CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74728

Trade Name Leuprolide Acetate Injection, 1mg/0.2ml

Generic Name Leuprolide Acetate Injection, 1mg/0.2ml

Sponsor Bedford Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74728

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
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Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74728

APPROVAL LETTER

ANDA 74-728

AUG - 4 1998

Bedford Laboratories
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

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, 1 mg/0.2 mL.

Reference is also made to your amendments dated March 12, 1996; and May 7, and July 8, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Leuprolide Acetate Injection, 1 mg/0.2 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lupron Injection, 1 mg/0.2 mL, of TAP Holdings, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified during the validation process.

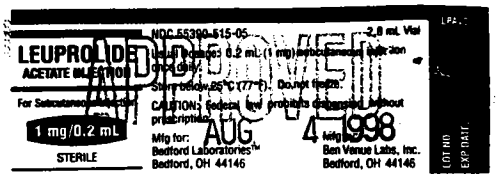
Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

FINAL PRINTED LABELING



BEN VENUE LAB.
PRINTED SIDE
C021495AB

1 1/2

1 3/8

2 1/2

Each 0.2 mL contains: leuprolide acetate, 1 mg (equivalent to 0.95 mg free base); sodium chloride for tonicity adjustment; benzyl alcohol, as preservative, 1.8 mg; in water for injection, pH may have been adjusted with sodium hydroxide and/or acetic acid. The pH range is 4.0 to 6.0.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

NDC 55390-515-05
2.8 mL Vial

LEUPROLIDE
ACETATE INJECTION

For Subcutaneous Injection

1 mg/ 0.2 mL

STERILE

BEDFORD LABORATORIES™

Usual Dosage: 0.2 mL (1 mg) subcutaneous injection once daily. See package insert for full prescribing information and patient use information.

Store below 25°C (77°F). Do not freeze. **Protect from light.** Retain vial in carton until contents are used.

CAUTION: Federal law prohibits dispensing without prescription.

NDC 55390-515-05
2.8 mL Vial

LEUPROLIDE
ACETATE INJECTION

For Subcutaneous Injection

1 mg/ 0.2 mL

STERILE

BEDFORD LABORATORIES™

LPAC00

0 55390-515-05 4

AUG 4 1998

LOT NO

EXP DATE

Ben Venue Leuprolide
Printed Side
C021495AB
Format Number: 184A

- **PMS 308**
- **Black**

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

Cardiovascular System - Angina, cardiac arrhythmias, myocardial infarction, pulmonary emboli.

Gastrointestinal System - Diarrhea, dysphagia, gastrointestinal bleeding, gastrointestinal disturbance, peptic ulcer, rectal polyps.

Endocrine System - Libido decrease, thyroid enlargement.

Musculoskeletal System - Joint pain.

Central/Peripheral Nervous System - Anxiety, blurred vision, lethargy, memory disorder, mood swings, nervousness, numbness, paresthesia, peripheral neuropathy, syncope/blackouts, taste disorders.

Respiratory System - Cough, pleural rub, pneumonia, pulmonary fibrosis.

Integumentary System - Carcinoma of skin/ear, dry skin, ecchymosis, hair loss, itching, local skin reactions, pigmentation, skin lesions.

Urogenital System - Bladder spasms, dysuria, incontinence, testicular pain, urinary obstruction.

Miscellaneous - Depression, diabetes, fatigue, fever/chills, hypoglycemia, increased BUN, increased calcium, increased creatinine, infection/inflammation, ophthalmologic disorders, swelling (temporal bone).

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

Cardiovascular System - Hypotension, transient ischemic attack/stroke.

Gastrointestinal System - Hepatic dysfunction.

Endocrine System Libido increase.

Hemic and Lymphatic System - Decreased WBC, hemoptysis.

Musculoskeletal System - Ankylosing spondylosis, pelvic fibrosis.

Central/Peripheral Nervous System - Hearing disorder, peripheral neuropathy, spinal fracture/paralysis.

Respiratory System - Pulmonary infiltrate, respiratory disorders.

Integumentary System - Hair growth.

Urogenital System - Penile swelling, prostate pain.

Miscellaneous - Hypoproteinemia, hard nodule in throat, weight gain, increased uric acid.

