Kasubick~~, Ph.D. FAX: ~~(216) 232-2772~~ 440 439 6398

FROM: Joseph Buccine PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Leuprolide Acetate Injection 1 mg/0.2 mL.

Reference is also made to your amendment(s) dated June 27, 1997.

Attached are _1_ pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

CHEMISTRY COMMENTS PROVIDED.

X:\new\ogdadmin\macros\faxfax.frm

BEDFORD
LABORATORIES™

June 27, 1997

ORIG AMENDMENT
N/A

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA -74-728/Major Amendment
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial

Dear Sir:

We would like to amend our unapproved abbreviated new drug application 74-728, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial by responding your letter dated March 14, 1997.

The number associated with the responses given below correspond to the number identifying the deficiencies in your communication. FDA 356h form is provided in Attachment I.

1/15/98

JUN 30 1997

GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2772

3/23/98

BEDFORD LABORATORIES™

Office of Generic Drugs
ANDA 74-728

Leuprolide Acetate Inj.
June 27, 1997
NA - Major letter

4

d.iii. We acknowledge your comment.

Leuprolide Acetate reference standard was and will be used
active drug substance.

solution. Active drug substance specification, test method and Certificate of Analysis for
94-0984 have been revised with appropriate revisions.

5. Full shelf-life (24 month) stability data is provided in Attachment ~~IV~~ V. We had enough number of vials to conduct 24 month sterility and ults are included in the updated stability data summary sheets. 1/20/95

VII 1/16/95

in Attachment VI, 062-05

B. Microbiology Deficiencies:

The test data for ; provided in Attachment X. VT 1/20/98

C. 1 esponded to the deficiencies regarding n March 20, 1997.

2. We acknowledge your comment.

We trusts this meets your approval. If you have any questions or comments, the phone numbers for contact are (216) 232-3320, ext, 218 direct and (216)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed

for Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

MAR 14 1997

ANDA: 74-728

APPLICANT: Bedford Laboratories, A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Leuprolide Acetate Injection, 5 mg/mL, 2.8 mL per vial.

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

If you have enough remaining vials, please provide 24 month sterility and results for the exhibit batch.

B. Microbiology Deficiencies:

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. responses of June 21 and August 16, 1996 are inadequate, so ; still deficient. The DMF holder is being notified by separate letter. Please respond to this deficiency letter only after you have learned that the DMF holder has responded to our letter.

2. Verification of your analytical methods by an FDA laboratory will be requested after you have satisfactorily responded to the deficiencies regarding the methods.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MAJOR AMENDMENT

MAR 14 1997

ANDA/AADA: 74-728

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT BEDFORD PHONE 216 232 3320 x 218
ATTN: ROBERT KASUBICK FAX 216 232 2772

FROM: JOSEPH BUCCINE PROJECT MANAGER (301-594-1841)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated 8-10-95, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for LEUPROLIDE ACETATE INJECTION 5 MG/ML

Reference is also made to your amendments dated 8-21-96, 8-23-96 AND 11-11-96

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

This is the second occasion major deficiencies are identified. Please call me within 30 days if you need help responding to the deficiencies. Joe

x:\new\ogdadmin\faxtrak\faxcov.mjr

BEDFORD
LABORATORIES™

November 11, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW AMENDMENT
A C

RE: ANDA -74-728/Follow-up to Major Amendment
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial

Dear Sir/Madam:

We would like to amend our unapproved Abbreviated New Drug Application, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial by providing Agency three month accelerated stability data for samples of exhibit batch to support the revised label temperature.