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with leuprolide acetate doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Leuprolide Acetate Injection is a sterile solution supplied in a 2.8 mL multiple-dose vial, **NDC 55390-515-05**. Store below 25°C (77°F). Do not freeze. **Protect from light** - Retain vial in carton until contents are used.

Each 0.2 mL contains 1 mg of leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid. The pH range is 4.0 to 6.0.

CAUTION - Federal law prohibits dispensing without prescription.

REFERENCE

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

INFORMATION FOR PATIENTS

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

WHAT IS LEUPROLIDE ACETATE?

Leuprolide Acetate Injection is chemically similar to gonadotropin releasing hormone (GnRH or LH-RH) a hormone which occurs naturally in your body.

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

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

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

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

DIRECTIONS FOR USING LEUPROLIDE ACETATE

1. Wash hands thoroughly with soap and water.
2. If using a new bottle for the first time, flip off the plastic cover to expose the gray rubber stopper. Wipe metal ring and rubber stopper with an alcohol wipe each time you use leuprolide acetate. Check the liquid in the container. If it is not clear or has particles in it, DO NOT USE IT. Exchange it at your pharmacy for another container.
3. Remove outer wrapping from one syringe. Pull plunger back until the tip of the plunger is at the 0.2 or 20 unit mark.
4. Take cover off needle. Push the needle through the center of the rubber stopper on the leuprolide acetate bottle.
5. Push the plunger all the way in to inject air into the bottle.
6. Keep the needle in the bottle and turn the bottle upside down. Check to make sure the tip of the needle is in the liquid. Slowly pull back on the plunger, until the syringe fills to the 0.2 or 20 unit mark.
7. Toward the end of a two-week period, the amount of leuprolide acetate left in the bottle will be small. Take special care to hold the bottle straight and to keep the needle tip in liquid while pulling back on the plunger.
8. Keeping the needle in the bottle and the bottle upside down, check for air bubbles in the syringe. If you see any, push the plunger *slowly* in to push the air bubble back into the bottle. Keep the tip of the needle in the liquid and pull the plunger back again to fill to the 0.2 or 20 unit mark.
9. Do this again if necessary to eliminate air bubbles. Remove needle from bottle and lay syringe down. DO NOT TOUCH THE NEEDLE OR ALLOW THE NEEDLE TO TOUCH ANY SURFACE.
10. To protect your skin, inject each daily dose at a different body spot.
11. Choose an injection spot. Cleanse the injection spot with another alcohol wipe.
12. Hold the syringe in one hand. Hold the skin taut, or pull up a little flesh with the other hand, as you were instructed.
13. Holding the syringe as you would a pencil, thrust the needle all the way into the skin at a 90 angle.
14. Hold an alcohol wipe down on your skin where the needle is inserted and withdraw the needle at the same angle it was inserted.
15. Use the disposable syringe only once and dispose of it properly as you were instructed. Needles thrown into a garbage bag could accidentally stick someone. NEVER LEAVE SYRINGES, NEEDLES OR DRUGS WHERE CHILDREN CAN REACH THEM.

SOME SPECIAL ADVICE

- You may experience hot flashes when using leuprolide acetate injection. During the first few weeks of treatment you may experience increased bone pain, increased difficulty in urinating, and less commonly but most importantly, you may experience the onset or aggravation of nerve symptoms. In any of these events, discuss the symptoms with your doctor.
- You may experience some irritation at the injection site, such as burning, itching or swelling. These reactions are usually mild and go away. If they do not, tell your doctor.
- Do not stop taking your injections because you feel better. You need an injection every day to make sure leuprolide acetate keeps working for you.
- Insulin syringes may be used with leuprolide acetate injection.
- When the drug level gets low, take special care to hold the bottle straight up and down and to keep the needle tip in liquid while pulling back on the plunger.
- Do not try to get every last drop out of the bottle. This will increase the possibility of drawing air into the syringe and getting an incomplete dose. Some extra drug has been provided so that you can withdraw the recommended number of doses.
- Tell your pharmacist when you will need leuprolide acetate injection so it will be at the pharmacy when you need it.
- Store below 25°C (77°F). Do not freeze.
- Do not leave your drug or hypodermic syringes where anyone can pick them up.
- Keep this and all other medications out of reach of children.