As we committed in the response to our major amendment, dated August 21, 1996, three month accelerated stability data for exhibit batch 753-00-0001 is provided in this amendment. Enough samples were stored under 40°C/75% RH for three months and testing was conducted based on submitted pre-approval stability protocol (SP96047.00). This stability protocol is provided to Agency in the response to last major amendment. A 24-month expiration date is requested, based on the stability data presented in this amendment.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (216)-232-3320, ext. 218 (direct) and (216)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
NOV 13 1996

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
LABORATORIES™

Mailed. Eric Schaefer 9/3/96

NEW CORRESP

RECEIVED

AUG 26 1996

GENERIC DRUGS

August 23, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA -74-728/Amendment to Major Amendment
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial

Dear Sir/Madam:

We would like to amend our response dated on August 21, 1996, [by replacing the pages 60 through 82] for unapproved Abbreviated New Drug Application, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial.

were inadvertently missed in Attachment V. Please replace the provided data in this amendment with pages 60 to 82 in the amendment dated August 21, 1996. We apologize for any inconvience this may have caused.

If the Agency needs any assistance in the review of this application, the phone numbers for contact are (216)-232-3320, ext. 218 (direct) and (216)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

for Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

Mailed 9/3/96

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
LABORATORIES™

August 21, 1996

RECEIVED

AUG 22 1996

GENERIC DRUGS

Review Completed 4/13/97

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA -74-728/Major Amendment**
PRODUCT: **Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial**

FDA DRUG AMENDMENT
AC

Dear Sir/Madam:

We would like to amend our unapproved Abbreviated New Drug Application, Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial by responding your letter dated May 15, 1996 and June 21, 1996.

FDA 356h form is provided in the Attachment I.

A. Chemistry Deficiencies

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2772

B. Microbiology Deficiencies

provided in the Attachment V (Pages 060-082)

The data summary is provided in Attachment V (Page 083). Please, please see NC dated 8/23/96.

3. Revalidation data summaries for .s provided in Attachment VI (Pages 084-105).

Thank you.

- 9/3/96

4.)

Attachment VII (Pages 106-117).

C. Labeling Deficiencies:

Based on Agency's comments which pertains to the letter dated June 21, 1996, vial label, carton labeling and package insert labeling have been updated. Side-by-side comparison of our proposed final printed label and labeling with our proposed draft label and labeling is provided in Attachment VIII (Pages 118-129). Regarding the comment 4.g.ii.(B), insulin syringes will be utilized for the product use and it is included in the final printed package insert labeling. Ben Venue Twelve copies of revised label and labeling have been provided in the Attachment VIII.

Also, due to the change in storage conditions, we have revised the pre-approval and post-approval stability protocols. Based on pre-approval stability protocol, we have placed enough samples from the exhibit batch under 40°C/75% RH for three months. As soon as the stability data is available, this application will be amended. Also, the change in the storage conditions has been reflected in the Sealing and Sampling Instructions in the scale-up records. These revised sections are provided in Attachment IX (Pages 131-142).

See follow-up submission dated 11/11/96.

In regards to this application, Ben Venue Laboratories acknowledges that, the manufacture and testing of the drug product will be performed in compliance with current GMPs at the time of approval.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (216)-232-3320, ext. 218 (direct) and (216)-232-2772 (fax).

2/12/97

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

/Attachments I to IX

ANDA 74-728

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
300 Northfield Road
Bedford, OH 44146

MAY 15 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leuprolide Acetate Injection, 5 mg/mL, 2.8 mL per vial.

Reference is also made to your amendment dated October 17, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Microbiology Deficiencies

C. Labeling Deficiencies

The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies within 10 working days of the date of this letter. Your response must be complete and incorporate ALL deficiencies, including any pending labeling deficiencies.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

B. Since neither the drug substance nor the drug product is covered by a compendial monograph, we will request verification of your analytical methods by an FDA laboratory.