Manufactured by Ben Venue Laboratories, Inc., Bedford, OH 44146

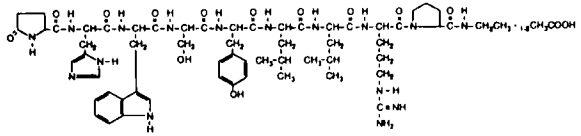
Manufactured for Bedford Laboratories™, Bedford, OH 44146

July 1996 LPAP00

LEUPROLIDE ACETATE INJECTION

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



Molecular Weight: 1269.48 Molecular Formula: $C_{59}H_{84}N_{16}O_{12}{\cdot}C_2H_4O_2$

Leuprolide Acetate Injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing 5 mg/mL of leuprolide acetate, sodium chloride for tonicity adjustment, 9 mg/mL of benzyl alcohol as a preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid. The pH range is 4.0 to 6.0.

CLINICAL PHARMACOLOGY

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

Leuprolide acetate is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

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

PRECAUTIONS

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

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

Information for Patients: See **INFORMATION FOR PATIENTS** which appears after the **HOW SUPPLIED** section.

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

Drug Interactions: None have been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. However, no clinical studies have been conducted with leuprolide acetate to assess the reversibility of fertility suppression.

Pregnancy Category X. See **CONTRAINDICATIONS** section.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by an increase in bone pain (see **WARNINGS** section). In a few cases a temporary worsening of existing hematuria and urinary tract obstruction occurred during the first week. Temporary weakness and paresthesia of the lower limbs have been reported in a few cases.

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

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

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

*Physiologic effect of decreased testosterone.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5 Cycle 5
2. ANDA # 74-728 FIRST GENERIC TOP 200

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION

The RLD is Lupron®, marketed by TAP Pharmaceuticals Inc., NDA 19-010.

Patent 4,005,063 expired 01/25/96. There is no exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Leuprolide Acetate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Cycle 1:

08/10/95 Original ANDA.
10/10/95 Refuse-to-file letter.
10/17/95 **Amendment** in response to RTF letter.
01/22/96 Microbiologist's Review #1: Not recommended for approval.
02/06/96 Bio letter re pHs of proposed drug and RLD.
03/12/96 NC in response to Bio letter of 2/6/96.
05/15/96 NA letter (chemistry and microbiology only, but refers to labeling).
06/21/96 NA letter (labeling only, but refers to stability storage conditions).

Cycle 2:

08/21/96 **Major amendment** (chemistry, microbiology, and labeling - the subject of Chemistry Review #2).

08/23/96 **Amendment to major amendment** of 8/21/96, according to Bedford. Coded NC by document room. Microbiology only.
09/19/96 Microbiologist's Review #2: Not recommended for approval.
09/25/96 Letter to firm: Division of Bioequivalence has no further questions.
11/11/96 **Follow-up to major amendment** of 8/21/96, according to Bedford. Coded AC by document room. Accelerated stability data - the subject of Chemistry Review #2.
01/13/97 Labeling approval summary.
03/14/97 NA-Major fax

Cycle 3:

05/27/97 Telecon between representatives of Bedford and members of OGD Chemistry Division I, clarifying what is meant in the deficiencies in the fax of 3/14/97, and reaching an understanding of what OGD wants.
06/27/97 **Major amendment.**
01/27/98 NA - Facsimile amendment requested.

Cycle 4:

03/03/98 Response to request of 1/27/98. The submission came in as a facsimile amendment, but after the 30 day deadline, so Mark Anderson recorded it as a **minor amendment** on 3/16/98.
04/07/98 NA - Facsimile amendment requested.

Cycle 5:

05/07/98 Response to request of 4/7/98. An incomplete submission came in as a facsimile amendment, but the complete submission came in after the 30 day deadline, so Sheila O'Keefe recorded it as a **minor amendment** on 5/11/98.

10. PHARMACOLOGICAL CATEGORY

Antineoplastic agent/Gonadotropin releasing hormone agonist, for the palliative treatment of advanced prostatic cancer.

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Subcutaneous Injection

14. STRENGTH

5 mg/mL, 2.8 mL per multiple-dose vial

15. CHEMICAL NAME AND STRUCTURE

The active ingredient is a synthetic nonapeptide agonist analog of luteinizing hormone - releasing hormone (LH-RH). The active ingredient is a monoacetate salt. The following name and structure are given in USAN and in the ANDA (page 065 of the original submission).

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide monoacetate (salt) $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ 1269.47 in USAN, 1270.5 in ANDA.

H--5-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro--NHEt . CH_3COOH
1 2 3 4 5 6 7 8 9

A more detailed structure is presented in the labeling insert on page 016 of the amendment of 10/17/95.

The gives the structure of leuprolide as pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt . points out that p-Glu stands for L-pyroglutamic acid, and the Merck Index shows that L-pyroglutamic acid and 5-oxo-L-proline are the same compound.

16. RECORDS AND REPORTS N/A

17. COMMENTS

Ken Muhvich recommended **approval** on the basis of sterility assurance on 7/15/97.

ANDA 74-728 is **incomplete** in the following Points:

31. Samples and Results

An MV request and package have been prepared and are being sent to the PHI-DO FDA lab.

33. Establishment Inspection

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

The following Points are **satisfactory** for ANDA 74-728:

32. Labeling (01/24/97, according to COMIS)
34. Bioequivalence Status (9/25/96)

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 74-728 can be **APPROVED**, pending Establishment Inspection and Methods Validation.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 5/27/98

Endorsed by M. Smela

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

BIOEQUIVALENCE REVIEW(S)

ANDA 74-728

SEP 25 1996

Bedford Laboratories
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford OH 44146

Dear Sir:

Reference is made to your abbreviated new drug application 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.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG _ 6 1996

Leuprolide Acetate
Injection, 1 mg/0.2 mL
2.8 mL per vial
ANDA #74-728
Reviewer: F. Nouravarsani
74728WA.396

Bedford Laboratories
Division of Ben Venue Lab.
Bedford, Ohio
Submission Date:
March 12, 1996

Review of a Waiver Request (Amendment)

Bedford Laboratories, Inc. had requested a waiver of bioequivalence study requirements under 21 CFR 320.22 for its test product, Leuprolide Acetate Injection, 1 mg/0.2 mL (2.8 mL multiple-dose vial). The listed reference product is Lupron, Leuprolide Acetate Injection, 1 mg/0.2 mL in 2.8 mL multiple-dose vial (N19010-001, April 09, 1985), manufactured for Tap Pharmaceuticals Inc. by Abbott Laboratories.

Leuprolide Acetate, an analog of the gonadotropin-releasing hormone is an inhibitor of gonadotropin secretion when it is used continuously in therapeutic doses. Lupron injection has been indicated in the palliative treatment of advanced prostatic cancer. Lupron is a sterile aqueous solution administered as subcutaneous injection. The recommended dose is a daily single dose of 1 mg (0.2 mL), injected subcutaneously. Leuprolide Acetate plasma half-life is approximately 3 hours. Its bioavailability of the subcutaneous administration is comparable with the intravenous administration (PDR, 1995).

Formulations of the test and reference products are compared in Table 1. **Note: The compositions of the reference product formulation should not be revealed under FOI.**

Deficiency of Previous Submission:

The firm was requested to clarify the basis for selecting solution pH range of 4.0 - 6.0.

Response to Deficiency:

The firm submitted results of stability study conducted at pH range of 4.0 to 6.2 at 27.5°C $\pm$ 2.5°C for 3 months. The recoveries were as follows:

pH	%Recovery

The firm also submitted results of a study conducted at pH range of 4.0 to 6.2 at 2-8°C, 27.5°C, 40°C, and 50°C for 2 months. The pH was found to change less than ±0.5 unit from the initial pH.

The firm measured the pH of the 2 samples of the reference product to be 4.9 and 5.9.

Comments:

1. The test product (first generic) is a sterile injectable solution of Leuprolide Acetate in water for injection, 1 mg/0.2 mL (2.8 mL multiple-dose vial).

2. Leuprolide Acetate, a white to off-white powder has water solubility of 250 mg/mL at 25° C (AHFS Drug Information, p. 606, 1993).

3. The concentration of sodium chloride (Table 1) for the test product is which is the same as the concentration of sodium chloride for the reference product, (from NDA 19-010, submission dated July 08, 1983).