C. Your bioequivalence response of March 12, 1996 is under review.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

5/14/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-728
ANDA #74-728/DUP/Division File
Field Copy
HFD-600/Reading File
HFD-613/L.Golson
HFD-610/J.Phillips

5/9/96

HFD-620/K.Muhvich

5/13/96

Endorsements:
HFD-627/E.L.Schaefer/5-2-96
HFD-613/L.Golson/5-7-96
HFD-613/J.Phillips/5-8-96
HFD-627/P.Schwartz, Ph.D./5-2-96
HFD-617/AMWeikel, CSO/5-5-96
X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\74728NA1.LF
F/T by MM May 9, 1996
Not Approvable - Major

5/5/96

5/9/96

5/13/96

5/14/96

ANDA 74-728

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
300 Northfield Road
Bedford, OH 44146

JUN 21 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Leuprolide Acetate Injection, 5 mg/mL, in 2.8 mL multiple dose vial.

Reference is made to our not approvable letter dated May 15, 1996.

The following comments pertain to labeling deficiencies as discussed in item C of the above cited correspondence.

1. GENERAL COMMENT:

Please note that the storage recommendations for the listed drug, Lupron Injection (Tap Holdings, NDA 19-010) have been changed from -

> Refrigerate until dispensed. Patient may store unrefrigerated below 86°F. Avoid freezing.

to -

> Store below 25°C(77°F). Do not freeze.

Please revise all labels and labeling accordingly.

2. CONTAINER

Usual dosage: 0.2 mL (1 mg)...
[NOTE: "Usual dosage" rather than "Usual dose" and include "1 mg".]

3. CARTON

a. See comment under Container.

b. Revise as follows -

Protect from light - Retain vial in carton until contents are used.

c. Include the pH range in the "Each 0.2 mL" statement.

4. INSERT

a. General Comment

Use "diethylstilbesterol" rather than "DES" throughout the text and in the tables.

b. DESCRIPTION

i. Revise the molecular weight to read -

1269.48

ii. Include the pH range in the last sentence.

c. CONTRAINDICATIONS

Delete the trademark "Factrel".

d. ADVERSE REACTIONS

On page 022, revise lines 17 and 18 as follows -

The following additional adverse reactions have been reported with leuprolide acetate during...

e. DOSAGE AND ADMINISTRATION

Revise the last paragraph to read as per 21 CFR 201.57(j).

f. HOW SUPPLIED

i. Revise storage recommendations as per General Comment.

ii. Revise "Protect from light" statement as per comment b under Container.

iii. In the "Caution: Federal law" statement, use

"without" rather than "with".

g. INFORMATION FOR PATIENTS

i. Under DIRECTIONS FOR USING LEUPROLIDE ACETATE, use "0.2" rather than ".2". [Note: in three places]

ii. Under SOME SPECIAL ADVICE -

A) At the bottom of page 026, delete the last line, since this is repeated at the top of page 027.

B) The fourth bullet refers to syringes being supplied with the product. Please note that Lupron Injection is marketed in a 14 day administration kit which contains one 2.8 mL vial, 14 syringes, and 24 alcohol swabs. Is this your intent also? If so, please include labeling for this package. If not, please revise this statement to indicate to the patient what type of syringes to use.

C) Revise the eighth bullet as per General Comment.

Please revise your labels and labeling, as instructed above, then prepare and submit final printed container labels, carton labeling, and package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

This letter addresses issues primarily involving labeling. However, the change in the storage recommendations, due to the change in labeling of the listed drug, will require changes in the pre-approval and post-approval stability protocols. The label storage temperature will now be represented by 25.0°C ± 2.0°C, and the accelerated condition will need to be 40°C.

Again, we refer you to our letter of May 15, 1996, for the requirements to reopen the file on this application.

Sincerely yours,

for/ 6-21-96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-728
Division File
HFD-610/EL Schaefer/Bill Russe
HFD-627/PSchwartz/ARudman (no copies
HFD-613/JC[illegible]/AVezza
HFD-600/P
njg/6/17/96/A:\new\firmsam\bedford\ltrs&rev\74728na1.lo
letter out

6/18/96
6/18/96
6/18/96

BEDFORD
LABORATORIES™

October 17, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA - 74-728/Amendment (Refusal to File)
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL fill

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 74-728, for Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL per vial, in reference to your letter dated October 10, 1995.