4. The concentration of benzyl alcohol (Table 1) for the test product is 9.0 mg/mL, which is the same as the concentration of benzyl alcohol for the reference product, 9.0 mg/mL (PDR, 1995).

5. The firm's specifications for the assay and pH of the finished test product is and 4.0 - 6.0, respectively by the Bedford Laboratories, Division of Ben Venue Lab. However, in order to maintain the above specifications, Ben Venue Lab. has tightened them to for the assay, and for the pH.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that Leuprolide Acetate Injection, 1 mg/0.2 mL (2.8 mL per vial) falls under CFR 320.22 b(1) of the Bioavailability/Bioequivalence Regulations, 1995. The waiver of in - vivo bioequivalence study for Leuprolide Acetate, 1 mg/0.2 mL (2.8 mL per vial) Injection of the Test product is granted.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED, RMHATRE 8/6/96

Concur: _____ Date: 8/6/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/7-10-96/74728WA.396

cc: ANDA #74-728 (original, duplicate) HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Note: The compositions of the reference product formulation should not be revealed under FOI.

Formulations Comparison:

Ingredients	Test (mg/mL)	Reference (mg/mL) (Tap Pharmaceuticals)
Leuprolide Acetate	5 (1mg/0.2mL)	5 (1mg/0.2mL)
Sodium Chloride (a)		
Benzyl Alcohol (b)	9 NF	9
Acetic Acid (c)	X USP	X
Sodium Hydroxide (c)	X NF	X
Water for Injection	X USP/EP	X
	X NF	X

(a) = to adjust tonicity

(b) = as a preservative

(c) = to adjust pH of the test product solution to 4.0 - 6.0, and the reference product solution to

X = ingredient present in the products.

JAN 1 1 1996

Leuprolide Acetate
Injection, 1 mg/0.2 mL
2.8 mL per vial
ANDA #74-728
Reviewer: F. Nouravarsani
74728W.095

Bedford Laboratories
Division of Ben Venue Lab.
Bedford, Ohio
Submission Date:
October 17, 1995

Review of a Waiver Request

Bedford Laboratories, Inc. has requested a waiver of bioequivalence study requirements under 21 CFR 320.22 for its test product, Leuprolide Acetate Injection, 1 mg/0.2 mL (2.8 mL multiple-dose vial). The listed reference product is Lupron, Leuprolide Acetate Injection, 1 mg/0.2 mL in 2.8 mL multiple-dose vial (N19010-001, April 09, 1985), manufactured for Tap Pharmaceuticals Inc. by Abbott Laboratories.

Leuprolide Acetate, an analog of the gonadotropin-releasing hormone is an inhibitor of gonadotropin secretion when it is used continuously in therapeutic doses. Lupron injection has been indicated in the palliative treatment of advanced prostatic cancer. Lupron is a sterile aqueous solution administered as subcutaneous injection. The recommended dose is a daily single dose of 1 mg (0.2 mL), injected subcutaneously. Leuprolide Acetate plasma half-life is approximately 3 hours. Its bioavailability of the subcutaneous administration is comparable with the intravenous administration (PDR, 1995).

Formulations of the test and reference products are compared in Table 1. **Note: The compositions of the reference product formulation should not be revealed under FOI.**

Comments:

1. The test product (first generic) is a sterile injectable solution of Leuprolide Acetate in water for injection, 1 mg/0.2 mL (2.8 mL multiple-dose vial).

2. Leuprolide Acetate, a white to off-white powder has water solubility of 250 mg/mL at 25° C (AHFS Drug Information, p. 606, 1993).

3. The firm's specifications for the assay and pH of the finished test product is 90% - 110%, and 4.0 - 6.0, respectively by the Bedford Laboratories, Division of Ben Venue Lab. However, in order to maintain the above specifications, Ben Venue Lab. has tightened them to 95% - 105% for the assay, and 4.5 - 5.5 for the pH.

The reference product's specification for the solution pH is 5.7 - 6.3 (from NDA 19-010, submission dated July 08, 1983). The

solution pH of the test product, 4.0 - 5.5 does not fall in the range of the solution pH of the reference product, 5.7 - 6.3.

4. The concentration of sodium chloride for the test product is 6.3 mg/mL, which is the same as the concentration of sodium chloride for the reference product, 6.3 mg/mL (from NDA 19-010, submission dated July 08, 1983).

5. The concentration of benzyl alcohol for the test product is 9.0 mg/mL, which is the same as the concentration of benzyl alcohol for the reference product, 9.0 mg/mL (PDR, 1995).

Deficiency:

The firm should explain the basis for selecting solution pH range of 4.0 - 6.0.

Recommendation:

The information submitted by Bedford Laboratories for Leuprolide Acetate, 1 mg/0.2 mL Injection was found incomplete by the Division of Bioequivalence. The firm should be informed of the deficiency.

Farahnaz Nouravarsani

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE Vamakant M. Mhatre 1/11/96

Concur: See 12/5/95 memo Date: 1/16/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/12-11-95/74728W.095

cc: ANDA #74-728 (original, duplicate) HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Note: The compositions of the reference product formulation should not be revealed under FOI.

Formulations Comparison:

Ingredients	Test (mg/mL)	Reference (mg/mL) (Tap Pharmaceuticals)
Leuprolide Acetate	5 (1mg/0.2mL)	5 (1mg/0.2mL)
Sodium Chloride (a)	6.3 USP	6.3
Benzyl Alcohol (b)	9 NF	9
Acetic Acid (c)	X USP	X
Sodium Hydroxide (c)	X NF	X
Water for Injection	X USP/EP	X
Nitrogen	X NF	X

(a) = to adjust tonicity

(b) = as a preservative

(c) = to adjust pH of the test product solution to 4.0 - 6.0, and the reference product solution to 5.7 - 6.3.

X = ingredient present in the products.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-728

CC: TR. TP. JC. RK. SA. MV. AB. PP.

FEB -6 1996

Bedford Laboratories
Attention: Robert V. Kasubic, Ph.D.
270 Northfield Road
Bedford OH 44146

Dear Sir:

Reference is made to the request for waiver of *in vivo* bioequivalence study, submitted on October 17, 1995, for Leuprolide Acetate Injection 1 mg/0.2 mL, 2.8 mL per vial.

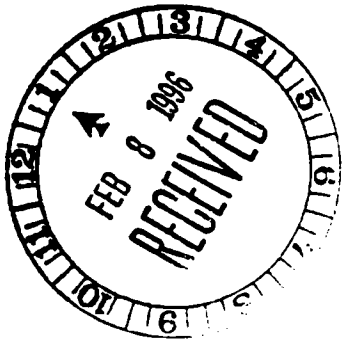
The Office of Generic Drugs has reviewed the waiver request and the following inquiry is provided for your consideration:

> The physicochemical properties of the test and reference listed drug should be essentially the same. The proposed pH range of 4.0 - 6.0 is different than that of the reference listed drug and needs to be resolved.

As described under 21 CFR 314.96 an action which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research



OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-728 **SPONSOR:** Bedford Laboratories
DRUG: Leuprolide Acetate
DOSAGE FORM: Injection
STRENGTH: 1 mg/0.2 mL, 2.8 mL per vial
TYPE OF STUDY: Waiver Request

SUMMARY:

The firm requested for waiver of bioequivalence study requirements for its test product, Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial. The reference listed product is Lupron Injection, Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial manufactured by Tap Pharmaceuticals, Inc.

WAIVER OF BIOEQUIVALENCE STUDY:

Waiver of bioequivalence study requirements for Leuprolide Acetate Injection, 1 mg/0.2 mL, 2.8 mL per vial may be granted under 21 CFR 320.22 b(1), 1995 of the Bioavailability/Bioequivalence Regulations.

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE ____ **DATE:** 8/8/1996

BRANCH CHIEF: R. Mhatre **BRANCH:** III

SIGNITURE: ____ **DATE:** 8/8/96

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: _____ **DATE:** 9/25/96

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: N/A **DATE:** _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74728

MICROBIOLOGY REVIEW(S)

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

January 22, 1996

A. 1. ANDA: **74-728**

APPLICANT: Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: **Leuprolide Acetate Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

5 mg/mL sterile solution; 2.8 mL fill contained in 5 cc multiple dose glass vials for subcutaneous administration.