Since submitted ANDA 74-728 has two labeled uses, Ben Venue would like to withdraw one labeled use, which is

. To reflect this change, Section I to Section V of the original application have been amended.

A revised Side by Side Comparison of Excipient, with a quantitative analysis included for both the listed drug product and the proposed drug product, in accordance with 21 CFR 314.94(a)(9)(iii). Also, included in this amendment are revised cGMP Certifications and Environmental Assessments from applicant, Bedford Laboratories.

We trust this meets your approval and with the requirements necessary to accept ANDA 74-728 for review. If you have any questions regarding this amendment, please call the undersigned at (216) 232-3320, ext. 218.

Sincerely,
for Bedford Laboratories,

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
OCT 18 1995
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2

ANDA 74-728

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, OH 44146

OCT 10 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 10, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Leuprolide Acetate Injection, 5 mg/mL, 2.8 mL per vial.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

The approved drug products upon which you base your application are the subject of two new drug applications (NDAs), each having different labeled uses. Since an ANDA can refer to only one reference listed drug, you must withdraw reference to one of the NDAs and its related use from this application and submit it as a separate ANDA.

While we note that you have addressed patent #4,005,063, expiring January 25, 1996, you have failed to address other patents existing for these drug products. We refer you to the current edition of Approved Drug Products with Therapeutic Equivalence Evaluations, 15th edition. Specifically, we refer to patent numbers 4,917,893, expiring March 24, 2004; #4,849,228, expiring July 18, 2006; #4,728,721, expiring March 1, 2005; #4,677,191, expiring June 30, 2004; and #4,652,441, expiring March 24, 2004. Under these patents there are also marketing exclusivities for New Product Exclusivity expiring April 16, 1996; and Orphan Drug Exclusivity expiring April 16, 2000. We strongly recommend using the current edition and supplements to this reference at all times. It would appear your patent/ exclusivity information came from the 13th edition.

While you have provided an environmental assessment and certification of compliance with all environmental laws for your manufacturing facility, Ben Venue, you have failed to provide an environmental assessment and certification of compliance for the applicant, Bedford Laboratories. Please provide this assessment and certification of compliance with all applicable environmental laws.

While we note that you have provided a qualitative comparison of the formulation between your proposed drug product, you must demonstrate that the proposed drug product is qualitatively **and quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. ph, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

10/10/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-728
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Act. Chief: 9/14/95 date
HFD-615/WRussell, CS 9/18/95 date.
HFD-610/CHopped, Actg. Chief, LP 9/19/95 date
HFD-625/MSmela, Sup. Chem date for 9/19/95
WP File\A:\rtfanda\74-728.rtf
F/T File hrw 9-18-95
ANDA Refuse to File!

Note: PI is recommended to transfer the CMC review of this peptide from Random 2 to Branch 4 (Dr. Schaefer) if and when it is filed due to expertise considerations
10/6/95

BEDFORD
LABORATORIES™

Return to file
8/15/95

August 10, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application
PRODUCT: Leuprolide Acetate Injection, 5 mg/mL; 2.8 mL fill

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Leuprolide Acetate Injection, 5 mg/mL, 2.8 mL fill. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Tap Pharmaceuticals, Inc., Lupron® Injection, N19010) as well as copies of the relevant pages of the **Approved Prescription Drug Products List with Therapeutics Equivalence Evaluations.**

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of our application (Leuprolide Acetate Injection; 5 mg/mL 2.8 mL fill). The drug product is a solution intended solely for subcutaneous administration and it contains the active ingredient in the same concentration as in the listed drug.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2772

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Three copies of analytical methods which were used to test this product and an analytical method validation package are enclosed separately along with this application.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol and the package insert is enclosed separately with this application. This drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216)-232-3320, ext. 218.

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.