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: For palliative treatment of advanced prostatic cancer

6. PHARMACOLOGICAL CATEGORY:

Antineoplastic agent/Gonadotropin releasing hormone agonist

B. 1. DATE OF INITIAL SUBMISSION:

August 10, 1995 (Received by OGD on 8/14/95)
- Subject of this Review

2. DATE OF AMENDMENT: N/A; no amendments were submitted that contained sterility assurance information by the time of this review

3. RELATED DOCUMENTS:

NDA 19-010 held by Tap Pharmaceuticals Inc. for the innovator drug product, **Lupron®**

4. ASSIGNED FOR REVIEW: January 16, 1996

C. REMARKS: Microbiological validation for the used to manufacture the subject drug product was found on pages 129 - 372 (Section XI). The information provided in the application was insufficient to determine if the applicant is taking the necessary steps to ensure the sterility of the subject drug product (Leuprolide Acetate Injection). For example, recent revalidation data for needs to be submitted.

D. CONCLUSIONS: The submissions are therefore not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft Letter to the Applicant".

1/22/96

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 1/22/96 1/22/96

cc:
Original ANDA 74-728
Field Copy

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #2

September 19, 1996

A. 1. ANDA: **74-728**

APPLICANT: Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: **Leuprolide Acetate Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

5 mg/mL sterile solution; 2.8 mL fill contained in 5 cc multiple dose glass vials for subcutaneous administration

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: For palliative treatment of advanced prostatic cancer

6. PHARMACOLOGICAL CATEGORY:

Antineoplastic agent/Gonadotropin releasing hormone agonist

B. 1. DATE OF INITIAL SUBMISSION: **August 10, 1995**

2. DATES OF AMENDMENTS:

August 21, 1996 (Received by OGD on 8/22/96)
Major Amendment - Subject of this Review

August 23, 1996 (Received by OGD on 8/26/96)
Amendment to 8/21/96 Major Amendment
- Subject of this Review

which were supposed to be provided in Attachment V of the amendment dated 8/21/96

3. RELATED DOCUMENTS:

NDA 19-010 held by Tap Pharmaceuticals Inc. for the innovator drug product, **Lupron®**

4. ASSIGNED FOR REVIEW: September 19, 1996

C. REMARKS: The information provided in the amendments was still insufficient to determine if the applicant is taking the necessary steps to ensure the sterility of the subject drug product [redacted] (Leuprolide Acetate Injection). Acceptable data still needs to be submitted.

D. CONCLUSIONS: The submissions are therefore not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft Letter to the Applicant".

9/19/96

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel
drafted by: KHMuhvich, 9/19/96

9/19/96

cc:

Original ANDA 74-728
Field Copy

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #3

July 15, 1997

A. 1. ANDA: **74-728**

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

2. PRODUCT NAMES: **Leuprolide Acetate Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

5 mg/mL sterile solution; 2.8 mL fill contained in 5 cc multiple dose glass vials for subcutaneous administration

4. METHOD(S) OF STERILIZATION: **Aseptic Filling**

5. PRINCIPLE INDICATIONS: For palliative treatment of advanced prostatic cancer

6. PHARMACOLOGICAL CATEGORY:

Antineoplastic agent/Gonadotropin releasing hormone agonist

B. 1. DATE OF INITIAL SUBMISSION: **August 10, 1995**

2. DATES OF AMENDMENTS:

August 21, 1996 - Major Amendment

August 23, 1996 - Major Amendment
Contained routine
which were supposed to be provided in Attachment V of the amendment dated 8/21/96

June 27, 1997 (Received by OGD on 6/30/97)
Major Amendment - Subject of this Review
Sent in response to the Division's letter dated 3/14/97

3. RELATED DOCUMENTS:

NDA 19-010 held by Tap Pharmaceuticals Inc. for the innovator drug product, **Lupron®**

3. RELATED DOCUMENTS (continued):

4. ASSIGNED FOR REVIEW: July 14, 1997

C. REMARKS: The information provided in the amendment was sufficient to determine that the applicant is now taking the necessary steps to ensure the sterility of the subject drug product (Leuprolide Acetate Injection).

D. CONCLUSIONS: The submissions are therefore recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes."

7/15/97

Kenneth H. Muhvich, Ph.D.

HFD-620/initialed by RPatel 7/17/97
drafted by: KHMuhvich, 7/15/97

cc:

Original ANDA 74-728
Field Copy